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Women in obstetrics and gynecology

Edited by
Isabella Fabietti, Elisa Bevilacqua and Zaleha Abdullah Mahdy

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Women in obstetrics and gynecology

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SYSTEMATIC REVIEW
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Prevalence of Psychosomatic and Genitourinary Syndrome Among Menopausal Women: A Systematic Review and Meta-Analysis

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Introduction: The menopausal transition represents the passage from reproductive to non-reproductive life and is characterized by a number of menstrual disturbances. We systematically reviewed the evidence on the prevalence of psychosomatic and genitourinary syndrome among menopausal women and compared the risk of symptoms between premenopausal, perimenopausal, and post-menopausal women.

Methods: We performed a systematic search in MEDLINE, CINAHL, and ScienceDirect through March 2021. Case series/reports, conference papers and proceedings, articles available only in abstract form, editorial reviews, letters of communication, commentaries, systematic reviews, and qualitative studies were excluded. Two reviewers independently extracted and assessed the quality of data using the Joanna Briggs Institute Meta-Analysis. The outcomes were assessed with random-effects model using the Review Manager software.

Results: In total, 29 studies had a low risk of bias and were included in the review. Our findings showed that the pooled prevalence of somatic symptoms in post-menopausal women (52.6%) was higher than in the premenopausal and perimenopausal stages (34.6 and 39.5%, respectively). There was a low prevalence of psychological symptoms in premenopausal women (28.4%). The genitourinary syndrome was highest among post-menopausal women (55.1%), followed by perimenopausal (31.9%) and premenopausal (19.2%) women.

Conclusion: Post-menopausal women have a higher risk of experiencing menopausal symptoms particularly genitourinary syndrome than premenopausal and perimenopausal women. It is pertinent for healthcare professionals to evaluate the symptoms in order to provide them with a better quality of life.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021235958

Keywords: menopause, prevalence, psychosomatic, genitourinary syndrome, symptom

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INTRODUCTION

Natural menopause occurs at a median age of 51 years in Western societies and is assumed to be caused by ovarian follicle exhaustion (1). Based on the Stages of Reproductive Aging Workshop (STRAW) criteria, menopause is defined as 12 or more months of amenorrhea following the final menstrual period (2). Perimenopause is defined as the onset of a varied cycle duration (early stage), two or more missing periods, and at least 2 months of amenorrhea (late-stage) (2). As the population ages, a growing proportion of women are living decades after menopause. At menopause, about 80% of women have vasomotor symptoms (VMS), such as hot flushes and night sweats, and about 20% find them bothersome enough to seek therapy (3).

Menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhea, for which there is no other obvious pathological or physiological cause. Menopause occurs with the final menstrual period which is known with certainty only in retrospect a year or more after the event. Perimenopause should include the time immediately prior to the menopause (when the endocrinological, biological and clinical features of approaching menopause commence) and the first year after menopause. The term premenopause is often used ambiguously, either to refer to the 1 or 2 years immediately before the menopause or to refer to the whole of the reproductive period prior to the menopause. The group recommended that the term be used consistently in the latter sense to encompass the entire reproductive period up to the final menstrual period. Post-menopause is defined as dating from the final menstrual period, regardless of whether the menopause was induced or spontaneous (4).

Methods for determining when perimenopause begins (5), and a distinct set of STRAW criteria was developed (2). A variety of menstruation disturbances characterize the menopausal transition. The VMS is a common occurrence, sometimes accompanied by psychosomatic symptoms such as mood swings, anxiety, stress, and genitourinary syndrome of menopause. This includes genital symptoms such as dryness, burning, and irritation, as well as sexual symptoms such as lack of lubrication, discomfort or pain, poor function, and urinary symptoms such as urgency, dysuria, and recurrent urinary tract infections (6). All these symptoms have a significantly negative impact on the quality of life of many women (7). The menopausal transition can be a difficult time in a woman's life when it comes to healthy aging. These distressing symptoms do not affect all middle-aged women. During the menopausal transition, a third of women do not report any problems. Another third has mild to moderate symptoms, and the remaining third has moderate to severe symptoms that necessitate therapy (8).

This systematic review and meta-analysis aimed to determine the prevalence of psychosomatic and genitourinary syndrome among menopausal women. It helps to understand the symptoms better and serves as a basis for more appropriate countermeasures to this natural phenomenon. This updated review could be used in primary preventative care to help patients control and prevent diseases that harm their quality of life and mental health.

MATERIALS AND METHODS

A systematic review and meta-analysis were conducted to assess the prevalence of psychosomatic and genitourinary syndrome among menopausal women. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (9) and registered in the PROSPERO (CRD42021235958).

Search Strategy and Eligibility Criteria

We (N.A.N.M.A., N.H.N.H.) performed a systematic search in MEDLINE (PubMed), CINAHL (EBSCOhost), and ScienceDirect using the search terms "psycholog*," "mental," "anxiety," "depression," "stress," and "menopaus*." These terms were adaptable to the different electronic databases. To determine their eligibility for inclusion in this study, all studies published from the beginning of the databases until March 2021 were retrieved. The search was limited to full-text articles written in English. The reference lists of the listed citations were cross-checked to locate other potentially eligible research.

The inclusion criteria were studies that reported the prevalence of psychosomatic and genitourinary syndrome among menopausal women. In this review, the definitions of premenopausal, perimenopausal and post-menopausal were as defined by the researchers in their studies. Studies with cross-sectional, case-control, and cohort designs published in English and conducted in the community or at a health institution level were included. Case series/reports, conference papers and proceedings, articles available only in abstract form, letters of communication, editorial reviews, systemic reviews, commentaries, and qualitative studies were excluded.

Study Selection and Quality Assessment

All the records identified using our search strategy were exported to EndNote X8 software (Clarivate Analytics, Philadelphia, PA). Duplicate articles were removed. To determine their appropriateness, the entire texts of the relevant research were obtained and thoroughly examined. A consensus discussion was held between the two reviewers (N.A.N.M.A., N.H.N.H.) in the event of a conflict, and a third reviewer (M.N.N.) was consulted. The search method is presented in the PRISMA flowchart, which shows the studies that were included and excluded with reasons for their exclusion (**Figure 1**).

To examine the data quality, a critical assessment was carried out using the Joanna Briggs Institute Critical Appraisal Checklist for cross-sectional, case-control, and cohort studies (10). Two reviewers (N.A.N.M.A., N.H.N.H.) performed independent bias evaluations. When more than 70% of the answers were "yes," the risk of bias was considered low, moderate when 50–69% of the answers were "yes," and high when up to 49% of the answers were "yes." This review omitted studies that had a moderate or high risk of bias.

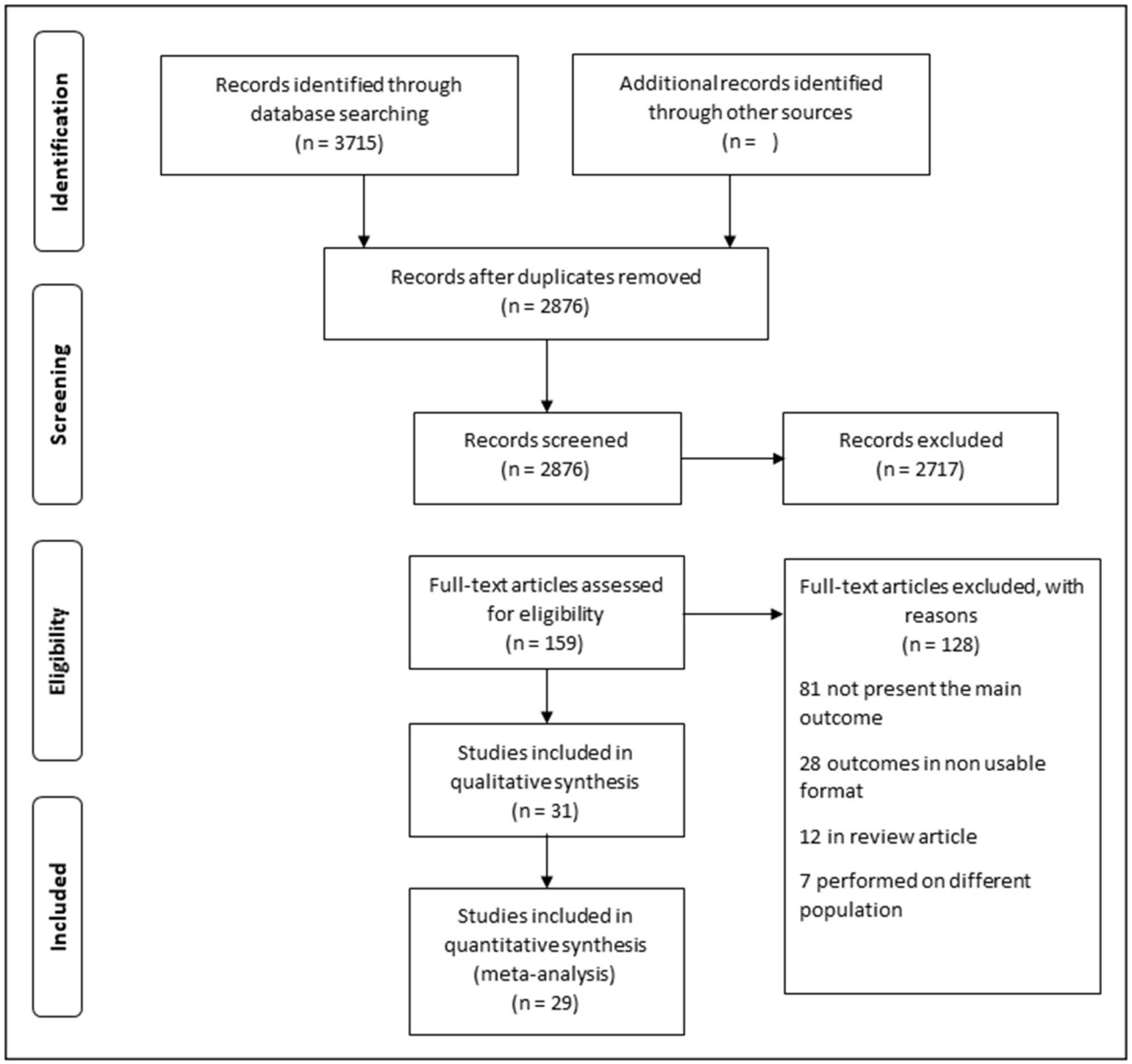

FIGURE 1 | Flowchart showing the studies on psychosomatic and genitourinary syndrome among menopausal women.

Data Extraction Process and Statistical Analysis

Two reviewers (N.A.N.M.A., N.H.N.H.) independently extracted the data using Microsoft Excel (Microsoft Corporation, Redmond, WA). The process included the first author, publication year, study design and setting, study location, study population, sample size, psychological impact, menopausal definition, and data in calculating the effect estimates for psychosomatic and genitourinary symptoms. In the event that disagreement occurred, it was dissolved by discussion between the two review authors or by the third author (M.N.N.).

The results were presented as odds ratios (OR) with 95% confidence intervals (CI). The analysis was performed using Review Manager software version 5.4 (Nordic Cochrane Centre, Copenhagen, Denmark). A random-effects model was employed to pool the data. The I^2 statistic was used to assess heterogeneity using the following guidelines: 0–40% may not be significant, 30–60% may represent moderate heterogeneity, 50–90% may represent substantial heterogeneity, and 75–100% may indicate significant heterogeneity (11). A subgroup analysis was performed on the basis of the study location (developed and developing countries) and comorbidities (presence or absence thereof) if an adequate number of studies were available.

TABLE 1 | Summary of the research articles included in the systematic review and meta-analysis on menopause ($n = 29$).

No	References	Country	Study design	Sample size (*n*)	Perimenopause (*n*)	Quality assessment (%)
1	Ahsan et al. (27)	India	Cross- sectional	187	92	87.5
2	Alam et al. (28)	Bangladesh	Cross- sectional	326	79	100
3	AlJoharah et al. (29)	Saudi Arabia	Cross-sectional	490	75	100
4	Arakane et al. (18)	Spain	Cross- sectional	340	72	100
5	Avis et al. (30)	United State	Cross-sectional	881	539	87.5
6	Chedraui et al. (13)	Ecuador	Cross-sectional	300	144	87.5
7	Chedraui et al. (20)	Ecuador	Cross-sectional	404	127	100
8	El Shafie et al. (31)	Oman	Cross-sectional	472	73	100
9	Engida et al. (32)	Africa	Cross-sectional	226	151	100
10	Moilanen et al. (17)	Finland	Cross-sectional	1,427	184	100
11	Becker et al. (33)	Israel	Cross-sectional	189	40	100
12	Kuninori et al. (34)	Japan	Cross-sectional	2,886	211	100
13	Chernicenko et al. (35)	Russia	Cross-sectional	416	416	100
14	Binfa et al. (36)	Chile	Cross-sectional	300	46	100
15	Coronado et al. (19)	Spain	Cross-sectional	308	69	87.5
16	Gozuyesil et al. (22)	Turkey	Cross-sectional	317	21	100
17	Ornat et al. (16)	Spain	Cross-sectional	260	61	87.5
18	Cuadros et al. (15)	Spain	Cross-sectional	235	6	100
19	da Silva et al. (37)	Brazil	Cross-sectional	1,415	143	100
20	Raczkiewicz et al. (38)	Poland	Cross-sectional	300	143	100
21	Shin et al. (24)	Korea	Cross-sectional	2,400	402	100
22	Sun et al. (26)	China	Cross-sectional	2,046	141	100
23	Fabbrini et al. (39)	Italy	Cross-sectional	334	42	87.5
24	Koirala et al. (40)	Nepal	Cross-sectional	240	86	87.5
25	Ryu et al. (23)	Korea	Cross-sectional	2,481		87.5
26	Chim et al. (14)	Singapore	Cross-sectional	495	124	87.5
27	Biri et al. (21)	Turkey	Cross-sectional	1,049		87.5
28	Abdelrahman et al. (12)	Jordan	Cross-sectional	193	35	100
29	Luo et al. (25)	China	Cohort	458	78	72.7

If publication bias was suspected, funnel plots and Egger's test were performed, with a *p*-value of <0.05 indicating statistical significance.

RESULTS

Study Characteristics

Through the electronic search, a total of 3,715 articles were identified, and 2,876 articles were found to be eligible after duplicate records were removed. A further 2,717 articles were excluded based on their titles or abstracts. The full texts of 159 articles were searched. Subsequently, 128 articles were excluded: 40 did not present the main outcomes, 41 had no outcomes of interest, 28 studies reported the outcomes in an unusable format, 12 were review articles, and seven were performed among different populations. Thirty-one studies underwent quality assessments, of which two had a moderate or high risk of bias and were excluded. The remaining 29 articles had a low risk of bias. Of these, 28 were cross-sectional studies, and one was a cohort. A quantitative assessment was then performed (**Figure 1**).

The women in the included studies were generally recruited from the general population or those who attended health clinics or gynecology clinics before starting treatment of menopausal complaints. They were not on treatment for menopausal symptoms except for a few studies that had <10% of the samples on hormone replacement therapy (12–16). One study reported that in all menopausal groups, women who used HRT did not differ from non-users in having at least one bothersome symptom (17).

Different countries were included in this review. Four studies were conducted in Spain (15, 16, 18, 19), two each in Ecuador (13, 20), Turkey (21, 22), Korea (23, 24), and China (25, 26), and one each in India (27), Bangladesh (28), Saudi Arabia (29), the United States (30), Oman (31), Africa (32), Finland (17), Israel (33), Japan (34), Russia (35), Chile (36), Brazil (37), Poland (38), Italy (39), Nepal (40), Singapore (14), and Jordan (12). The smallest sample size was 187 (27) and the largest 2,886 (34). Overall, this study included 21,375 women (**Table 1**).

Prevalence of Premenopausal, Perimenopausal, and Post-menopausal Women

Twenty-two studies were included in the estimation of the prevalence of premenopausal women. A wide range was

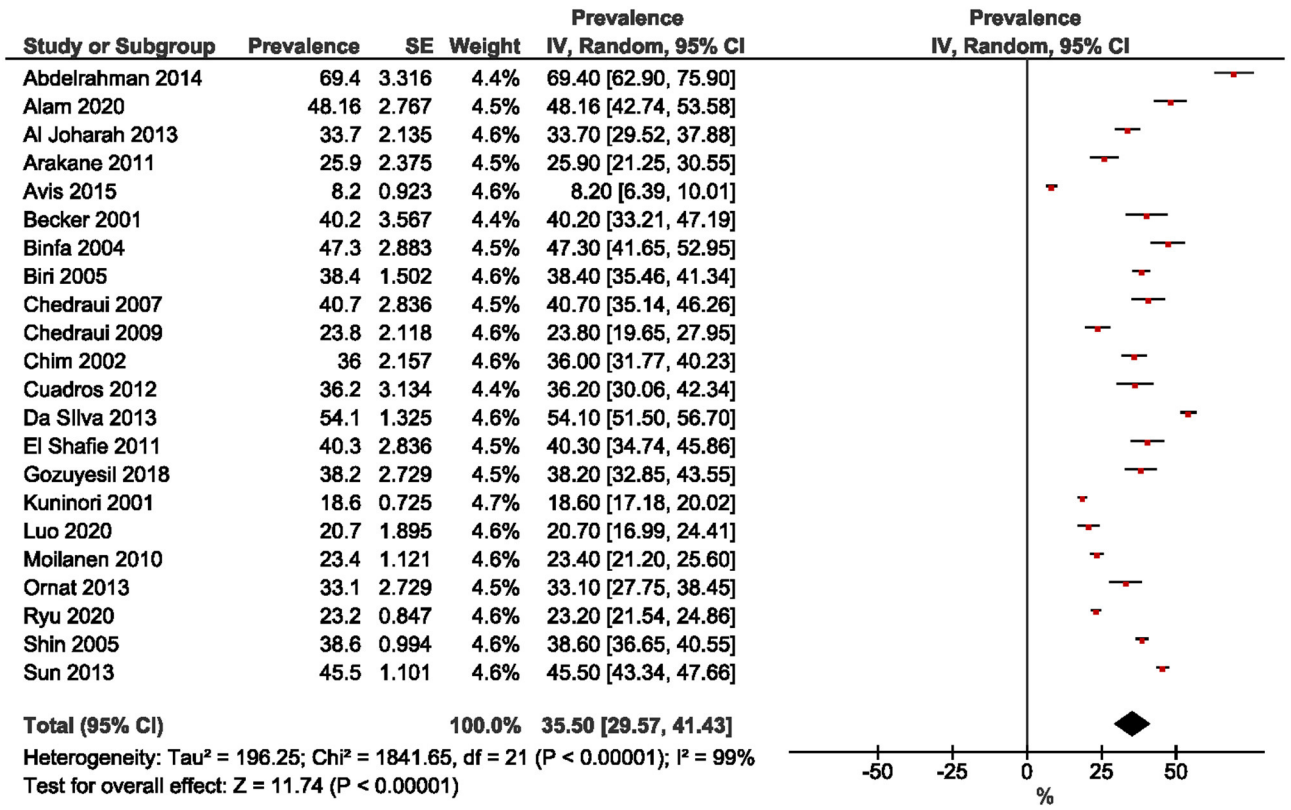

FIGURE 2 | Forest plot of the prevalence of premenopausal women.

observed, from 8.2% (30) to 69.4% (12). The overall pooled prevalence of premenopausal women was 35.5% (95% CI: 29.57, 41.43; **Figure 2**). The prevalence of perimenopausal women was estimated from 26 studies and ranged from 2.55% (15) to 66.81% (32). The pooled prevalence was 24.18% (95% CI: 19.46, 28.90; **Figure 3**). The prevalence of post-menopausal women was derived from 28 studies and ranged from 11.3% (13) to 76.80% (23). The pooled prevalence was 45.49% (95% CI: 38.26, 52.72; **Figure 4**). Egger's test showed significant publication bias for premenopausal ($P = 0.026$), perimenopausal ($P < 0.001$), and postmenopausal ($P = 0.014$) women.

Prevalence of Symptoms Among Menopausal Women

The Menopause Rating Scale was used to determine the prevalence of menopausal symptoms, which comprises 11 items divided into three subscales: (a) somatic symptoms: hot flashes, cardiac symptoms, sleep disturbances, and joint and muscle discomfort; (b) psychological symptoms: depressive mood, irritability, anxiety, and physical and mental exhaustion; and (c) genitourinary syndrome: sexual problems, bladder problems, and vaginal dryness.

Table 2 shows the percentage of women who experienced symptoms according to the menopausal stage. Somatic symptoms in post-menopausal women were higher (52.6%) compared to the premenopausal and perimenopausal stages (34.6 and 39.5%, respectively). The prevalence of psychological symptoms in premenopausal women was low (28.4%) but nearly the same among post-menopausal (49.4%) and perimenopausal (42.1%) women. The prevalence of genitourinary syndrome was different in all three groups: the highest prevalence was among post-menopausal women (55.1%), followed by perimenopausal (31.9%) and premenopausal (19.2%) women.

In terms of somatic symptoms, post-menopausal women had the highest prevalence (52.6%) of hot flashes, which were present in 34.6% of premenopausal and 39.5% of perimenopausal women. The prevalence of cardiac symptoms and sleep disturbances was <50% across all three menopausal phases. Meanwhile, for joint and muscle discomfort, post-menopausal women had the highest prevalence (69.9%).

Among the psychological symptoms, perimenopausal women had the highest prevalence of depressive mood (51.9%) and anxiety (54.6%), followed by post-menopausal and then premenopausal women. The prevalence of irritability and physical and mental exhaustion was highest among post-menopausal women at 51.7 and 52.2%, respectively. Post-menopausal women had the highest prevalence of genitourinary syndrome: 56.1% had sexual

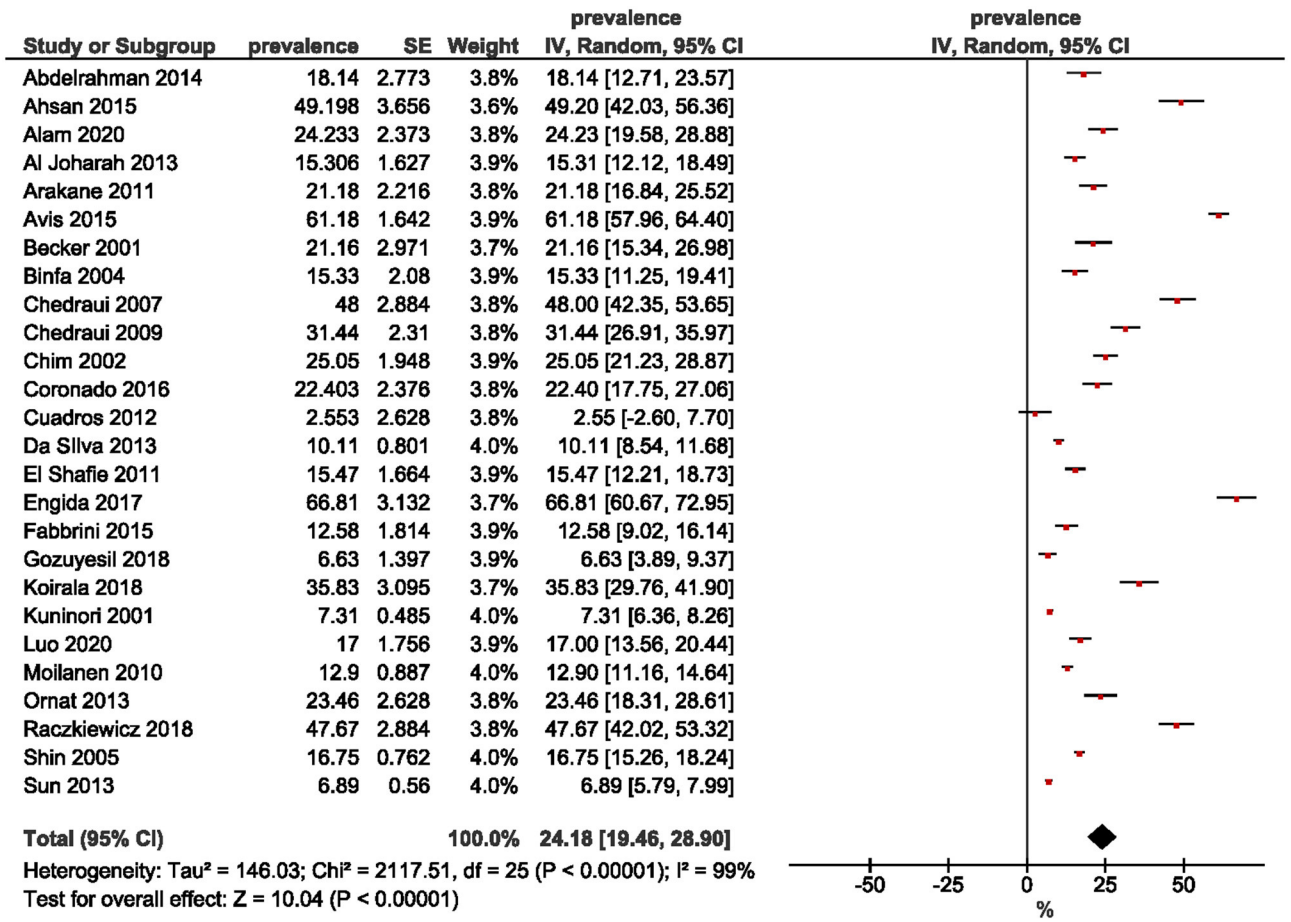

FIGURE 3 | Forest plot of the prevalence of perimenopausal women.

problems, 62.1% had bladder problems, and 39.9% had vaginal dryness.

Comparison of Symptoms Between Premenopausal and Perimenopausal Women

Symptoms between premenopausal and perimenopausal women were compared using the Menopause Rating Scale. For somatic symptoms, there were significant differences in the occurrence of hot flashes (OR: 4.16; 95% CI: 2.15, 8.02), cardiac symptoms (OR: 1.69; 95% CI: 1.04, 2.76), and sleep disturbances (OR: 1.51; 95% CI: 1.13, 2.01) between the groups, but no difference for joint and muscle discomfort (OR: 1.47; 95% CI: 0.04, 58.31). There were no significant differences in psychological symptoms aside from physical and mental exhaustion, where the prevalence was higher among perimenopausal than premenopausal women (OR: 2.19; 95% CI: 1.33, 3.58). For genitourinary syndrome, a significant difference was only apparent for sexual problems (OR: 9.62; 95% CI: 5.87, 15.76).

Comparison of Symptoms Between Premenopausal and Post-menopausal Women

A comparison of somatic symptoms between premenopausal and post-menopausal women showed a significant difference for all four symptoms. The odds of experiencing hot flashes were 4.72 (95% CI: 1.99, 11.21) times higher among post-menopausal than premenopausal women. The findings were similar for cardiac symptoms (OR: 4.66; 95% CI: 1.28, 16.92), sleep disturbances (OR: 2.24; 95% CI: 1.84, 2.73), and joint and muscle discomfort (OR: 2.08; 95% CI: 1.68, 2.57). In terms of psychological symptoms, anxiety was the only symptom showing no significant difference between the women (OR: 1.18; 95% CI: 0.72, 1.92). There was a significant difference for the rest of the symptoms; namely, depression (OR: 1.39; 95% CI: 1.09, 1.76), irritability (OR: 2.18; 95% CI: 1.12, 4.23), and physical and mental exhaustion (OR: 4.07; 95% CI: 1.45, 11.44), while for the genitourinary syndrome, there was a significant difference for sexual (OR: 9.01; 95% CI: 4.68, 17.36) and bladder problems (OR: 2.72; 95% CI: 1.75, 4.23).

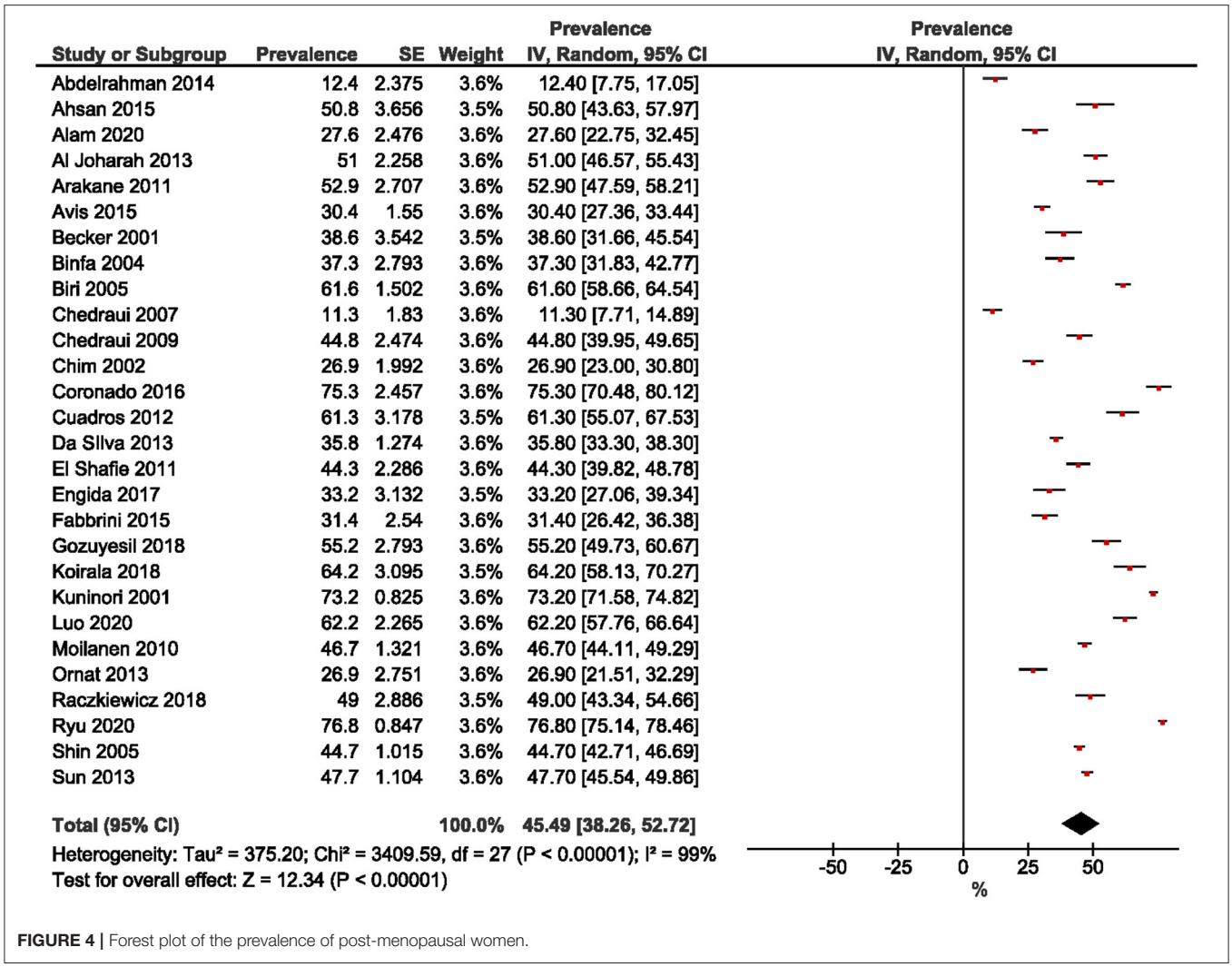

FIGURE 4 | Forest plot of the prevalence of post-menopausal women.

Comparison of Symptoms Between Perimenopausal and Post-menopausal Women

In the comparison of symptoms between perimenopausal and post-menopausal women, sleep disturbances were the only somatic symptom showing a significant difference (OR: 0.7; 95% CI: 0.53, 0.92) in favor of perimenopausal women. Among the psychological symptoms, physical and mental exhaustion was the only symptom for which there was a significant difference (OR: 0.31; 95% CI: 0.12, 0.83). Lastly, in terms of the genitourinary syndrome, there was only a significant difference for bladder problems (OR: 0.23; 95% CI: 0.09, 0.62).

DISCUSSION

This study aimed to determine the pooled prevalence of psychosomatic and genitourinary syndrome among menopausal women. In this meta-analysis, the pooled prevalence of premenopausal, perimenopausal, and post-menopausal women was 35.5, 24.18, and 45.49%, respectively. The wide range of prevalence for each of the three menopausal stages was due to the different study settings, where 21 (12, 13, 15, 16, 18–24, 27, 29–31, 36–40) studies were conducted in medical centers, and eight (14, 17, 25, 28, 32–35) were in the community. Methodological techniques such as sampling methods and tools, together with study implementation may also account for differences in estimated prevalence among studies.

In subscale of somatic symptoms, the prevalence of hot flashes is 24–93% among post-menopausal women, with the symptoms varying from mild to severe in the general population (41). The first 2 years after menopause are when hot flashes are most common, but they can last for years: 64% of women have reported symptoms lasting for 5 years, 26% for 10 years, and 10% for more than 10 years (42). Comparison between perimenopausal and post-menopausal women had nearly the same prevalence (52.9 and 59.7%, respectively). Notably, the odds of having hot flashes during perimenopause and post-menopause increased about four times compared to during premenopause. Menopausal symptoms emerge early in the premenopausal stage, even before

TABLE 2 | The prevalence of symptoms among menopausal women according to menopausal stage.

Symptom	Prevalence (%)		
	Premenopausal	**Perimenopausal**	**Post-menopausal**
(a) Somatic symptom	**34.6**	**39.5**	**52.6**
Hot flashes	22.2 (13, 17, 31)	52.9 (13,17,27,31,32)	59.7 (13, 17,27,31, 2)
Cardiac symptom	11.0 (13,17,31)	26.4 (13,17 27,31,32)	41.8 (13,17,27,31, 32)
Sleep disturbance	24.9 (13,17,18,24,26,31)	36.4 (13,17,24,26,27,29,31,32,39)	45.1 (13,17,18,24,26,27,31,38)
Joint and muscle discomfort	53.8 (13,21,31)	46.4 (13,31,32)	69.9 (13,21,31,32)
(b) Psychological symptom	**28.4**	**42.1**	**49.4**
Depressive mood	32.4 (13,17,21,31)	51.9 (13,17,27,31,32)	43.7 (13,17,27,31,32)
Anxiety	35.8 (13,21,31)	54.6 (13,27,31,32)	52.0 (13,21,27,31,32)
Irritability	23.6 (13,17,21,31)	27 (13,17,31,32)	51.7 (13,17,31,32)
Physical and mental exhaustion	21.5 (13,17,31)	31.9 (13,17,31,32)	52.2 (13,17,31,32)
(c) Genitourinary syndrome of menopuse	**19.2**	**31.9**	**55.1**
Sexual problem	22.4 (13,31)	45 (13,32,32)	56.1 (13,31,32)
Bladder problem	33.6 (13,31)	31.9 (13,27,31,32)	62.1 (13,27,31,32)
Vaginal dryness	3.9 (13,31)	31.9 (13,31,32)	39.9 (31,32)

monthly irregularities appear (43). Menopausal symptoms were seen in young premenopausal women (aged 40–44 years) with normal menstrual cycles, but their frequency increased with age and menopausal phase (43). The symptoms lasted for years and continued until five or more years post menopause with the same frequency and intensity as during the menopausal transition (44, 45).

In this study, post-menopausal women had the highest prevalence of cardiac symptoms at 52.6%, reflecting their risk of having cardiovascular disease. A meta-analysis on the development of cardiovascular disease among menopausal women reported that vasomotor and other menopausal symptoms were associated with an increased risk of chronic heart disease, stroke, and cardiovascular disease (46). Meanwhile, the prevalence of sleep disturbances and joint and muscle discomfort among premenopausal women was 24.9 and 53.8%, respectively, which was similar to the results of a systematic review of middle-aged Asian women, where the prevalence of sleep disturbances was 6.1–54% and joint and muscle discomfort 10.3–82.1% (47).

In the sleep disturbances subgroup, all the findings were significant, with post-menopausal women at higher risk of sleep disturbances than premenopausal (OR: 2.24) and perimenopausal (OR: 0.70) women. Similar findings were published in a meta-analysis in 2014, where the odds for post-menopausal women were 1.67 times higher than for premenopausal women and 1.09 times higher than for perimenopausal women (48). This significant association is also supported by other reviews (49, 50). Increased sleep disturbances during the menopausal transition are likely due to hot flashes occurring during the night because women with hot flashes may also experience nocturnal awakening unrelated to VMS (49). Around 60–80% of women experience hot flashes during the menopausal transition (51). They persist for 4–5 years (52) and commonly lead to sleep disturbances among perimenopausal and post-menopausal women.

Menopause can be psychologically distressing for women. Subscale of psychological symptoms showed that the occurrence of clinical depression in this study did not increase significantly among premenopausal and post-menopausal women, with perimenopausal women as the reference group. However, depression was 1.39 times more likely for post-menopausal than premenopausal women. A meta-analysis found similar results: post-menopausal women were 1.5 times more likely to experience depression than premenopausal women (53). The study also reported that post-menopausal women were 4.3 times more predisposed to major depression than premenopausal women (53). Depressive symptoms are more common during the menopausal transition for a variety of reasons, with earlier depression being one of them (54).

In our study, perimenopausal women had the highest prevalence of anxiety, which is consistent with the theory that anxiety levels rise throughout menopause and diminish following menopause (55, 56). We found that irritability was highest among post-menopausal women, which is not consistent with other studies (57–60). Women in the early stages of menopause show significantly higher levels of irritability than premenopausal and post-menopausal women. Moreover, we found a higher risk of exhaustion among post-menopausal women than the other groups: perimenopausal women had a 1.78 times higher risk of developing psychological symptoms than premenopausal women and a 1.83 higher risk than premenopausal women.

Concerning genitourinary syndrome, the prevalence of sexual problems and vaginal dryness in post-menopausal women was 56.1 and 39.9%, respectively. This is similar to a large cohort study (61) among a Western population, where the estimated prevalence of vulvovaginal symptoms was found to be 45–63%. A study in Korea (62) found that 49% of post-menopausal women experienced the same symptoms. A study in Turkey revealed that low sexual function was higher among post-menopausal than premenopausal women (63). Reports have shown that 40% of women who experience vulvovaginal symptoms have sexual

dysfunction, 24% lack sexual desire, 34% have arousal difficulties, and 19% experience difficulties with orgasm (64).

STRENGTHS AND LIMITATIONS

This review demonstrated the prevalence for each menopausal phase and the associated symptoms across different countries. By expressing the symptoms quantitatively, they could be compared, thus providing a comprehensive overview of the various studies' results. In general, a meta-analysis of prevalence study can provide useful information about disease burden, such as finding discrepancies between populations and regions (65). However, this study was not without limitations. Diverse instruments were used to determine the symptoms during the menopausal transition, which reduced the comparability of the results. This review only included English-language publications; however, there is no evidence of a systematic bias in the use of language restrictions in systematic review-based meta-analyses in conventional medicine (66). We attempted to produce convincing evidence by including high quality studies. Two moderate and low quality studies were excluded from the review. However, the exclusion itself may possibly introduce potential biases in the review process.

CONCLUSIONS

This review demonstrated that post-menopausal women are at a higher risk of menopausal symptoms than premenopausal and perimenopausal women. Additionally, post-menopausal women have a significantly higher risk of experiencing genitourinary syndrome than other groups of symptoms compared to premenopausal and perimenopausal women. Healthcare practitioners must regularly evaluate the symptoms of postmenopausal women in order to offer them a higher quality of life. Future research should focus on various phases of menopausal symptoms in order to acquire a comprehensive picture of menopause.

SEARCH STRATEGY

1. psychology
2. mental
3. anxiety
4. depression
5. stress
6. #1 OR #2 OR #3 OR #4 OR #5
7. menopause
8. #6 AND #7

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

NHNH, MNN, and ISB: conceptualization and methodology. NHNH and MNN: validation, resources, and visualization. NHNH, MNN, ISB, and NANMA: formal analysis, investigation, and writing—review and editing. NHNH, MNN, and NANMA: data curation. NANMA: writing—original draft preparation. NHNH: supervision. MNN: project administration. All authors have read and agreed to the published version of the manuscript.

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REFERENCES

1. Dratva J, Real FG, Schindler C, Ackermann-Liebrich U, Gerbase MW, Probst-Hensch NM, et al. Is age at menopause increasing across Europe? Results on age at menopause and determinants from two population-based studies. *Menopause.* (2009) 16:2:385–94. doi: 10.1097/gme.0b013e31818aefef
2. Soules MR, Sherman S, Parrott E, Rebar R, Santoro N, Utian W, et al. Executive summary: stages of reproductive aging workshop (STRAW). *Climacteric.* (2001) 4:4:267–72. doi: 10.1080/cmt.4.4.267.272
3. Hunter M, Rendall M. Bio-psycho-socio-cultural perspectives on menopause. *Best Pract Res Clin Obstet Gynaecol.* (2007) 21:2:261–74. doi: 10.1016/j.bpobgyn.2006.11.001
4. WHO. *Scientific Group on Research on the Menopause in the 1990s*. World Health Organization Technical Report Series 866. Geneva: World Health Organization (1994).
5. Brambilla DJ, Mckinlay SM, Johannes CB. Defining the perimenopause for application in epidemiologic investigations. *Am J Epidemiol.* (1994) 140:12:1091–5. doi: 10.1093/oxfordjournals.aje.a117209
6. Portman DJ, Gass ML. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. *Maturitas.* (2014) 79:3:349–54. doi: 10.1016/j.maturitas.2014.07.013
7. Areti A, Michalis M, Aikaterini L, George K, Rallou L, Konstantinos P. Psychosomatic and vasomotor symptom changes during transition to menopause [article]. *Menopause Rev*. (2019) 18:2:110–5. doi: 10.5114/pm.2019.86835
8. Alder J, Urech C. *Psychotherapie in der Frauenheilkunde*. Vol. 56. Gottingen: Hogrefe Verlag (2014).
9. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med.* (2009) 151:4:264–9, W64. doi: 10.7326/0003-4819-151-4-200908180-00135
10. Aromataris E, Munn Z. *JBI Manual for Evidence Synthesis*. Adelaide: The Joanna Briggs Institute (2020). Chapter 5 p. Available online at: https://synthesismanual.jbi.global (accessed 03 March 2021).
11. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. *Cochrane Handbook for Systematic Reviews of Interventions Version 6.1 (Updated September 2020)*. 2n ed. Cochrane (2020). Available online at: www.training.cochrane.org/handbook (accessed 30 March 2021).
12. Abdelrahman R, Abushaikha L, al-Motlaq M. Predictors of psychological well-being and stress among Jordanian menopausal women. *Qual Life Res.* (2014) 23:167. doi: 10.1007/s11136-013-0464-z
13. Chedraui P, Aguirre W, Hidalgo L, Fayad L. Assessing menopausal symptoms among healthy middle aged women with the Menopause

Rating Scale. *Maturitas.* (2007) 57: 271–8. doi: 10.1016/j.maturitas.2007.01.009
14. Chim H, Tan BHI, Ang CC, Chew EMD, Chong YS, Saw SM. The prevalence of menopausal symptoms in a community in Singapore. *Maturitas.* (2002) 41:275–82. doi: 10.1016/S0378-5122(01)00299-7
15. Cuadros JL, Fernández-Alonso AM, Cuadros-Celorrio AM, Fernández-Luzón N, Guadix-Peinado MJ, del Cid-Martín N, et al. Perceived stress, insomnia and related factors in women around the menopause. *Maturitas.* (2012) 72:367–72. doi: 10.1016/j.maturitas.2012.05.012
16. Ornat L, Martínez-Dearth R, Muñoz A, Franco P, Alonso B, Tajada M, et al. Sexual function, satisfaction with life and menopausal symptoms in middle-aged women. *Maturitas.* (2013) 75:261–9. doi: 10.1016/j.maturitas.2013.04.007
17. Moilanen J, Aalto AM, Hemminki E, Aro AR, Raitanen J, Luoto R. Prevalence of menopause symptoms and their association with lifestyle among Finnish middle-aged women. *Maturitas.* (2010) 67:368–74. doi: 10.1016/j.maturitas.2010.08.007
18. Arakane M, Castillo C, Rosero MF, Peñafiel R, Pérez-López FR, Chedraui P. Factors relating to insomnia during the menopausal transition as evaluated by the Insomnia Severity Index. *Maturitas.* (2011) 69:157–61. doi: 10.1016/j.maturitas.2011.02.015
19. Coronado PJ, Sánchez-Borrego R, Ruiz MA, Baquedano L, Sánchez S, Argudo C, et al. Psychometric attributes of the cervantes short-form questionnaire for measuring health-related quality of life in menopausal women. *Maturitas.* (2016) 84:55–62. doi: 10.1016/j.maturitas.2015.10.013
20. Chedraui P, Pérez-López FR, Morales B, Hidalgo L. Depressive symptoms in climacteric women are related to menopausal symptom intensity and partner factors. *Climacteric.* (2009) 12:395–403. doi: 10.1080/13697130902718150
21. Biri A, Bakar C, Maral I, Karabacak O, Bumin MA. Women with and without menopause over age of 40 in Turkey: consequences and treatment options. *Maturitas.* (2005) 50:167–76. doi: 10.1016/j.maturitas.2004.05.013
22. Gozuyesil E, Gokyildiz Surucu S, Alan S. Sexual function and quality-of-life-related problems during the menopausal period. *J Health Psychol.* (2018) 23:1769–80. doi: 10.1177/1359105317742194
23. Ryu KJ, Park H, Kim YJ, Yi KW, Shin JH, Hur JY, et al. Comparison of various menopausal symptoms and risk factor analysis in Korean women according to stage of menopause. *Maturitas.* (2020) 140:41–8. doi: 10.1016/j.maturitas.2020.05.023
24. Shin C, Lee S, Lee T, Shin K, Yi H, Kimm K, et al. Prevalence of insomnia and its relationship to menopausal status in middle-aged Korean women. *Psychiatry Clin Neurosci.* (2005) 59:395–02. doi: 10.1111/j.1440-1819.2005.01391.x
25. Luo M, Li J, Tang R, Li HJ, Liu B, Peng Y, et al. Insomnia symptoms in relation to menopause among middle-aged Chinese women: findings from a longitudinal cohort study. *Maturitas.* (2020) 141:1–8. doi: 10.1016/j.maturitas.2020.06.010
26. Sun D, Shao H, Li C, Tao M. Sleep disturbance and correlates in menopausal women in Shanghai. *J Psychosom Res.* (2014) 76:237–41. doi: 10.1016/j.jpsychores.2013.12.002
27. Ahsan M, Mallick AK, Singh R, Prasad RR. Assessment of menopausal symptoms during perimenopause and postmenopause in tertiary Care hospital [article in journal/newspaper]. *J Basic Clin Reprod Sci.* (2015) 4:14–9. doi: 10.4103/2278-960X.153516
28. Alam MM, Ahmed S, Dipti RK, Siddiquee R-EJ, Hawlader MDH. The prevalence and associated factors of depression during pre-, peri-, and post-menopausal period among the middle-aged women of Dhaka city. *Asian J Psychiatr.* (2020) 54:102312. doi: 10.1016/j.ajp.2020.102312
29. AlJoharah MA, Salwa AT, Fawzia Ahmed H. Assessment of symptoms of menopause and their severity among Saudi women in Riyadh. *Ann Saudi Med.* (2013) 1:63–7.
30. Avis NE, Crawford SL, Greendale G, Bromberger JT, Everson-Rose SA, Gold EB, et al. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med.* (2015) 175:531–9. doi: 10.1001/jamainternmed.2014.8063
31. El Shafie K, Al Farsi Y, Al Zadjali N, Al Adawi S, Al Busaidi Z, Al Shafaee M. Menopausal symptoms among healthy, middle-aged Omani women as assessed with the Menopause Rating Scale. *Menopause.* (2011) 18:1113–9. doi: 10.1097/gme.0b013e31821b82ee
32. Engida Y, Natnael E, Stephanie L, Berhanu D. Prevalence and severity of menopause symptoms among perimenopausal and postmenopausal women aged 30-49 years in Gulele sub-city of Addis Ababa, Ethiopia [article]. *BMC Womens Health.* (2017) 17:1–8. doi: 10.1186/s12905-017-0484-x
33. Becker D, Lomranz J, Pines A, Shmotkin D, Nitza E, Bennamitay G, et al. Psychological distress around menopause. *Psychosomatics.* (2001) 42:252–7. doi: 10.1176/appi.psy.42.3.252
34. Kuninori S, Yosuke Y, Iwao S, Masato H, Masami N, Shosui M, et al. Vasomotor and other menopausal symptoms influenced by menopausal stage and psychosocial factors in Japanese middle-aged women [text]. *J Occup Health*. (2001) 43:356–64.
35. Chernichenko I, Ryzhak G. Perimenopausal disorders: age-related, psychological, and social predictors of their emergence. *Adv Gerontol.* (2012) 2:144. doi: 10.1134/S207905701202004X
36. Binfa L, Castelo-Branco C, Blümel JE, Cancelo MaJ, Bonilla H, Muñoz I, et al. Influence of psycho-social factors on climacteric symptoms. *Maturitas.* (2004) 48:425–31. doi: 10.1016/j.maturitas.2003.11.002
37. da Silva AR, d'Andretta Tanaka AC. Factors associated with menopausal symptom severity in middle-aged Brazilian women from the Brazilian Western Amazon. *Maturitas.* (2013) 76:64–9. doi: 10.1016/j.maturitas.2013.05.015
38. Raczkiewicz D, Owoc A, Wierzbińska-Stepniak A, Bojar I. Metabolic syndrome in peri - and postmenopausal women performing intellectual work. *Ann Agric Environ Med.* (2018) 25:610–5. doi: 10.26444/aaem/74451
39. Fabbrini M, Aricò I, Tramonti F, Condurso R, Carnicelli L, De Rosa A, et al. *Sleep disorders in menopause: results from an Italian Multicentric Study*. Archives italiennes de biologie. (2015) 153:204–13.
40. Koirala S, Manandhar N. Quality of life of peri and postmenopausal women attending outpatient department of obstretics and gynecology of a tertiary care hospital. *J Nepal Health Res Counc.* (2018) 16:32–5. doi: 10.3126/jnhrc.v16i1.19360
41. Kronenberg F. Hot flashes: epidemiology and physiologya. *Ann N Y Acad Sci.* (1990) 592:52–86. doi: 10.1111/j.1749-6632.1990.tb30316.x
42. Feldman BM, Voda A, Gronseth E. The prevalence of hot flash and associated variables among perimenopausal women. *Res Nurs Health.* (1985) 8:261–8. doi: 10.1002/nur.4770080308
43. Blümel J, Chedraui P, Baron G, Belzares E, Bencosme A, Calle A, et al. Menopausal symptoms appear before the menopause and persist 5 years beyond: a detailed analysis of a multinational study. *Climacteric.* (2012) 15:542–51. doi: 10.3109/13697137.2012.658462
44. Avis NE, Stellato R, Crawford S, Johannes C, Longcope C. Is there an association between menopause status and sexual functioning? *Menopause.* (2000) 7:297–309. doi: 10.1097/00042192-200007050-00004
45. Mckinlay SM, Brambilla DJ, Posner JG. "Reprint of" the normal menopause transition. *Maturitas.* (2008) 61:1–2, 4–16. doi: 10.1016/j.maturitas.2008.09.005
46. Muka T, Oliver-Williams C, Colpani V, Kunutsor S, Chowdhury S, Chowdhury R, et al. Association of vasomotor and other menopausal symptoms with risk of cardiovascular disease: a systematic review and meta-analysis. *PLoS ONE.* (2016) 11:e0157417. doi: 10.1371/journal.pone.0157417
47. Islam MR, Gartoulla P, Bell RJ, Fradkin P, Davis SR. Prevalence of menopausal symptoms in Asian midlife women: a systematic review. *Climacteric.* (2015) 18:157–76. doi: 10.3109/13697137.2014.937689
48. Xu Q, Lang CP. Examining the relationship between subjective sleep disturbance and menopause: a systematic review and meta-analysis. *Menopause.* (2014) 21:1301–18. doi: 10.1097/GME.0000000000000240
49. Joffe H, Massler A, Sharkey KM. Evaluation and management of sleep disturbance during the menopause transition. *Semin Reprod Med.* (2010) 28:404. doi: 10.1055/s-0030-1262900
50. Guidozzi F. Sleep and sleep disorders in menopausal women. *Climacteric.* (2013) 16:214–9. doi: 10.3109/13697137.2012.753873
51. Gold EB, Sternfeld B, Kelsey JL, Brown C, Mouton C, Reame N, et al. Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40–55 years of age. *Am J Epidemiol.* (2000) 152:463–73. doi: 10.1093/aje/152.5.463
52. Politi MC, Schleinitz MD, Col NF. Revisiting the duration of vasomotor symptoms of menopause: a meta-analysis. *J Gen Intern Med.* (2008) 23:1507–13. doi: 10.1007/s11606-008-0655-4

53. Weber MT, Maki PM, McDermott MP. Cognition and mood in perimenopause: a systematic review and meta-analysis. *J Steroid Biochem Mol Biol.* (2014) 142:90–8. doi: 10.1016/j.jsbmb.2013.06.001
54. Freeman EW, Sammel MD, Boorman DW, Zhang R. Longitudinal pattern of depressive symptoms around natural menopause. *JAMA Psychiatry.* (2014) 71:36–43. doi: 10.1001/jamapsychiatry.2013.2819
55. Bromberger JT, Meyer PM, Kravitz HM, Sommer B, Cordal A, Powell L, et al. Psychologic distress and natural menopause: a multiethnic community study. *Am J Public Health.* (2001) 91:1435–42. doi: 10.2105/AJPH.91.9.1435
56. Freeman EW, Sammel MD, Lin H, Gracia CR, Kapoor S, Ferdousi T. The role of anxiety and hormonal changes in menopausal hot flashes. *Menopause.* (2005) 12:258–66. doi: 10.1097/01.GME.0000142440.49698.B7
57. Mauas V, Kopala-Sibley DC, Zuroff DC. Depressive symptoms in the transition to menopause: the roles of irritability, personality vulnerability, and self-regulation. *Arch Womens Ment Health.* (2014) 17:279–89. doi: 10.1007/s00737-014-0434-7
58. Avis NE, Brambilla D, McKinlay SM, Vass K. A longitudinal analysis of the association between menopause and depression results from the Massachusetts women's health study. *Ann Epidemiol.* (1994) 4:214–20. doi: 10.1016/1047-2797(94)90099-X
59. Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Arch Gen Psychiatry.* (2006) 63:375–82. doi: 10.1001/archpsyc.63.4.375
60. Schmidt PJ, Murphy J, Haq N, Rubinow D, Danaceau M. Stressful life events, personal losses, and perimenopause-related depression. *Arch Womens Ment Health.* (2004) 7:19–26. doi: 10.1007/s00737-003-0036-2
61. Nappi RE, Kokot-Kierepa M. Women's voices in the menopause: results from an international survey on vaginal atrophy. *Maturitas.* (2010) 67:233–8. doi: 10.1016/j.maturitas.2010.08.001
62. Chae HD, Choi SY, Cho EJ, Cho YM, Lee SR, Lee ES, et al. Awareness and experience of menopausal symptom and hormone therapy in korean postmenopausal women. *J Menopausal Med.* (2014) 20:7. doi: 10.6118/jmm.2014.20.1.7
63. Verit FF, Verit A, Billurcu N. Low sexual function and its associated risk factors in pre-and postmenopausal women without clinically significant depression. *Maturitas.* (2009) 64:38–42. doi: 10.1016/j.maturitas.2009.07.002
64. Levine KB, Williams RE, Hartmann KE. Vulvovaginal atrophy is strongly associated with female sexual dysfunction among sexually active postmenopausal women. *Menopause.* (2008) 15:661–6. doi: 10.1097/gme.0b013e31815a5168
65. Borges Migliavaca C, Stein C, Colpani V, Barker TH, Munn Z, Falavigna M, et al. How are systematic reviews of prevalence conducted? A methodological study. *BMC Med Res Methodol.* (2020) 20:96. doi: 10.1186/s12874-020-00975-3
66. Morrison A, Polisena J, Husereau D, Moulton K, Clark M, Fiander M, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. *Int J Technol Assess Health Care.* (2012) 28:138–44. doi: 10.1017/S0266462312000086

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Clinical Factors and Perinatal Outcomes Associated With Short Latency Period in Twin Pregnancies With Preterm Premature Rupture of Membranes Before 34 Weeks: A Retrospective Study

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Background: There is a lack of literature on short latency period (SLP) in twin pregnancies with preterm premature rupture of membranes (PPROM). Thus, the aim of this study was to identify the clinical factors and perinatal outcomes associated with SLP in twin pregnancies with PPROM and to establish a predictive model to identify SLP.

Methods: Twin pregnancies with PPROM between 24 0/7 and 33 6/7 weeks were included and a retrospective analysis was performed. Patients were divided into two groups based on the latency period after PPROM: Group 1 ≤24 h (defined as SLP) and Group 2 >24 h (defined as long latency period, LLP), the clinical factors and perinatal outcomes were compared between the two groups. Binary logistic regression and receiver operating characteristic curve analyses were used to identify the independent clinical factors associated with latency period after PPROM and assess the predictive accuracy for SLP.

Results: 98 and 92 pregnant women had short and long latency period, respectively. Prolonged latency significantly increased the occurrence of chorioamnionitis. Neonatal outcomes were not affected by latency duration after PPROM. Binary regression analysis revealed that higher gestational age (GA) at PPROM ($P = 0.038$), presence of uterine contractions ($P < 0.001$), Bishop score > 4 ($P = 0.030$), serum procalcitonin levels ≥0.05 ng/mL upon admission, and absence of use of tocolytic agents ($P < 0.001$) were significant independent predictors of a SLP. A predictive model developed using these predictors had an area under the curve (AUC) of 0.838, and the presence of uterine contractions alone had an AUC of = 0.711.

Conclusion: Uterine contraction was the most important prognosticator for a SLP. A latency period of >24 h was associated with chorioamnionitis, but adverse neonatal outcomes were not observed.

Keywords: twin pregnancies, preterm premature rupture of membranes, latency period, clinical factors, perinatal outcomes

INTRODUCTION

Preterm premature rupture of membranes (PPROM) occurs in 3% of all pregnancies, and approximately one-third of premature births are caused by or are related to PPROM, which is an important factor in neonatal morbidity and mortality (1–4). With the widespread use of assisted reproductive technology and ovulation induction, the rate of twin pregnancies has gradually increased. PPROM and preterm birth are more common in twin pregnancies; the incidence of PPROM in twin pregnancies is 7–10%, while it is only 2–4% for singleton pregnancies (3, 5, 6). The high incidence of PPROM in twins may mean that the mechanism is different from that in singletons, which may be related to uterine over-distension, increased intrauterine volume, cervical insufficiency, or elevated levels of sex hormones in twin pregnancies. Compared with singleton pregnancies, PPROM in twins tends to occur at an earlier gestational age (GA), and the time from membrane rupture to delivery is shorter (5, 7). However, there are no clinical practice guidelines specifically for PPROM in twin pregnancies, and management strategies only refer to singletons. The GA is the most important factor in determining neonatal outcomes after PPROM. In the absence of evidence of infection or other complications, expectant management is usually used to extend the GA as far as possible to reduce complications associated with preterm birth, and induced labor or cesarean section is performed at 34 weeks (3).

The latency period is defined as the time from rupture of membranes to delivery. There are many factors that affect the latency period after PPROM, but no risk factors have been identified, including the GA at PPROM, multiple pregnancies, oligohydramnios, cervical length, use of prophylactic antibiotics, and tocolysis (7–10). Multiple studies have shown that compared with singleton pregnancies, latency in twin pregnancies after PPROM was significantly shorter, with the median latency period being 3.6–4 days for twins and 6.2–7 days for singletons (11, 12). Twins were more likely to get delivered within 48 h (45.5% vs. 22.9%) or 72 h (11% vs. 4%) (6, 8). Twin pregnancies remained an independent risk factor for a short latency when controlling for other confounding factors (12, 13). In contrast, the results of a retrospective cohort study indicated that there was no statistical difference in the latency of twins and singletons in women presenting with PPROM (11). Additionally, a recent study has focused on identifying the clinical factors of latency period exceeding 48 h after PPROM (10), and a previous study modeled the latency period according to maternal and pregnancy characteristics, but these were mainly singleton pregnancies and only a small number of those with twins (14).

However, to date, there is a lack of information in the literature on the early recognition of short latency period (SLP) in twin pregnancies with PPROM. We have hardly found any research on infection indicators, such as serum inflammatory markers and vaginal microorganism culture that affected the latency period in twin pregnancies with PPROM.

In the present study, we aimed to identify clinical factors and perinatal outcomes of latency period within 24 h in twin pregnancies with PPROM before 34 weeks. Most previous studies were committed to exploring the clinical characteristics of singleton pregnancies, while ignoring the urgent healthcare needs of women with twin pregnancies. Identifying the significant predictors of a SLP in twin pregnancies with PPROM will provide a more appropriate clinical management and personalized treatment. Physicians could provide consultations, strengthen prenatal monitoring, and perform intrauterine transfers in time. The main purpose of this study was to identify the clinical factors associated with a SLP, to prolong the latency period, and to improve the perinatal outcomes in twin pregnancies with PPROM.

MATERIALS AND METHODS

Participant Selection

This retrospective study reviewed the medical records of twin pregnant women with PPROM between 24 0/7 and 33 6/7 weeks who were admitted to the Obstetrics Department at Chongqing Health Center for Women and Children, a single tertiary referral center in Chongqing, China, from 1 January 2017 to 31 April 2021. We excluded women with any of the following conditions: at least one intrauterine death on admission, couples who gave up the pregnancy for induced labor, and with complications of monochorionic-diamniotic twins (for example, twin-to-twin transfusion syndrome and twin anemia polycythaemia sequence). The study was approved by the Ethics Committee of Chongqing Health Center for Women and children.

Diagnostic Criteria and Definitions

PPROM Diagnostic Criteria

Rupture of membranes occurred at <37 weeks of gestation before labor. Diagnosis was based on pregnant women with a history of vaginal discharge, and on sterile speculum examination, leakage of amniotic fluid from the cervical os, or pooling of amniotic fluid in the posterior vaginal vault. If the characteristic findings were not significant, we performed an ultrasound examination to assess amniotic fluid volume, measured insulin-like growth factor binding protein-1, or conducted fern tests to assist in the diagnosis.

Determination of the GA

The GA was determined based on the first day of the woman's last menstruation and the crown-rump length measured by ultrasound in early pregnancy. GA was also estimated based on the date of embryo transfer when the pregnancy was conceived through assisted reproductive technology (ART).

Definition of Clinical Chorioamnionitis

Maternal body temperature $\geq$38°C accompanied by any of the following criteria can be diagnosed with clinical chorioamnionitis: malodorous vaginal discharge, fetal tachycardia (baseline $\geq$160 beats per minute), maternal tachycardia ($\geq$110 beats per minute), maternal peripheral blood leukocyte count $\geq 15 \times 10^9$/L, or the uterus is irritated with presence of uterine tenderness.

TABLE 1 | Comparison of clinical factors associated with short latency period.

Factors	Group 1 ($n = 98$)	Group 2 ($n = 92$)	Overall	*P*-value
Latency period (hours)	7 (5–12.5)	72.5 (46.5–147.5)	22 (7–70.5)	**<0.001**
Maternal age (year)	30.0 ± 3.2	30.5 ± 4.2	30.3 ± 3.7	0.362
At work	50 (51%)	45 (48.9%)	95 (50%)	0.772
Primipara	87 (88.8%)	80 (87%)	167 (87.9%)	0.701
History of PPROM or preterm birth	0 (0%)	1 (1.1%)	1 (0.5%)	0.484
Prepregnancy BMI (Kg/m^2)	21.4 (19.0–23.6)	21.1 (19.4–23.1)	21.3 (19.2–23.6)	0.870
GA at PPROM (weeks)	32 3/7 (31 0/7–33 3/7)	31 4/7 (29 3 /7–32 6/7)	32 1 /7 (30 0/7–33 1/7)	**0.001**
White blood cell ($*10^9/L$)	9 (7–11)	9 (8–11)	9 (7–11)	0.622
Neutrophil ratio (%)	77.5 ± 8.4	78.2 ± 6.8	77.8 ± 7.6	0.519
C-reactive protein (mg/L)	5 (2–13)	5 (1–10)	5 (2–11)	0.401
Procalcitonin ≥0.05 ng/mL	50 (57.5%)	37 (42%)	87 (49.7%)	**0.041**
Conception by IVF	72 (73.5%)	69 (75.0%)	141 (74.2%)	0.810
Dichorionic diamniotic	86 (87.8%)	78 (84.8%)	164 (86.3%)	0.551
Bishop score >4	64 (65.3%)	25 (27.2%)	89 (46.8%)	**<0.001**
Presence of contraction	69 (70.4%)	26 (28.3%)	95 (50.0%)	**<0.001**
Use tocolytic agent	14 (14.3%)	45 (48.9%)	59 (31.1%)	**<0.001**
Positive GBS	5 (10.2%)	1 (1.8%)	6 (5.7%)	0.064
Positive vaginal microbial	13 (21.7%)	21 (24.4%)	34 (23.3%)	0.699
Gestational diabetes mellitus	29 (29.6%)	22 (23.9%)	51 (26.8%)	0.377
ICP	13 (13.3%)	6 (6.5%)	(10.0%)	0.122
HDP	9 (9.2%)	5 (5.4%)	14 (7.4%)	0.323
Cervical insufficiency	5 (5.1%)	2 (2.2%)	7 (3.7%)	0.284

Data are presented as n (%) or median (Interquartile, Q1–Q3) or mean ± standard deviation.
All unknown data were not included in the analysis.
PPROM, preterm premature rupture of membranes; BMI, body mass index; GA, gestational age; IVF, in vitro fertilization; GBS, group B streptococcus; ICP, intrahepatic cholestasis of pregnancy; HDCP, hypertensive disorder of pregnancy.

Management of PPROM

All patients of expectant management received dexamethasone (four intramuscular doses of 6 mg 12 h apart) for maturation of the fetal lungs and intravenous broad-spectrum prophylaxis (ampicillin, ceftezole, or clarithromycin) for 48 h, followed by oral amoxicillin and erythromycin for 5 days to prevent infection. Magnesium sulfate was routinely administered for fetal neuroprotective effects. Nifedipine, indomethacin, atosiban, and ritodrine were used as tocolytic agents depending on the status of the pregnant woman.

The status of the mother and fetus was closely monitored until delivery. Pregnant women underwent a vaginal examination on admission to obtain the Bishop score, and secretions were taken for microbial and group B streptococcus (GBS) cultures. The patients were checked daily by obstetricians. Maternal serum inflammatory markers, specifically blood routine examination, and C-reactive protein (CRP) and procalcitonin (PCT) levels were checked every 3 days. Ultrasound scans were performed every 3–4 days to evaluate the amniotic fluid volume and the status of the fetus. A single deepest pocket ≤ 2 cm was considered oligohydramnios. Non-stress test was initiated at 32 weeks daily to assess the status of the fetus and earlier GA for high risk patients.

When clinical chorioamnionitis was diagnosed, if premature birth was inevitable, if there were indications for delivery of the mother and/or fetus, or if GA reached 34 weeks, the pregnancy was terminated by induction of labor or cesarean section depending on the patient's desire, obstetric history and fetal status.

Data Collection

We obtained maternal and fetal clinical information from patients' electronic medical records from the hospital information system. The database contains the following parameters: (1) Maternal parameters including the age, working condition, parity, history of preterm birth, and history of PPROM; (2) Information regarding current pregnancy including prepregnancy body mass index (BMI, kg/m^2), mode of conception, chorionicity, GA at PPROM, maternal inflammatory markers (serum white blood cell count, neutrophil ratio and CRP, and PCT levels) before the administration of antibiotics or steroids, Bishop score [refer to the original text for (15)], uterine contractions, vaginal microbiological culture, GBS, use of tocolytic agents, pregnancy comorbidities (gestational diabetes mellitus, intrahepatic cholestasis of pregnancy, hypertensive disorder of pregnancy, cervical insufficiency); (3) Obstetric outcomes including clinical chorioamnionitis, placental

TABLE 2 | Binary logistic regression models of short latency period.

Factors	OR (95% CI)	Comparison	*P*-value
GA at PPROM (days)	1.03 (1.00–1.05)	continuous	**0.038**
Uterine contraction	5.57 (2.26–13.75)	Present ref absent	**<0.001**
Bishop score	2.67 (1.10–6.48)	>4 ref ≤4	**0.030**
Use of tocolytic agent	6.50 (2.68–15.79)	Present ref absent	**<0.001**
Serum PCT (ng/mL)	2.03 (0.96–4.30)	≥0.05 ref <0.05	0.066

Ref, reference; OR, odds ratio; CI, confidence interval; GA, gestational age; PPROM, preterm premature rupture of membranes; PCT, procalcitonin.
OR > 1 indicates improved odds of short latency period relative to the comparison group.

abruption, cord prolapse, oligohydramnios, GA at delivery, mode of delivery, indication of termination of pregnancy, and latency period; (4) Fetal parameters including birth weight, neonatal death, admission to the neonatal intensive care unit (NICU), and major neonatal complications (respiratory distress syndrome, neonatal sepsis, intraventricular hemorrhage, necrotising enterocolitis, respiratory distress syndrome, bronchopulmonary dysplasia, and retinopathy of prematurity.

Pregnant women with PPROM were categorized into two groups based on the latency period. Patients in Group 1 had a latency period of ≤24 h, whereas those in Group 2 had a latency period of >24 h. Clinical factors and perinatal outcomes were compared between the two groups.

Statistical Analyses

Data were analyzed using SPSS version 25.0 (IBM, Armonk, NY, USA). Descriptive statistics were used to analyse the patients' clinical factors and perinatal outcomes, and the chi-squared test or Fisher's exact test was used to analyse categorical variables. After assessing normality, the statistical significance of the continuous variables was assessed using the Student's *t*-test or the Mann-Whitney U test, and was also summarized as the mean ± standard deviation or the median with interquartile range. Following univariate analysis, binary logistic regression was performed to identify the independent factors of a SLP. Odds ratios (OR) and 95 % confidence intervals (CI) were calculated. Receiver operating characteristic (ROC) curves were used to assess the predictive accuracy of the SLP with twin pregnancies complicated by PPROM. $P \leq 0.050$ was considered as statistically significant.

RESULTS

Patient Characteristics

A total of 190 women with twin pregnancies (including 164 dichorionic diamniotic twins and 26 monochorionic diamniotic twins) with PPROM between 24 0/7 weeks and 33 6/7 weeks were included in the final analysis, of which 98 (51.6%) patients were in Group 1 and 92 patients (48.4 %) in Group 2. The mean maternal age of these patients was 30.3 ± 3.7 years. The median GA at PPROM was 32 1/7 weeks (Q1:30 0/7 weeks to Q3:33 1/7 weeks), and the median latency period was 22 hours (Q1:7 to Q3:71 h).

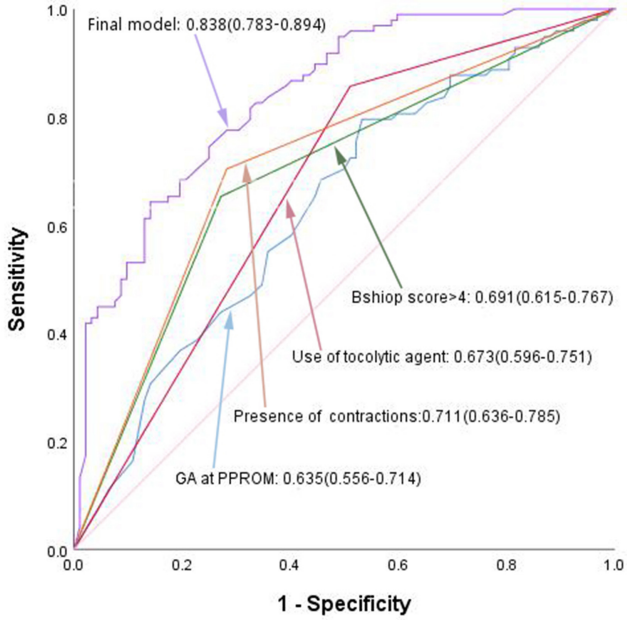

FIGURE 1 | ROC curves of the final predictive model, compared to separate independent predictor. GA, gestational age; PPROM, preterm premature rupture of membranes.

The clinical factors of short and long latency periods are described in **Table 1**. The maternal age, working condition, primipara, *in-vitro* fertilization conception, chorionicity, prepregnancy BMI, maternal inflammatory markers (except PCT), the positive rate of vaginal microbiological and GBS, and presence of pregnancy complications were similar between the two groups. Pregnant women with a SLP were more likely to have a high GA at PPROM, a Bishop score >4, serum PCT levels ≥0.05 ng/mL, uterine contractions upon admission, and not received tocolytic agents.

Binary Regression Analysis and Predictive Model of SLP

The final predictive model had five main factors, as listed in **Table 2**. In the binary logistic regression analysis to identify predictors of latency period, higher GA at PPROM ($P = 0.020$), and presence of uterine contraction ($p < 0.001$) demonstrated a significant independent association with a SLP. We also found that a Bishop score > 4 lowered the OR of the long latency period, and the use of tocolytic agents increased the OR of the SLP. Our model did not demonstrate an independent association of PCT ≥0.05 ng/mL with SLP.

The predictive accuracy of the final model was assessed using the area under the AUC curve. The final model using these independent variables had an AUC of 0.838, as shown in **Figure 1**. Among the four clinical features of independent prediction, the presence of uterine contraction predicted a short latency period with the highest accuracy (AUC = 0.711), and the

TABLE 3 | Perinatal outcomes associated with PPROM according to latency period.

Factors	Group 1 (n = 98/196)	Group 2 (n = 92/184)	Overall	*P*-value
Obstetric outcomes				
GA at delivery (weeks)	32 4/7 (31 1/7–33 3/7)	32 3/7 (29 6/7–33 3/7)	32 3/7 (30 3/7–33 /7)	0.566
Placental abruption	6 (6.1%)	4 (4.3%)	10 (5.3%)	0.748
Cord prolapse	6 (6.1%)	2 (2.2%)	8 (4.2%)	0.176
Oligohydramnios	19 (19.4%)	23 (25.0%)	42 (22.1%)	0.352
Clinical chorioamnionitis	6 (6.1%)	15 (16.3%)	21 (11.1%)	**0.025**
Cesarean section	86 (87.8%)	80 (87.0%)	166 (87.4%)	0.868
Indications for termination				**<0.001**
Preterm labor	69 (70.4%)	45 (48.9%)	114 (60.0%)	
Complications	29 (29.6%)	38 (41.3%)	67 (35.3%)	
Pregnancy lasted 34 weeks	0 (0%)	9 (9.8%)	9 (4.7%)	
Neonatal outcomes				
Birth weight (Kg)	1.80 (1.55–2.00)	1.65 (1.34–1.93)	1.74 (1.43–1.95)	**0.020**
Foetal or neonatal death	8 (4.1%)	15 (8.2%)	23 (6.1%)	0.096
Admission to NICU	54 (28.7%)	54 (32.0%)	108 (30.3%)	0.507
Neonatal sepsis	36 (19.1%)	42 (24.9%)	78 (21.8%)	0.193
Respiratory distress syndrome	64 (34.0%)	53 (31.4%)	117 (32.8%)	0.590
Necrotizing enterocolitis	14 (7.4%)	22 (13.0%)	36 (10.1%)	0.081
Intraventricular hemorrhage	15 (8.0%)	12 (7.1%)	27 (7.6%)	0.754
Retinopathy of prematurity	22 (11.7%)	20 (11.8%)	42 (11.7%)	0.969
Bronchopulmonary dysplasia	12 (6.4%)	15 (8.9%)	27 (7.6%)	0.374

The result of neonatal complications excluded dead fetus and newborns.
GA, gestational age; NICU, neonatal intensive care unit.

other three factors alone were not very strong in predicting SLP (AUC = 0.635–0.691).

Perinatal Outcomes

We examined differences in perinatal outcomes according to latency period (**Table 3**). A latency period of ≥24 h was associated with an increased risk of chorioamnionitis, but there was no significant difference in placental abruption, cord prolapse, oligohydramnios, the GA at delivery, and the mode of delivery between the two groups. The indications for termination of pregnancy in Group 1 were mostly preterm labor (70.4%), followed by maternal or fetal complications, and none of the pregnancies lasted until 34 weeks. In addition, the median birth weight was high in patients with a SLP ($p = 0.02$). Twenty-three fetuses (6.1%) experienced intrauterine demise or neonatal death in total, independent of the latency period. All statistical neonatal outcomes (except birth weight) between the two groups were not statistically significant.

DISCUSSION

Recently, substantial studies have highlighted the clinical factors associated with a LLP (defined latency period ≥48, 72 h, 7 days, or even 14 days) among singleton pregnancies with PPROM (7, 9, 10). There are also studies that focus on comparing the latency period of PPROM between twin and singleton pregnancies (5, 12), but few have individually identified these characteristics of SLP in twin pregnancies with PPROM. In this study, we identified clinical factors associated with a latency period of ≤24 h in twin pregnancies with PPROM before 34 weeks of gestation. Our results revealed that patients who were considered to have a SLP were prone to have the following characteristics: a high GA at PPROM, presence of uterine contractions, Bishop score >4, serum PCT levels ≥0.05 ng/mL, and absence of use of tocolytic agents in univariate analyses. This finding is significant because it might identify a SLP upon admission and transfer pregnant women to appropriate hospitals in time to attempt to receive novel therapeutic regimens and improve perinatal outcomes.

The standpoint that PPROM in twin pregnancies tends to have a SLP than singleton pregnancies is widely recognized (5, 12–14). A recent study has shown that the median latency period was 4 days in twins after PPROM (12), and a Chinese study indicated that half of pregnant women deliver 2 days after PPROM (13). In this study, the median latency period of twin pregnancies with PPROM was 22 h, which was shorter than that reported in other studies (5, 12, 13). The main reason is that the median GA at PPROM was 32 1/7 weeks in this study, which is negatively correlated with the latency period; however, the mean GA at PPROM was 29.1 weeks and at delivery was 29.3 weeks in other studies (5, 12). Furthermore, in a study of 49 twin pregnancies, the median GA at PROM was 31 weeks, and the median latency period was 0 days, which is similar to our observations (16). Our

results are consistent with majority of studies, which have shown an inverse correlation between the latency period and GA at PPROM (9, 13, 17). However, other studies have failed to observe any correlation between the latency period and GA (10, 18).

When controlling for other confounding factors, we identified four significant predictors of a SLP in a multivariate analysis. The predictive model (AUC, 0.838) may adequately evaluate SLP at admission to change traditional treatments that might eventually improve perinatal outcomes. In summary, there are multiple avenues to experience a SLP, but the strongest factor may be the presence of uterine contractions (alone AUC, 0.711), while early and high doses of tocolytic agents may prolong the latency period. A similar correlation was found in the study by Phupong et al., who found that prophylactic tocolysis was a major factor associated with a latency period ≥2 days after PPROM (9). Some scholars have reported that the need for tocolysis can predict a SLP (10). The reason for this difference is that the time of tocolysis was different among the studies. In the former study, it was administered before uterine contractions, and in the latter, after contractions. In our institution, tocolytic agents are used to suppress uterine contractions instead of being routinely administrated. The indication of termination of pregnancy in most patients who delivered within 24 h after PPROM was premature labor. Therefore, based on the above research results, prophylactic tocolysis may prolong the latency period.

Recent data indicated that cervical length and cervical dilation at admission were inversely associated with the latency period in twin preganncies complicated by PPROM (17, 19). However, to date, there has been almost no report on the relationship between the Bishop score and latency period. The Bishop score may currently be the best tool for assessing cervical status, and it is a good predictor of vaginal delivery (15, 20). Our data suggest that a SLP was more likely to have a Bishop score >4, and more research is needed to explore the relationship between the Bishop score and latency period in PPROM.

Intraamniotic infection has been associated with the initiation and progression of PPROM (21). High maternal serum inflammatory markers, such as leukocytes, CRP, and PCT, may be risk factors for intrauterine infection. Asadi et al. suggested that CRP had high accuracy in predicting chorioamnionitis in PPROM and found that patients diagnosed with chorioamnionitis had significantly high serum levels of CRP both on admission and before termination of pregnancy (22). A prospective study indicated that maternal serum PCT level used 0.054 ng/mL as the cut-off value for the prediction of histological chorioamnionitis had high specificity and sensitivity in PPROM (23). Few previous studies have investigated the effect of inflammatory markers on the latency period after PPROM in twin pregnancies..... In this study, we discovered that the latency period within 24 h after PPROM was more be inclined to have a high maternal serum PCT level (>0.05 g/mL) in univariate analysis; however, the correlation disappeared after controlling for other confounding factors and that no correlation was observed between other inflammatory markers and the latency period. In general, the value of maternal PCT determination in the diagnosis of latency period is unsatisfactory in twin pregnancies with PPROM (16). Further prospective and large sample research is needed to investigate the role of inflammatory markers in the latency period after PPROM.

Our study demonstrates that the occurrence of chorioamnionitis is related to prolonged latency. An inseparable relationship between PPROM and chorioamnionitis has been confirmed in numerous studies (7, 8, 24, 25). Obstetricians terminate the pregnancy when combined with clinical chorioamnionitis, thus shortening the time from rupture of membranes to delivery (24). On the contrary, pregnant women showing prolonged latency periods are at an increased risk of chorioamnionitis, as we observed (7, 8). This is due to a prolonged latency allowing microorganisms more time to enter the uterine cavity after PPROM, leading to an increase in the chance of infection (26). Therefore, it is necessary to closely monitor clinical signs and inflammatory markers and administer antibiotics appropriately after PPROM.

We found that prolonged latency was unrelated to perinatal outcomes, Unlike chorioamnionitis, neonatal sepsis was not related to the duration of latency; this finding has also been confirmed by several other studies (27–29). Two studies revealed that a prolonged latency period was associated with a decreased incidence of neonatal mortality or morbidity (13, 29). There are also research reported neonatal outcomes were not affected by latency duration after PPROM (7, 10, 28). Compared with singleton pregnancies with PPROM, twins were less likely to be complicated by chorioamnionitis or placental abruption (5, 11), but tend to have adverse neonatal outcomes (12). In addition, we observed that newborns who were delivered within 24 h after PPROM had an increased birth weight, which is different from the findings of other studies (7, 12), which may be because the GA at PPROM was high.

Indeed, some study population have been reported in our previous article (30), and the main purpose of which was to describe perinatal outcomes of twin pregnancies with PPROM. However, there is no overlap in reported data since the parameters related to latency period was not analyzed in previous paper. This study is the first to explore the clinical factors and perinatal outcomes of SLP in twin pregnancies with PPROM and has a large sample size. This is also the first study to investigate the relationship between GBS, vaginal microbiological culture, and latency period in twins, although the results were not statistically different. Our study had two limitations. First, this was a retrospective study, and potential confounding variables could not be ruled out; prospective randomized studies with adequate cases should be performed to obtain more reliable results. Second, only a small number of placentas underwent histopathological examination, and the association between the latency period and histological chorioamnionitis could not be investigated. Further prospective studies should focus on the associations revealed by this analysis.

CONCLUSION

The present study provides evidence to identify a SLP according to clinical factors. Our study showed that a high GA at PPROM, presence of uterine contractions, Bishop score>4,

and absence of use of tocolytic agents were associated with a shortened latency period in twin pregnancies with PPROM. The most important prognosticator was the presence of uterine contraction. A latency period >24 h was associated with chorioamnionitis, but adverse neonatal outcomes were not observed. Accordingly, the data presented in this study can be used by obstetricians to provide consultation and provide predict the latency period for the ease of intrauterine transfer and personalized treatment. Additionally, more studies are needed to achieve a reliable and feasible model for clinically useful calculations.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethics Committee of Chongqing Health Center for Women and Children. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SZ, LM, and LW designed the study. SZ and LM drafted the manuscript. XM and QQ conducted the statistical analysis. YY and SZ collected the data. LW and WZ revised the manuscript. All authors have read and approved the final study.

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REFERENCES

1. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet.* (2008) 371:75–84. doi: 10.1016/S0140-6736(08)60074-4
2. Sentilhes L, Sénat MV, Ancel PY, Azria E, Benoist G, Blanc J, et al. Prevention of spontaneous preterm birth: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF). *Eur J Obstet Gynecol Reprod Biol.* (2017) 210:217–24. doi: 10.1016/j.ejogrb.2016.12.035
3. Prelabor rupture of membranes: ACOG practice bulletin, Number 217. *Obstetr Gynecol.* (2020) 135:e80–97. doi: 10.1097/AOG.0000000000003700
4. Vogel JP, Chawanpaiboon S, Moller AB, Watananirun K, Bonet M, Lumbiganon P. The global epidemiology of preterm birth. *Best Pract Res Clin Obstetr Gynaecol.* (2018) 52:3–12. doi: 10.1016/j.bpobgyn.2018.04.003
5. Kibel M, Barrett J, Tward C, Pittini A, Kahn M, Melamed N. The natural history of preterm premature rupture of membranes in twin pregnancies. *J Maternal Fetal Neonatal Med.* (2017) 30:1829–35. doi: 10.1080/14767058.2016.1228052
6. Norwitz ER, Edusa V, Park JS. Maternal physiology and complications of multiple pregnancy. *Semin Perinatol.* (2005) 29:338–48. doi: 10.1053/j.semperi.2005.08.002
7. Ekin A, Gezer C, Taner CE, Ozeren M, Uyar I, Gulhan I. Risk factors and perinatal outcomes associated with latency in preterm premature rupture of membranes between 24 and 34 weeks of gestation. *Arch Gynecol Obstet.* (2014) 290:449–55. doi: 10.1007/s00404-014-3227-3
8. Test G, Levy A, Wiznitzer A, Mazor M, Holcberg G, Zlotnik A, et al. Factors affecting the latency period in patients with preterm premature rupture of membranes. *Arch Gynecol Obstet.* (2011) 283:707–10. doi: 10.1007/s00404-010-1448-7
9. Phupong V, Kulmala L. Factors associated with latency period in preterm prelabor rupture of membranes. *J Matern Fetal Neonatal Med.* (2016) 29:2650–3. doi: 10.3109/14767058.2015.1095884
10. Rouzaire M, Corvaisier M, Roumeau V, Mulliez A, Sendy F, Delabaere A, et al. Predictors of short latency period exceeding 48 h after preterm premature rupture of membranes. *J Clin Med.* (2021) 10:150. doi: 10.3390/jcm10010150
11. Ehsanipoor RM, Arora N, Lagrew DC, Wing DA, Chung JH. Twin versus singleton pregnancies complicated by preterm premature rupture of membranes. *J Matern Fetal Neonatal Med.* (2012) 25:658–61. doi: 10.3109/14767058.2011.584924
12. Madden N, Andrikopoulou M, Overton E, Gyamfi-Bannerman C. Latency period after preterm premature rupture of membranes: singletons versus twins. *Am J Perinatol.* (2021). doi: 10.1055/s-0041-1727277
13. Yu H, Wang X, Gao H, You Y, Xing A. Perinatal outcomes of pregnancies complicated by preterm premature rupture of the membranes before 34 weeks of gestation in a tertiary center in China: a retrospective review. *Biosci Trends.* (2015) 9:35–41. doi: 10.5582/bst.2014.01058
14. Pasquier JC, Rabilloud M, Picaud JC, Claris O, Ecochard R, Moret S, et al. Modeling the duration of the latency period after preterm premature rupture of the membranes according to maternal and pregnancy characteristics: DOMINOS study. *Eur J Obstet Gynecol Reprod Biol.* (2008) 139:157–63. doi: 10.1016/j.ejogrb.2007.12.017
15. Bishop EH. Pelvic scoring for elective induction. *Obstet Gynecol.* (1964) 24:266–8.
16. Trentacoste SV, Jean-Pierre C, Baergen R, Chasen ST. Outcomes of preterm premature rupture of membranes in twin pregnancies. *J Matern Fetal Neonatal Med.* (2008) 21:555–7. doi: 10.1080/14767050802131929
17. Mendez-Figueroa H, Dahlke JD, Viteri OA, Chauhan SP, Rouse DJ, Sibai BM, et al. Neonatal and infant outcomes in twin gestations with preterm premature rupture of membranes at 24-31 weeks of gestation. *Obstet Gynecol.* (2014) 124:323–31. doi: 10.1097/AOG.0000000000000369
18. Atarjavdan L, Khazaeipour Z, Shahbazi F. Correlation of myometrial thickness and the latency interval of women with preterm premature rupture of the membranes. *Arch Gynecol Obstet.* (2011) 284:1339–43. doi: 10.1007/s00404-011-1841-x
19. Tigdi J, Luksts J, Stewart A, Morais M. Cervical length as a predictor of latency to labour in twin pregnancies complicated by preterm pre-labour rupture of membranes: a retrospective study. *J Obstetr Gynaecol Can.* (2020) 42:1230–4. doi: 10.1016/j.jogc.2020.03.018
20. Kolkman DG, Verhoeven CJ, Brinkhorst SJ, van der Post JA, Pajkrt E, Opmeer BC, et al. The Bishop score as a predictor of labor induction success: a systematic review. *Am J Perinatol.* (2013) 30:625–30. doi: 10.1055/s-0032-1331024
21. Gomez R, Romero R, Edwin SS, David C. Pathogenesis of preterm labor and preterm premature rupture of membranes associated with intraamniotic infection. *Infect Dis Clin North Am.* (1997) 11:135–76. doi: 10.1016/S0891-5520(05)70347-0

22. Asadi N, Faraji A, Keshavarzi A, Akbarzadeh-Jahromi M, Yoosefi S. Predictive value of procalcitonin, C-reactive protein, and white blood cells for chorioamnionitis among women with preterm premature rupture of membranes. *Int J Gynaecol Obstet.* (2019) 147:83–8. doi: 10.1002/ijgo.12907
23. Oludag T, Gode F, Caglayan E, Saatli B, Okyay RE, Altunyurt S. Value of maternal procalcitonin levels for predicting subclinical intra-amniotic infection in preterm premature rupture of membranes. *J Obstet Gynaecol Res.* (2014) 40:954–60. doi: 10.1111/jog.12273
24. Dagklis T, Petousis S, Margioula-Siarkou C, Mavromatidis G, Kalogiannidis I, Prapas N, et al. Parameters affecting latency period in PPROM cases: a 10-year experience of a single institution. *J Matern Fetal Neonatal Med.* (2013) 26:1455–8. doi: 10.3109/14767058.2013.784257
25. Frenette P, Dodds L, Armson BA, Jangaard K. Preterm prelabour rupture of membranes: effect of latency on neonatal and maternal outcomes. *J Obstetr Gynaecol Can.* (2013) 35:710–7. doi: 10.1016/S1701-2163(15)30861-6
26. Shim SS, Romero R, Hong JS, Park CW, Jun JK, Kim BI, et al. Clinical significance of intra-amniotic inflammation in patients with preterm premature rupture of membranes. *Am J Obstet Gynecol.* (2004) 191:1339–45. doi: 10.1016/j.ajog.2004.06.085
27. Choi EK, Kim SY, Heo JM, Park KH, Kim HY, Choi BM, et al. Perinatal outcomes associated with latency in late preterm premature rupture of membranes. *Int J Environ Res Public Health.* (2021) 18:672. doi: 10.3390/ijerph18020672
28. Lorthe E, Ancel PY, Torchin H, Kaminski M, Langer B, Subtil D, et al. Impact of latency duration on the prognosis of preterm infants after preterm premature rupture of membranes at 24 to 32 weeks' gestation: a national population-based cohort study. *J Pediatr.* (2017) 182:47–52.e42. doi: 10.1016/j.jpeds.2016.11.074
29. Nayot D, Penava D, Da Silva O, Richardson BS, de Vrijer B. Neonatal outcomes are associated with latency after preterm premature rupture of membranes. *J Perinatol.* (2012) 32:970–7. doi: 10.1038/jp.2012.15
30. Zhou S, Yang Y, Zhang X, Mu X, Quan Q, Zhong Q, et al. Perinatal outcomes of twin pregnancies with preterm premature rupture of the membranes at 24-34 weeks' gestation. *Sci Rep.* (2021) 11:23419. doi: 10.1038/s41598-021-02884-x

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Prediction of Endometrial Carcinoma Using the Combination of Electronic Health Records and an Ensemble Machine Learning Method

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Endometrial carcinoma (EC) is a common cause of cancer death in women, and having an early accurate prediction model to identify this disease is crucial. The aim of this study was to develop a new machine learning (ML) model-based diagnostic prediction model for EC. We collected data from consecutive patients between November 2012 and January 2021 at tertiary hospitals in central China. Inclusion criteria included women undergoing endometrial biopsy, dilation and curettage, or hysterectomy. A total of 9 features, including patient demographics, vital signs, and laboratory and ultrasound results, were selected in the final analysis. This new model was combined with three top optimal ML methods, namely, logistic regression, gradient-boosted decision tree, and random forest. A total of 1,922 patients were eligible for final analysis and modeling. The ensemble model, called TJHPEC, was validated in an internal validation cohort and two external validation cohorts. The results showed that the AUC values were 0.9346, 0.8341, and 0.8649 for the prediction of total EC and 0.9347, 0.8073, and 0.871 for prediction of stage I EC. Nine clinical features were confirmed to be highly related to the prediction of EC in TJHPEC. In conclusion, our new model may be accurate for identifying EC, especially in the early stage, in the general population of central China.

Keywords: machine learning, ensemble method, prediction, endometrial carcinoma (EC), model

INTRODUCTION

Globally, cancer of the corpus uteri (typically referred to as endometrial carcinoma, EC) ranked as the 6th most common type of cancer and 14th main cause of cancer death in women and caused an estimated 320,000 new cases and 76,000 deaths in 2012 (1). In China, the age-standardized incidence of EC had a significant upward trend in the period of 2000–2011 (2). Data from the China-Global Cancer Observatory has shown that EC ranked 10th for the incidence and mortality of cancer and caused 73,253 new cases and 13,329 deaths in 2018 (WHO CHINA CANCER 2018). The poor prognosis of EC was closely connected with the higher stage. The 5-year relative survival rates of EC decreased by 79% with staging from 95% for stage I to 16% for stage IV (3).

To improve the survival rates for women with EC, researchers have developed a series of prediction models to facilitate the early diagnosis of symptomatic patients, especially those with postmenopausal bleeding (4, 5). Current data provide some advice for the application of limiting transvaginal sonography screening for higher-risk groups identified according to epidemiological risk factors. This combination has improved the diagnostic sensitivity and specificity to 84 and 90%, respectively (5). However, this well-established model can be implemented only in postmenopausal women.

The application of big data to medicine has prompted recent advances in data analytics. The application of artificial intelligence in diagnostics will help doctors improve accuracy in various fields such as medical imaging, bioinformatics, and electronic health records (EHRs) (6–9). Recently, Pergialiotis et al. used artificial neural networks (NNs), and classification and regression trees for the prediction of EC in postmenopausal women in Greece. Compared with traditional statistical analysis (classical regression analysis), the artificial NNs had superior predictive accuracy, with a sensitivity of 86.8% and specificity of 83.3% (10). However, the restricted population and lack of interpretability have led to the limited use of this model. Hart et al. used random forest (RF) and NN models based only on personal health records for predicting EC risk and stratifying the population included in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. This trial enrolled participants 55–75 years of age between November 1993 and July 2001, and the AUC values of these models in the study by Hart et al. were 0.96 and 0.91, respectively (11). However, the narrow data and the restricted population involved in the models confined its positive predictive value and application. And Troisi et al. had combined a serum metabolomic signature of endometrial carcinoma with an ensemble machine learning algorithm for endometrial cancer screening with >99% accuracy lately (12). However, this accurate predictive model just focused on postmenopausal women.

To fill the gap applications of these models, we aimed to develop a new computer-assisted predictive model for the early detection of EC that may assist in clinical decision-making for the general population of China.

METHODS

Study Population

Our retrospective research was conducted in the Department of Obstetrics and Gynecology at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (TJH), and the Department of Obstetrics and Gynecology at the affiliated Renhe Hospital of China Three Gorges University (RHH). Data from consecutive selected patients were collected between November 2012 and January 2021. Inclusion criteria included women undergoing endometrial biopsy, dilation and curettage, or hysterectomy. Women with endometrial atypia hyperplasia, any prior malignancy, current pregnancy, or severe infectious disease were excluded. This study was approved by the Medical Ethics Committee of Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology and filed in the Medical Ethics Committee of the affiliated Renhe Hospital of China Three Gorges University-as a sub-center of this study.

Study Definitions

According to the endometrial pathology diagnoses, patients were classified into two categories: the case group with EC and the control group without EC (referred as benign group). The benign group consisted of women with a normal endometrium, endometrial polyps, hyperplasia without atypia, or submucosal uterine fibroids. The case group included women with endometrioid adenocarcinoma or other types such as clear cell carcinoma of the endometrium, endometrial stromal sarcoma, serous carcinoma, carcinosarcoma, or large- or small-cell neuroendocrine carcinoma. The details are shown in **Supplementary Table 1**.

Data Preprocessing

A total of 3,755 consecutive patients with EC or benign gynecological disease were enrolled. Patients were removed if the incomplete data accounted for >20% of those used in the model development and internal validation cohort. Fifty-two features relating to clinical characteristics, laboratory test results, and ultrasound data were extracted from EHRs. About 23% of cases were deleted because of missing data (**Figure 1**). Utility of predictive mean matching was conducted using R version 4.0.2 (R Development Core Team, Vienna, Austria; https://www.R-project.org/) to fill in missing data. The feature selection was conducted using least absolute shrinkage and selection operator (LASSO) regression. Nine features were introduced into the final analytic cohort (**Figure 2**). The definition of variables was shown in **Supplementary Table 6**.

Model Development

The data from TJH obtained between November 2012 and August 2019 were randomly divided into two cohorts—the training and internal validation cohorts—at a ratio of 4:1, respectively. The data from RHH and from TJH obtained between September 2019 and January 2021 were used as two external validation cohorts (termed here the RHH cohort and TJH2 cohort, respectively). The training cohort was analyzed using six machine learning (ML) models, namely, logistic regression (LR), support vector machine (SVM), K-nearest neighbor (KNN), RF, gradient-boosted decision tree (GBDT), and NN. Five-fold cross-validation was applied to fine-tune the parameters of these models (**Supplementary Figure 2**). Ultimately, an ensemble model, named TJHPEC, was generated from the three top-ranked predictive models (LR, RF, and GBDT). Specifically, the incidence risk probability of each estimator (LR, RF, and GBDT) was integrated by manually assigning weights of 0.2, 0.2, and 0.6, respectively. The well-fitted models were then tested using the test cohort. A normalized probability of risk for EC ranging from 0 to 1 was produced by each model. We selected the threshold of 0.34 to assign the predicted incidence risk label by optimizing the F1 score for the training and validation cohorts. Probabilities of <0.34 were assigned to non-EC and otherwise to EC for all ML methods (**Supplementary Figure 1**). Python was used for model

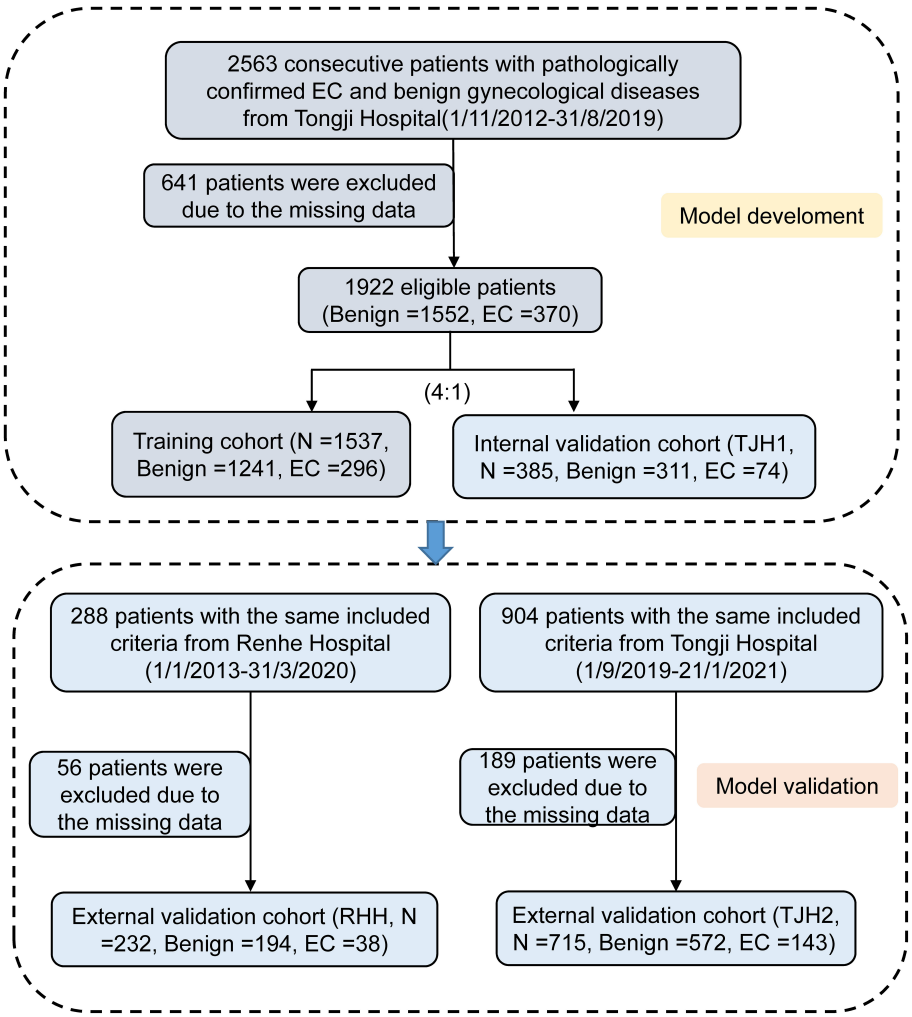

FIGURE 1 | Flow chart of group allocation. EC, endometrial carcinoma.

training and prediction. The LR, SVM, KNN, RF, GBDT, and NN models were called using the methods Logistic Regression, SVC, KNeighborsClassifier, RandomForestClassifier, Gradient BoostingClassifier, and MLPClassifier with prominent settings after five-fold cross-validation. To make the data more Gaussian-like, StandardScaler was used to standardize the features before training and prediction by subtracting the mean and scaling to unit variance.

Data Analysis

The non-parametric Kruskal–Wallis test was used to analyze the clinical characteristics as continuous variables, and the chi-squared test for categorical variables. Multiple imputation with predictive mean matching was conducted to impute missing data for continuous variables. LR was applied as a traditional method for the prediction of EC. The predictive model was estimated using the receiver-operating characteristic (ROC) curve, and the accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), F1 score, Cohen's kappa, Brier score, and related 95% confidence intervals (CIs) were calculated. All statistical analyses were performed using R version 4.0.2 (R Development Core Team). LR and RF models were performed in the Python 3.7.0 (https://www.python.org/) environment. For all tests, $p < 0.05$ was considered to be significant. The schematic diagram of our predictive model was summarized in **Supplementary Figure 2**.

RESULTS

Patients' Characteristics

To establish this diagnostic prediction model, 2,563 consecutive patients with pathologically confirmed EC and benign gynecological disease were enrolled at Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, between November 2012 and August 2019. A total of 641 patients were excluded for missing data, and the remaining 1,922 patients had data that were eligible for analysis and modeling. The EHRs of 1,537 patients were randomly

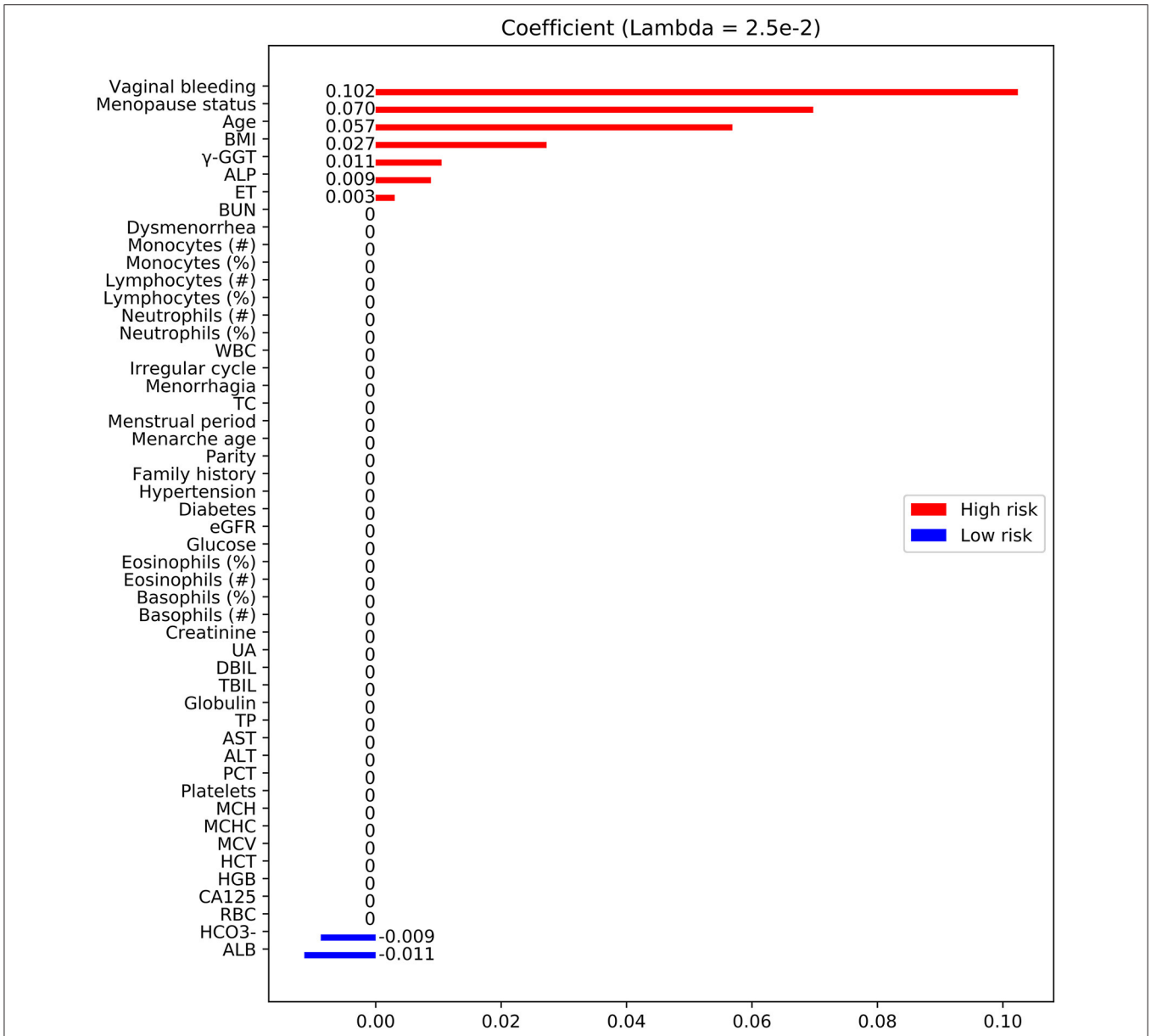

FIGURE 2 | Feature selection using LASSO. Feature coefficients revealed high-risk (red bar) and low-risk (blue bar) features, which were selected using LASSO with an optimal lambda value of 2.5×10^{-3}. BMI, body mass index; TBIL, total bilirubin; ALP, alkaline phosphatase; BUN, blood urea nitrogen; γ-GGT, γ-glutamyl transpeptidase; ET, endometrial thickness; TC, total cholesterol; AST, aspartate aminotransferase; CA-125, cancer antigen 125; UA, uric acid; Diabetes, type 2 diabetes; Family history, family history of malignant diseases; WBC, white blood cell; RBC, red blood cell; ALT, alanine aminotransferase; HGB, hemoglobin; PCT, thrombocytocrit; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; HCT, hematocrit; eGFR, estimated glomerular filtration rate; MCHC, mean corpuscular hemoglobin concentration; TP, total protein; DBIL, direct bilirubin; ALB, albumin; HCO_3^-, concentrations of bicarbonate.

assigned to the training cohort, and the other 385 patients were assigned to the group for internal validation (TJH1 cohort). For external validation, the EHRs of 288 patients with roughly the same characteristics as the RHH cohort and 904 from the TJH2 cohort were considered. Of these cohorts, 56 patients in the first group were excluded because of missing data, and the remaining 232 patients were eligible; 189 patients in the TJH2 cohort were excluded, and the remaining 715 patients were eligible. The detailed flowchart and disease classification are shown in **Figure 1** and **Supplementary Table 1**, respectively.

The demographics of the eligible patients included in the validation are presented in **Table 1**.

Selection of Features

Fifty features were extracted from the EHRs, and <20% of these had missing data (**Table 1**; **Supplementary Table 2**). Nine

TABLE 1 | Demographic characteristics in the validation cohorts.

Characteristic (Mean ± SD) or *N* (%)	TJH1 cohort		RHH cohort		TJH2 cohort	
	Benign (*n* = 311)	EC (*n* = 74)	Benign (*n* = 194)	EC (*n* = 38)	Benign (*n* = 572)	EC (*n* = 143)
Age, years	40 ± 11	54 ± 8	43 ± 10	54 ± 10	42 ± 11	54 ± 8
BMI, kg/m^2	22.1 ± 3.3	24.5 ± 4.0	22.5 ± 3.0	24.3 ± 3.7	22.8 ± 3.4	24.9 ± 3.6
Menstrual history						
Menopause status	32 (10.3)	42 (56.8)	23 (11.9)	25 (65.8)	63 (11)	78 (54.5)
Symptoms						
Vaginal bleeding	108 (34.7)	68 (91.9)	106 (54.6)	32 (84.2)	227 (39.7)	128 (89.5)
Laboratory tests						
ALB, g/L	41.7 ± 4.4	38.8 ± 5.7	41.9 ± 6.0	40.7 ± 4.8	42.9 ± 4.2	41.8 ± 3.9
ALP, U/L	54 ± 19	65 ± 22	60 ± 20	78 ± 23	62 ± 26	71 ± 20
γ-GGT, U/L	18 ± 17	27 ± 27	17 ± 15	21 ± 13	20 ± 25	26 ± 23
HCO_3^-, mmol/L	24.0 ± 2.3	23.7 ± 3.1	25.9 ± 2.3	27.2 ± 2.5	23.7 ± 2.2	23.7 ± 2.3
Ultrasound						
ET, mm	8.2 ± 4.7	8.1 ± 7.7	9.7 ± 4.3	14.9 ± 6.9	7.3 ± 4.4	6.1 ± 5.8

BMI, body mass index; ET, endometrial thickness; CA-125, cancer antigen 125.

TABLE 2 | Performance indices of the four predictive models for total EC in the validation cohorts.

	TJHPEC	LR	RF	GBDT
Internal validation cohort (TJH1)				
AUC (95% CI)	0.9346 (0.9108–0.9584)	0.9175 (0.8901–0.9449)	0.932 (0.9077–0.9563)	0.9335 (0.9095–0.9575)
Accuracy (95% CI)	91.17% (88.33–94.00%)	88.83% (85.68–91.98%)	89.61% (86.56–92.66%)	90.65% (87.74–93.56%)
Sensitivity (95% CI)	86.49% (78.70–94.28%)	79.73% (70.57–88.89%)	89.19% (82.11–96.26%)	86.49% (78.70–94.28%)
Specificity (95% CI)	92.28% (89.32–95.25%)	91.00% (87.82–94.18%)	89.71% (86.33–93.09%)	91.64% (88.56–94.72%)
PPV (95% CI)	72.73% (63.42–82.03%)	67.82% (58.00–77.63%)	67.35% (58.06–76.63%)	71.11% (61.75–80.48%)
NPV (95% CI)	96.63% (94.58–98.68%)	94.97% (92.48–97.45%)	97.21% (95.31–99.12%)	96.61% (94.55–98.68%)
F1	0.7901	0.7329	0.7674	0.7805
Kappa	0.7347	0.6629	0.7022	0.7218
Brier score	0.088	0.112	0.104	0.094
External validation cohort (RHH)				
AUC (95% CI)	0.8341 (0.777–0.8912)	0.831 (0.7732–0.8888)	0.8196 (0.7593–0.8799)	0.8265 (0.7677–0.8853)
Accuracy (95% CI)	81.03% (75.99–86.08%)	78.02% (72.69–83.35%)	77.16% (71.75–82.56%)	80.60% (75.52–85.69%)
Sensitivity (95% CI)	57.89% (42.20–73.59%)	60.53% (44.99–76.07%)	71.05% (56.63–85.47%)	60.53% (44.99–76.07%)
Specificity (95% CI)	85.57% (80.62–90.51%)	81.44% (75.97–86.91%)	78.35% (72.56–84.15%)	84.54% (79.45–89.62%)
PPV (95% CI)	44.00% (30.24–57.76%)	38.98% (26.54–51.43%)	39.13% (27.61–50.65%)	43.40% (30.05–56.74%)
NPV (95% CI)	91.21% (87.09–95.32%)	91.33% (87.14–95.52%)	93.25% (89.40–97.10%)	91.62% (87.56–95.68%)
F1	0.5	0.4742	0.5047	0.5055
Kappa	0.3857	0.3434	0.372	0.3889
Brier score	0.19	0.22	0.228	0.194
External validation cohort (TJH2)				
AUC (95% CI)	0.8649 (0.8377–0.8921)	0.8574 (0.8293–0.8855)	0.8544 (0.8259–0.8829)	0.8607 (0.833–0.8884)
Accuracy (95% CI)	80.98% (78.10–83.86%)	78.88% (75.89–81.87%)	79.30% (76.33–82.27%)	81.12% (78.25–83.99%)
Sensitivity (95% CI)	80.42% (73.92–86.92%)	81.82% (75.50–88.14%)	86.01% (80.33–91.70%)	81.12% (74.70–87.53%)
Specificity (95% CI)	81.12% (77.91–84.33%)	78.15% (74.76–81.53%)	77.62% (74.21–81.04%)	81.12% (77.91–84.33%)
PPV (95% CI)	51.57% (45.01–58.13%)	48.35% (42.05–54.64%)	49.00% (42.82–55.19%)	51.79% (45.24–58.33%)
NPV (95% CI)	94.31% (92.26–96.36%)	94.50% (92.45–96.56%)	95.69% (93.84–97.54%)	94.50% (92.48–96.52%)
F1	0.6284	0.6078	0.6244	0.6322
Kappa	0.5087	0.4761	0.4959	0.5133
Brier score	0.19	0.211	0.207	0.189

GBDT, gradient-boosted decision tree; LR, logistic regression; RF, random forest; AUC, area under the receiver-operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value; 95% CI, 95% confidence interval.

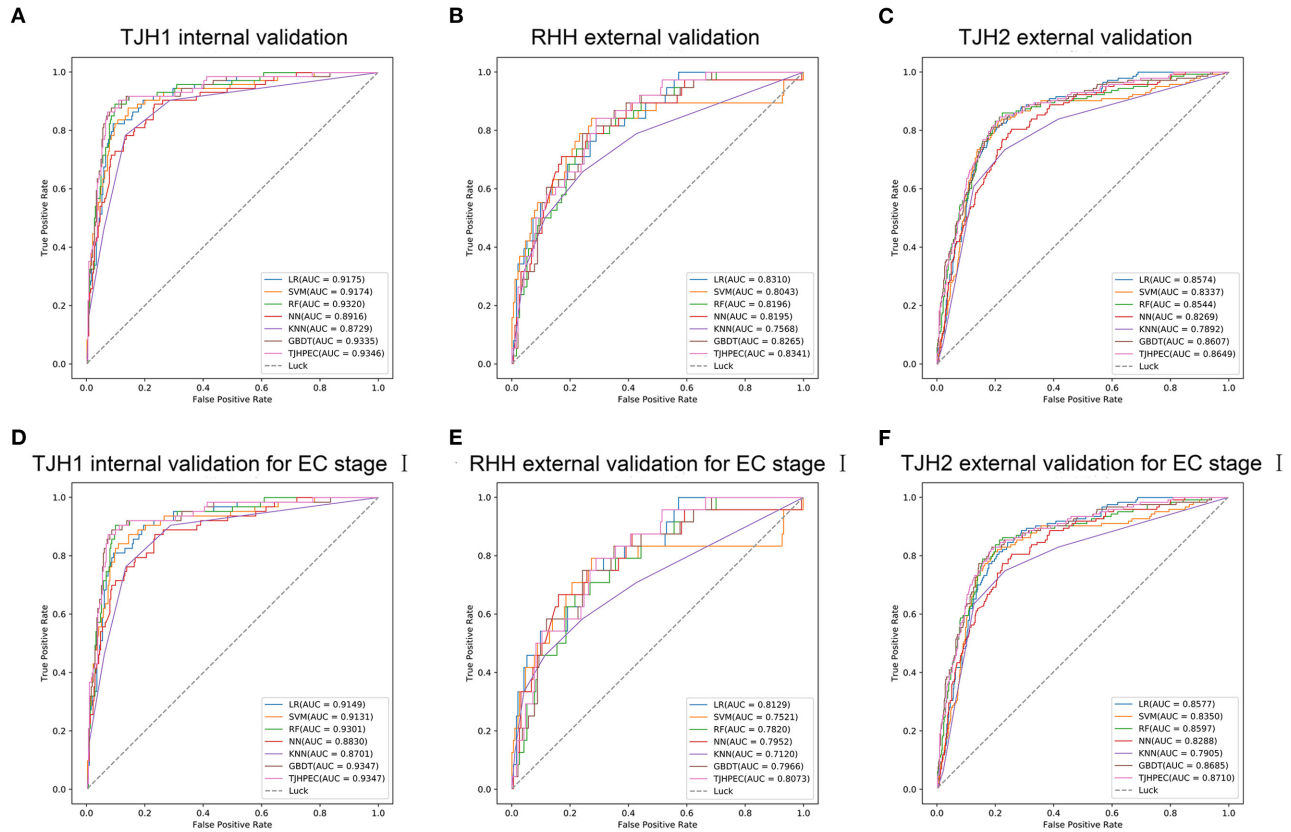

FIGURE 3 | Evaluation of the efficiency of the diagnostic prediction of models (LR, SVM, RF, NN, KNN, GBDT, and TJHPEC) using ROC curves for the total EC cohorts (**A**, TJH1 internal validation set; **B**, RHH external validation set; **C**, TJH2 external validation set) and stage I EC cohorts (**D**, TJH1 internal validation set; **E**, RHH external validation set; **F**, TJH2 external validation set).

of the 50 features were selected by LASSO analysis for the final modeling (**Figure 2**), which yielded 7 features associated with a high risk of EC: vaginal bleeding, menopause status, age, body mass index (BMI), alkaline phosphatase, endometrial thickness (ET), γ-glutamyl transpeptidase (γ-GGT). The 2 features associated with a low risk of EC were concentrations of bicarbonate, albumin.

Performance of Models in the Internal and External Validations

Initially, we adopted six ML models (LR, SVM, GBDT, NN, KNN, and RF) to predict EC in these cohorts (**Table 2**; **Supplementary Table 3**). The top three diagnostic–predictive models (RF, GBDT, and LR) were fused to create a new ensemble model, named TJHPEC. The decision-making threshold of 0.34 and the best achievable F1 score were derived to achieve the optimum classifier for the prediction of EC, and this showed the best predictive power among other models in our test cohorts (**Table 2**).

The area under the ROC curve (AUC) for the TJHPEC was 0.9346 (95% CI 0.9108–0.9584) for the internal validation cohort (TJH1) and indicated near-perfect discriminative ability. For the RHH cohort, the AUC of the TJHPEC was 0.8341 (95% CI 0.777–0.8912). The AUC for the TJH2 cohort was 0.8649 (95% CI 0.8377–0.8921). The accuracy, sensitivity, and specificity were 91.17% (95% CI 88.33–94%), 86.49% (95% CI 78.7–94.28%), and 92.28% (95% CI 89.32–95.25%), respectively, in the TJH1 cohort; 81.03% (95% CI 75.99–86.08%), 57.89% (95% CI 42.2–73.59%), and 85.57% (95% CI 80.62–90.51%), respectively, in the RHH cohort; and 80.98% (95% CI 78.1–83.86%), 80.42% (95% CI 73.92–86.92%), and 81.12% (95% CI 77.91–84.33%), respectively, in the TJH2 cohort (**Table 2**).

The Brier score is used to measure the accuracy of a probabilistic prediction. The Brier scores for the TJHPEC were 0.088, 0.19, and 0.19 for the TJH1, RHH, and TJH2 cohorts, respectively (**Table 2**). The parameters of predictive power in the three other models are shown in **Supplementary Table 2**. The ROC curves for the seven models (TJHPEC, RF, NN, GBDT, KNN, LR, and SVM) applied to the test cohort are shown in **Figure 3**.

ROC curves for the TJHPEC model for identifying stage I EC were created according to the International Federation of Gynecology and Obstetrics system and are shown in **Figure 3** and **Table 3**. The AUC values were 0.9347 (95% CI 0.9102–0.9592), 0.8073 (95% CI 0.7335–0.8811), and 0.871 (95% CI 0.8435–0.8985) for the TJH1, RHH, and TJH2 cohorts, respectively. The predictive parameters for the seven models are shown in **Table 3** and **Supplementary Table 4**.

TABLE 3 | Performance indices of the four predictive models for stage I EC in validation cohorts.

	TJHPEC	LR	RF	GBDT
Internal validation cohort (TJH1)				
AUC (95% CI)	0.9347 (0.9102–0.9592)	0.9149 (0.8859–0.9439)	0.9301 (0.9046–0.9556)	0.9347 (0.9102–0.9592)
Accuracy (95% CI)	91.44% (88.61–94.28%)	89.04% (85.87–92.20%)	89.84% (86.78–92.90%)	90.91% (88.00–93.82%)
Sensitivity (95% CI)	87.30% (79.08–95.52%)	79.37% (69.37–89.36%)	90.48% (83.23–97.72%)	87.30% (79.08–95.52%)
Specificity (95% CI)	92.28% (89.32–95.25%)	91.00% (87.82–94.18%)	89.71% (86.33–93.09%)	91.64% (88.56–94.72%)
PPV (95% CI)	69.62% (59.48–79.76%)	64.10% (53.46–74.75%)	64.04% (54.08–74.01%)	67.90% (57.73–78.07%)
NPV (95% CI)	97.29% (95.43–99.14%)	95.61% (93.27–97.94%)	97.89% (96.23–99.56%)	97.27% (95.40–99.14%)
F1	0.7746	0.7092	0.75	0.7639
Kappa	0.7227	0.6426	0.6886	0.7087
Brier score	0.086	0.11	0.102	0.091
External validation cohort (RHH)				
AUC (95% CI)	0.8073 (0.7335–0.8811)	0.8129 (0.7405–0.8853)	0.782 (0.7019–0.8621)	0.7966 (0.7201–0.8731)
Accuracy (95% CI)	82.11% (77.02–87.20%)	78.44% (72.98–83.90%)	77.06% (71.48–82.65%)	81.65% (76.51–86.79%)
Sensitivity (95% CI)	54.17% (34.23–74.10%)	54.17% (34.23–74.10%)	66.67% (47.81–85.53%)	58.33% (38.61–78.06%)
Specificity (95% CI)	85.57% (80.62–90.51%)	81.44% (75.97–86.91%)	78.35% (72.56–84.15%)	84.54% (79.45–89.62%)
PPV (95% CI)	31.71% (17.46–45.95%)	26.53% (14.17–38.89%)	27.59% (16.08–39.09%)	31.82% (18.06–45.58%)
NPV (95% CI)	93.79% (90.23–97.34%)	93.49% (89.77–97.21%)	95.00% (91.62–98.38%)	94.25% (90.79–97.71%)
F1	0.4	0.3562	0.3902	0.4118
Kappa	0.3032	0.2445	0.2778	0.314
Brier score	0.179	0.216	0.229	0.183
External validation cohort (TJH2)				
AUC (95% CI)	0.871 (0.8435–0.8985)	0.8577 (0.8284–0.887)	0.8597 (0.8307–0.8887)	0.8685 (0.8407–0.8963)
Accuracy (95% CI)	81.29% (78.40–84.19%)	78.71% (75.66–81.75%)	79.14% (76.12–82.16%)	81.44% (78.55–84.33%)
Sensitivity (95% CI)	82.11% (75.34–88.89%)	81.30% (74.41–88.19%)	86.18% (80.08–92.28%)	82.93% (76.28–89.58%)
Specificity (95% CI)	81.12% (77.91–84.33%)	78.15% (74.76–81.53%)	77.62% (74.21–81.04%)	81.12% (77.91–84.33%)
PPV (95% CI)	48.33% (41.55–55.10%)	44.44% (37.95–50.94%)	45.30% (38.92–51.68%)	48.57% (41.81–55.33%)
NPV (95% CI)	95.47% (93.62–97.32%)	95.11% (93.16–97.06%)	96.31% (94.59–98.03%)	95.67% (93.86–97.48%)
F1	0.6084	0.5747	0.5938	0.6126
Kappa	0.4962	0.4485	0.4711	0.5013
Brier score	0.187	0.213	0.209	0.186

GBDT, gradient-boosted decision tree; LR, logistic regression; RF, random forest; AUC, area under the receiver-operating characteristic curve; PPV, positive predictive value; NPV, negative predictive value; 95% CI, 95% confidence interval.

EC-Related Features in the New Model

The relationships between clinical variables and the probability of prediction in the four models are presented in **Figure 4**. The eight top-ranked features were highly associated with the prediction of EC in the TJHPEC model: age, vaginal bleeding, γ-GGT level, menopause status, concentrations of bicarbonate, albumin, body mass index (BMI) and endometrial thickness (ET) (**Supplementary Table 5**).

DISCUSSION

The increasing cancer burden has prompted research on the development of efficient detection tools or models for early diagnosis and prediction of prognosis (13, 14). However, at present, there is no standard EC screening method for the general population. In this retrospective case–control study, we developed an HER- and ML-based computer-assisted ensemble model for diagnosing EC in women in central China. Our analysis showed that the TJHPEC model surpassed the other six ML models for identifying EC in the internal and two external validation cohorts with respective accuracy rates of 91.17, 81.03, and 80.98%, and AUC values of 0.9346, 0.8341, and 0.8649. This new model had a superior prognostic efficacy than the feed-forward artificial NN model described by Pergialiotis et al. (10) who reported a predictive accuracy rate of 85.4% in their internal validation of the model's prediction of the risk of symptomatic postmenopausal women experiencing EC. Moreover, our model had an efficient diagnostic capability for the detection of early EC.

The performance of this new model was slightly worse for the two external validation cohorts than for the internal validation set (**Table 2**). The TJH2 external validation was a temporal validation that was retrieved from the same hospital as the training and internal validation datasets but at different times. About 40% of patients were missing data for one essential feature (ET) in this dataset vertically, whereas for other features, <20% of patients were missing data; on the horizontal, up to 5 of 9 variables were missing. These may have contributed to the lower predictive ability for the TJH2 cohort although we used predictive mean matching to fill in missing data. The RHH set was a geographic validation. Data for the RHH cohort were from a tertiary hospital,

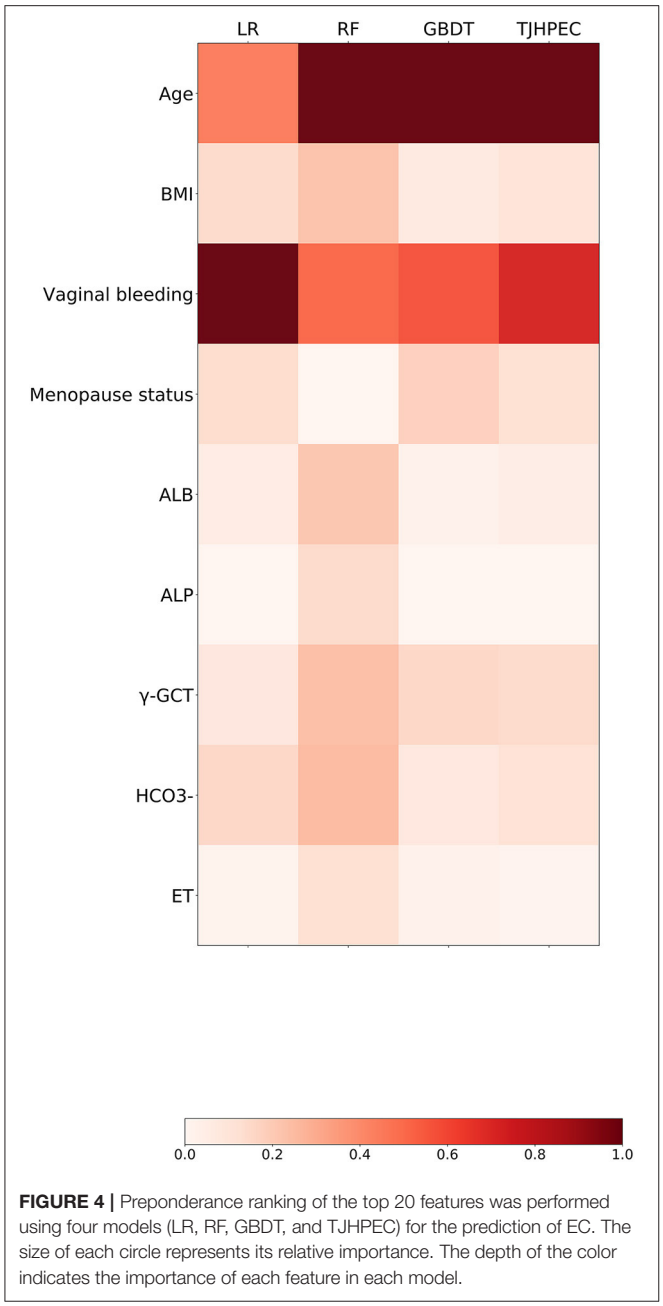

FIGURE 4 | Preponderance ranking of the top 20 features was performed using four models (LR, RF, GBDT, and TJHPEC) for the prediction of EC. The size of each circle represents its relative importance. The depth of the color indicates the importance of each feature in each model.

which means that our TJHPEC model may be generalized to other settings. However, data for essential factors such as BMI were also missing for about 40% of patients and the up to 5 variables' data missing also existed, and the patient baseline characteristics were more heterogeneous because of different testing instruments, reagents, and/or reference ranges. The small population may be another reason for the poorer prediction performance in the RHH cohort. Missing data on some variables is inevitable in real-world practice, and our results recommended that all clinical features are needed to take full advantage of this model.

The cohort for training and testing was obtained from 10 years of EHRs relating to the pathology of the endometrium. For some benign disorders, certain characteristics are not part of the routine checkup, which may explain some of the missing data. Although most of the included patients had a rate of missing data of <20%, we still obtained a multidimensional cohort involving features relating to demographics, crucial symptoms and signs, laboratory test results, and tumor-related characteristics shown on ultrasound. Our model currently used nine clinical variables, which are commonly included in the routine physical examinations at most hospitals, makes this new model more practical. The essential risk factors, such as age, vaginal bleeding, menopause status and BMI in our model were also verified in most traditional statistical models, which makes our prediction model more interpretable.

An epidemiological risk model for the prediction of EC was conducted in a large cohort in Western Europe. The risk factors in this model were BMI, menopausal status, ages at menarche and at menopause, oral contraceptive use. The analyses were performed for the total group and by different categories of BMI, parity, age at first full-term pregnancy, duration of menopausal hormone therapy, and smoking status (specific for pre-, peri-, and postmenopausal women). The predicted efficiency over 5 years increased up to 77% compared with the 71% for a model based on age alone (15). Pfeiffer's group developed a predictive model of EC in two large cohorts of US white women aged $\geq$ 50 years. Their final relative risk model included BMI, menopausal hormone therapy, parity, premenopausal, age at menopause, smoking, and oral contraceptive use, and the AUC was only 0.68 for the validation cohort (16). By comparison, some of the risk factors are not appropriate for evaluation in the Chinese population given the lower prevalence of oral contraceptive and hormone-replacement use than in Europe and the United States (17). Consequently, we did not include these in our model. In addition to demographics and crucial symptoms, our model included laboratory test results and tumor-related characteristics shown on ultrasound, such as γ-GGT, ET, and levels of bicarbonate, albumin, alkaline phosphatase. These have not been included in the other predictive models.

One of the strengths of this study is the wide application scope of TJHPEC. Most previous research involved postmenopausal or older women. Our new TJHPEC model can be used in the general population. Another strength of our research is that our ensemble model TJHPEC had an efficient predictive performance for identifying all cases as well as the early stage of EC.

The main limitation of our research is the retrospective cohort design and the limited training data that were collected from a single institution and produced some missing or unbalanced data. Although we conducted temporal and geographic external validations, the results were not as good as for internal validation because of the small sample sizes, discrepancies in testing instruments, and some missing data. Another limitation is the geographic restriction because the sample population was all from central China. Further prospective studies that include external validation and larger multiracial cohorts are needed to confirm the reliability and to expand the applicable scope of our model.

In conclusion, this study describes a new predictive model of EC in the general population of central China. This model may help clinicians to select more appropriate clinical strategies and to reduce the need for invasive workup and the economic burden. In the future, a larger prospective cohort study from multiple centers will be conducted to validate and warrant the model's predictive efficiency.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Tongji Hospital Affiliated to Tongji Medical College of Huazhong University of Science and Technology. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

WW, WS, and SW: conception and design. WW, SY, and YX: provision of study material or patients. SY, YX, and QZ: collection and/or assembly of data. SY, YX, and XZ: data analysis and interpretation. WW, SY, YX, WS, and SW: manuscript writing. WW, YX, SY, QZ, XZ, ZL, WS, and SW: final approval of manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.851890/full#supplementary-material

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer.* (2015) 136:E359–86. doi: 10.1002/ijc.29210
2. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. *CA Cancer J Clin.* (2016) 66:115–32. doi: 10.3322/caac.21338
3. Clarke MA, Long BJ, Del Mar Morillo A, Arbyn M, Bakkum-Gamez JN, Wentzensen N. Association of endometrial cancer risk with postmenopausal bleeding in women: a systematic review and meta-analysis. *JAMA Intern Med.* (2018) 178:1210–22. doi: 10.1001/jamainternmed.2018.2820
4. Burbos N, Musonda P, Giarenis I, Shiner AM, Giamougiannis P, Morris EP, et al. Predicting the risk of endometrial cancer in postmenopausal women presenting with vaginal bleeding: the Norwich DEFAB risk assessment tool. *Br J Cancer.* (2010) 102:1201–6. doi: 10.1038/sj.bjc.6605620
5. Jacobs I, Gentry-Maharaj A, Burnell M, Manchanda R, Singh N, Sharma A, et al. Sensitivity of transvaginal ultrasound screening for endometrial cancer in postmenopausal women: a case-control study within the UKCTOCS cohort. *Lancet Oncol.* (2011) 12:38–48. doi: 10.1016/S1470-2045(10)70268-0
6. Wichmann JL, Willemink MJ, De Cecco CN. Artificial intelligence and machine learning in radiology: current state and considerations for routine clinical implementation. *Invest Radiol.* (2020) 55:619–27. doi: 10.1097/RLI.0000000000000673
7. Liang H, Tsui BY, Ni H, Valentim CCS, Baxter SL, Liu G, et al. Evaluation and accurate diagnoses of pediatric diseases using artificial intelligence. *Nat Med.* (2019) 25:433–8. doi: 10.1038/s41591-018-0335-9
8. Lecointre L, Dana J, Lodi M, Akladios C, Gallix B. Artificial intelligence-based radiomics models in endometrial cancer: a systematic review. *Eur J Surg Oncol.* (2021) 47:2734–41. doi: 10.1016/j.ejso.2021.06.023
9. Tan X, Su AT, Hajiabadi H, Tran M, Nguyen Q. Applying machine learning for integration of multi-modal genomics data and imaging data to quantify heterogeneity in tumour tissues. *Methods Mol Biol.* (2021) 2190:209–28. doi: 10.1007/978-1-0716-0826-5_10
10. Pergialiotis V, Pouliakis A, Parthenis C, Damaskou V, Chrelias C, Papantoniou N, et al. The utility of artificial neural networks and classification and regression trees for the prediction of endometrial cancer in postmenopausal women. *Public Health.* (2018) 164:1–6. doi: 10.1016/j.puhe.2018.07.012
11. Hart GR, Yan V, Huang GS, Liang Y, Nartowt BJ, Muhammad W, et al. Population-based screening for endometrial cancer: human vs. machine intelligence. *Front Artif Intellig.* (2020) 3:539879. doi: 10.3389/frai.2020.539879
12. Troisi J, Raffone A, Travaglino A, Belli G, Belli C, Anand S, et al. Development and validation of a serum metabolomic signature for endometrial cancer screening in postmenopausal women. *JAMA Network Open.* (2020) 3:e2018327. doi: 10.1001/jamanetworkopen.2020.18327
13. Sadoughi F, Kazemy Z, Hamedan F, Owji L, Rahmanikatigari M, Azadboni TT. Artificial intelligence methods for the diagnosis of breast cancer by image processing: a review. *Breast Cancer.* (2018) 10:219–30. doi: 10.2147/BCTT.S175311
14. Huang S, Yang J, Fong S, Zhao Q. Artificial intelligence in cancer diagnosis and prognosis: opportunities and challenges. *Cancer Lett.* (2020) 471:61–71. doi: 10.1016/j.canlet.2019.12.007
15. Husing A, Dossus L, Ferrari P, Tjonneland A, Hansen L, Fagherazzi G, et al. An epidemiological model for prediction of endometrial cancer risk in Europe. *Eur J Epidemiol.* (2016) 31:51–60. doi: 10.1007/s10654-015-0030-9
16. Pfeiffer RM, Park Y, Kreimer AR, Lacey JV Jr, Pee D, Greenlee RT, et al. Risk prediction for breast, endometrial, and ovarian cancer in white women aged 50 y or older: derivation and validation from population-based cohort studies. *PLoS Med.* (2013) 10:e1001492. doi: 10.1371/journal.pmed.1001492
17. Li L, Ji J, Wang JB, Niyazi M, Qiao YL, Boffetta P. Attributable causes of breast cancer and ovarian cancer in china: reproductive factors, oral

contraceptives and hormone replacement therapy. *Chin J Cancer Res.* (2012) 24:9–17. doi: 10.1007/s11670-012-0009-y

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Incidence Rates of Myomectomy-Related Mortality and Venous Thromboembolism in South Korea: A Population-Based Study

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Background: Uterine leiomyomas are the most commonly observed pathologies, with an estimated prevalence of 4. 5–68.6%. We aimed to calculate myomectomy-related mortality and venous thromboembolism incidence rates in the Republic of Korea.

Methods: The data of patients who underwent myomectomy (2009–2018) were obtained from the Health Insurance Review and Assessment Service-National Inpatient Sample. The mortality rate after myomectomy was calculated using the leiomyoma diagnostic codes and myomectomy procedure codes. The incidence rates of venous thromboembolism, deep vein thrombosis, and pulmonary embolism were calculated using their diagnostic codes, with concomitant use of an antithrombotic agent during the same period or within 90 days after myomectomy.

Results: The data of 23,549 women aged 15–55 years who underwent myomectomy were extracted. The myomectomy rate was 14.6 ± 0.1 per 10,000 patients. The average age was 39.39 ± 0.04 years. One patient who underwent myomectomy died; this patient did not have concomitant venous thromboembolism. The post-myomectomy mortality rate was 1.3 ± 0.8 per 10,000 patients. The incidence rates of venous thromboembolism, deep vein thrombosis, and pulmonary embolism after myomectomy were 5.7 ± 1.6 per 10,000 patients, 4.4 ± 1.4 per 10,000 patients, and 2.5 ± 1 per 10,000 patients, respectively. The conversion rate to hysterectomy was 2.9 ± 1.1 per 10,000 patients.

Conclusion: The current mortality rate after myomectomy (0.013%) is substantially lower than that described in previous studies at the turn of the 20th century. The incidence of venous thromboembolism is also considerably lower than that in the general population worldwide.

Keywords: fibroids, leiomyoma, mortality, myomectomy, venous thromboembolism

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INTRODUCTION

Uterine leiomyomas, commonly known as fibroids, are among the most common problems encountered by gynecologists, with a prevalence estimated at 4.5–68.6% (1). A research by Baird et al. showed that leiomyomas are discovered by ultrasonography in more than 80% of women of African lineage and in ∼70% of white women by the age of 50 years (2). They frequently cause abnormal uterine bleeding and pelvic pain and are implicated in infertility.

The contemporary options for symptomatic treatment of leiomyoma comprise expectant management, medical therapy, and surgical treatment or interventional radiology procedures (3).

Uterine leiomyomas are the most common indications for hysterectomy. Many patients with symptomatic leiomyomas want to have the option of future childbearing or simply want to conserve their uterus. For these women, the removal of the leiomyomas alone with reconstruction and preservation of the uterus is a significant option.

Ammussat performed the first myomectomy in 1840 (4). Successful abdominal myomectomy was performed as early as 1845 by Washington and John Atlee. Washington Atlee finally published his experience after 14 abdominal myomectomies, with five deaths in his patient group (5). At the turn of the 20th century, compared with the mortality rate of 6–7% for abdominal hysterectomy, abdominal myomectomy was associated with a mortality rate of 40% (4, 6). Victor Bonney is accredited with advocating and popularizing the procedure in the 1920's (7–9).

Hysterectomy may be required intraoperatively to control bleeding. In the Tufts series described by Iverson et al. (10), conversion to intraoperative hysterectomy was necessary in two of 103 patients who underwent myomectomy (10). In the Yale series described by LaMorte et al. (11), one of the 128 patients required a hysterectomy (11). Approximately 1–4% of open myomectomies are converted to hysterectomy (12, 13). Laparoscopic myomectomies are converted to laparotomy in 8% of the procedures (14). All patients undergoing abdominal or laparoscopic myomectomies should be counseled on the possibility of the above mentioned complications when obtaining consent (14). Furthermore, there are very few studies that elucidate the optimal time for conception after myomectomyA prudent plan is to permit patients to heal for a minimum of few months prior to attempting conception (15). Many studies have reported complications, such as bleeding, infection, visceral injury, bladder and ureter injury, thromboembolism, and uterine rupture in pregnancies occurring after myomectomy (10, 11). Venous thromboembolism (VTE) has long been recognized as a possible complication and leading cause of death in patients undergoing pelvic surgery (16).

Although myomectomy is a common operation in the field of gynecology, there are very few reports on the current mortality rate after myomectomy. Hence, this study aimed to determine the mortality rate after myomectomy in the Republic of Korea using the National Health Insurance Database. Additionally, we determined the VTE rate in this study population.

METHODS

Study Setting and Participants

Almost all residents of the Republic of Korea are protected by the insurance provided by the National Health Insurance Corporation (NHIC). The Health Insurance Review and Assessment Service (HIRA) decides if the medical fee claimed by healthcare institutions is appropriate and recommends reimbursement by the NHIC in an unbiased manner. Therefore, the HIRA shares a significant part of the NHIC data (17). The HIRA collates the HIRA-National Inpatient Sample (HIRA-NIS) every year, extracting the data of one million people (this includes 10–13% of patients who have been hospitalized at least once and 1% of patients who have never been hospitalized during a single calendar year) enrolled in the health insurance service for medical research. The HIRA patient samples are considered representative of the population, as demonstrated by similar results of studies that used the HIRA-NIS and complete health insurance data (18, 19). This cross-sectional study used the HIRA-NIS 2009–2018 data (Serial numbers: HIRA-NIS-2009-0068/2010-0137/2011-0194/2012-0117/2013-0041/2014-0132/2015-0123/2016-0100/2017-0030/2018-0058) (17). We used the diagnostic codes included in the claims that were classified as per the International Classification of Diseases (ICD-10), the surgical and treatment codes from the Health Insurance Medical Care Expenses (2017–2018 version), and the HIRA Drug Ingredients Codes (drug codes) to select the participants.

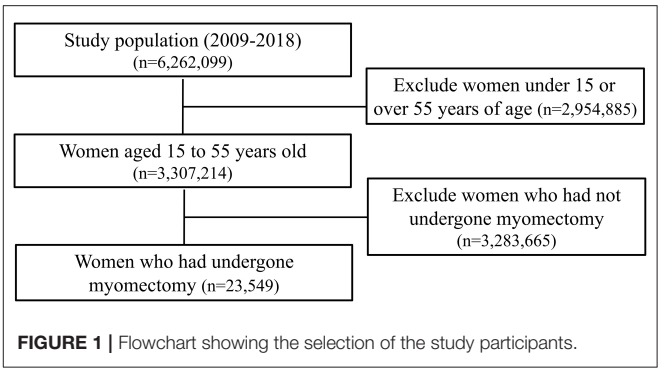

FIGURE 1 | Flowchart showing the selection of the study participants.

Case Definition

Female patients aged 15–55 years who had leiomyoma diagnostic codes simultaneously with myomectomy treatment codes (laparotomic/laparoscopic and not hysteroscopic myomectomies/myomectomy during cesarean section) were enrolled in the study (**Figure 1**). Patients who died from uterine leiomyomas were defined using a code for death within 90 days of myomectomy; in these cases, if there was a diagnostic code related to cancer in the main or sub-diagnosis on the date of death or if there was a diagnostic code that was not connected to hemorrhage or infection (e.g., trauma due to an accident), "death due to myomectomy" was excluded. In addition, patients with two or more outpatient visits after myomectomy were not defined using the "death due to myomectomy" code.

Patients with venous thromboembolism (VTE), deep vein thrombosis (DVT), and pulmonary embolism (PE) were defined as those who had VTE, DVT, and PE diagnostic codes, respectively, with concomitant use of an antithrombotic agent during the same time period or within 90 days after myomectomy (**Table 1**). Those diagnosed with VTE, DVT, and PE before or 90 days after myomectomy were excluded from this study. Conversion to hysterectomy during myomectomy

TABLE 1 | Diagnostic and procedural codes used in this study.

Names	Description	Code
Myomectomy	Simple myomectomy	R4121
	Complex myomectomy	R4122
	Simple abdominal myomectomy	R4124
	Complex abdominal myomectomy	R4127
	Simple laparoscopic myomectomy	R4128
	Complex laparoscopic myomectomy	R4129
VTE	DVT, not otherwise specified	I80.2
	Embolism or thrombosis of lower extremity	I80.3
	Pulmonary thrombosis, pulmonary thromboembolism, or pulmonary infarction	I26
DVT	DVT, not otherwise specified	I80.2
	Embolism or thrombosis of lower extremity	I80.3
PE	Pulmonary thrombosis, pulmonary thromboembolism, or pulmonary infarction	I26
Drug	Aspirin	11070XXX, 11080XXX, 11090XXX, 11100XXX, A0550XXX, 48970XXX, 51790XXX
	DOAC	51140XXX, 61370XXX, 61700XX, 64360XXX
	Fondaparinux	45013XXX
	LMWH	1521XXX, 14023XXX
	UFH	1686XXX
	Warfarin	24910XXX

DOAC, direct oral anticoagulants; DVT, deep vein thrombosis; LMWH, low molecular weight heparin; PE, pulmonary embolism; VTE, venous thromboembolism; UFH, unfractionated heparin.

was defined as having both myomectomy and hysterectomy codes simultaneously.

Patients on Medicaid (or an equivalent) for medical insurance were categorized as having a low socioeconomic status (SES). Patients' age was categorized using 5-year intervals. The Charlson comorbidity index (CCI) was verified through diagnostic codes used from January 1 of each year to December 31 of the same year. The CCI was scored in accordance with the method proposed by Quan et al. and categorized into 0, 1, 2, 3, or more (20). The hospitals were classified based on size as clinics, hospitals, general hospitals, and senior general hospitals.

Statistical Analysis

All statistical analyses in this study were performed using the statistical program R version 3.5.0 (the R Foundation for Statistical Computing, Vienna, Austria). All statistical calculations were performed using two-tailed tests and significance was set at $p < 0.05$. All continuous data are expressed as mean ± standard error, and all categorical data are expressed as total numbers (%). Two different sampling weights were used for the data in this study. The weighted *t*-test was utilized for the mean comparison of continuous variables, and the chi-square test was used for the comparison of categorical variables. The weighted mean was used to calculate the mean of the continuous variables, and the weighted ratio was used to calculate the ratio of the continuous variables. If there were missing values, the listwise deletion method was used.

Ethics

This research study was conducted retrospectively using data obtained for clinical purposes. The Institutional Review Board (IRB) of Sanggye Paik Hospital of Inje University granted an official waiver of ethical approval and informed consent (IRB approval number: SGPAIK 2020-07-006) for this study.

RESULTS

In this study, the data of 23,549 women aged 15–55 years who underwent myomectomy were extracted from a database of 3,307,214 women, recorded between 2009 and 2018 (**Figure 1**). The number of myomectomies performed increased annually over the years (**Figure 2**). The average age was 39.39 ± 0.04 years, and VTE was reported in two patients. Patient characteristics are shown in **Table 2**. One patient who underwent myomectomy died. However, concomitant VTE was not observed in this patient (**Table 3**). Among women aged 15 to 55 years, the myomectomy rate was 14.6 ± 0.1 per 10,000 patients (**Table 4**). The mortality rate after myomectomy was 1.3 ± 0.8 per 10,000 patients (**Table 4**). The incidence rates of VTE, DVT, and PE after myomectomy were 5.7 ± 1.6 per 10,000, 4.4 ± 1.4 per 10,000, and 2.5 ± 1 per 10,000, respectively (**Table 4**). The conversion rate to hysterectomy during myomectomy was 2.9 ± 1.1 per 10,000 patients (**Table 4**).

DISCUSSION

To our knowledge, this is the first report on the mortality rate after myomectomy from a large database of over 6 million patients. Based on data obtained from the HIRA-NIS, we found that the mortality rate after myomectomy was 0.013% among women aged 15–55 years. The mortality rate after myomectomy was considerably lower than that reported in the past. One patient who underwent myomectomy died, and this patient did not have concomitant VTE. The incidence rates of VTE, DVT, and PE after myomectomy were 0.057, 0.044, and 0.025%, respectively. The conversion rate to hysterectomy after myomectomy was 0.029%. These values were also considerably low.

Uterine leiomyomas (myomas or fibroids) are the most common type of pelvic tumors in women, with a lifetime risk of approximately 70–80% (2). There are many treatment options for leiomyoma-related symptoms, including expectant treatment, medical treatment, non-excisional procedures (magnetic resonance guided focused ultrasound, endometrial ablation, uterine artery embolization), and surgery (radiofrequency

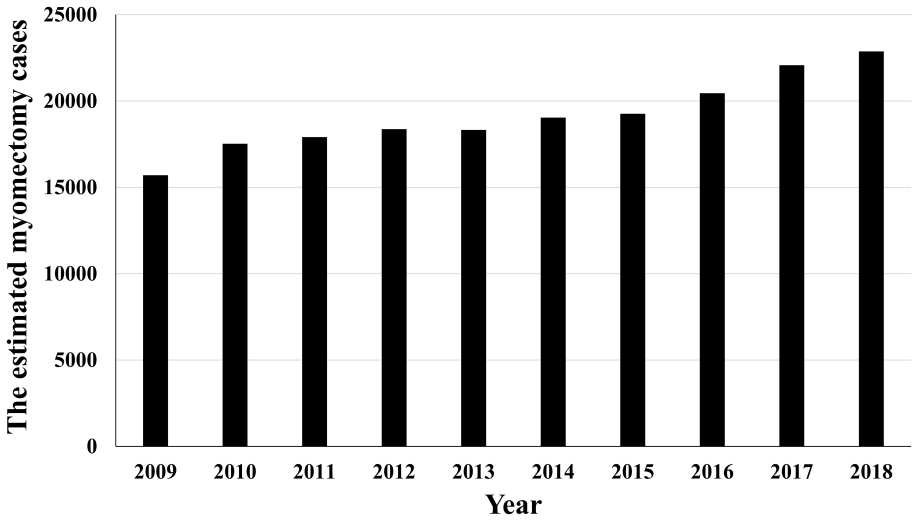

FIGURE 2 | The estimated number of myomectomy cases in different years from the HIRA-NISHIRA-NIS database.

TABLE 2 | Characteristics of myomectomy in HIRA-NPS 2009-2018.

	Non-VTE (*N* = 23,547)	VTE (*N* = 2)	*p*
Age	39.39 ± 0.04	42.93 ± 3.65	0.45
SES			1[a]
Mid∼high SES	23,246 (98.7%)	2 (100.0%)	
Low SES	301 (1.3%)	0 (0.0%)	
Hospital grade			0.791[a]
Clinic	4,134 (17.6%)	1 (50.0%)	
Hospital	6,473 (27.5%)	0 (0.0%)	
General hospital	7,630 (32.4%)	1 (50.0%)	
Senior general hospital	5,310 (22.6%)	0 (0.0%)	
CCI			0.097[a]
0	17,857 (75.8%)	1 (50.0%)	
1	2,834 (12.0%)	0 (0.0%)	
2	2,253 (9.6%)	0 (0.0%)	
3∼	603 (2.6%)	1 (50.0%)	

CCI, charlson comorbidity index; HIRA, health insurance review and assessment service; NPS, national patient sample; SES, socioeconomic status; VTE, venous thromboembolism.
[a]*Fisher's exact test.*

TABLE 3 | VTE according to age per 5 years or death in myomectomy patients (HIRA-NPS 2009-2018).

	Non-VTE (*N* = 23,547)	VTE (*N* = 2)	*p*-value
Death			1[a]
No	23,546 (100.0%)	2 (100.0%)	
Yes	1 (0.0%)	0 (0.0%)	
Age per 5 years			0.592[a]
∼20	16 (0.1%)	0 (0.0%)	
∼25	233 (1.0%)	0 (0.0%)	
∼30	1,761 (7.5%)	0 (0.0%)	
∼35	4,145 (17.6%)	0 (0.0%)	
∼40	5,606 (23.8%)	1 (50.0%)	
∼45	6,530 (27.7%)	0 (0.0%)	
∼50	4,002 (17.0%)	1 (50.0%)	
∼55	1,254 (5.3%)	0 (0.0%)	
DVT			<0.001[a]
No	23,547 (100.0%)	1 (50.0%)	
Yes	0 (0.0%)	1 (50.0%)	
PE			<0.001[a]
No	23,547 (100.0%)	1 (50.0%)	
Yes	0 (0.0%)	1 (50.0%)	

DVT, deep vein thrombosis; HIRA, health insurance review and assessment service; NPS, national patient sample; PE, pulmonary embolism; VTE, venous thromboembolism.
[a]*Fisher's exact test.*

ablation, myomectomy, hysterectomy) (3). Myomectomy is performed to remove leiomyomas surgically from the uterus, keeping the uterus in place for women who wish to become pregnant or retain the uterus.

At the turn of the 20th century, compared with the mortality rate of 6–7% for abdominal hysterectomy, abdominal myomectomy was associated with a mortality rate of 40% (4–6). Hemorrhage and embolism have been the main causes of death in patients who underwent myomectomy (6). There are three possible complications associated with the operation, namely hemorrhage, postoperative morbidity, and mortality. The incidence of these complications was observed to gradually reduce with improvements in surgical techniques. Severe hemorrhage may be addressed using a number of techniques, including intraoperative blood salvage, uterine artery ligation, tourniquet application, use of vasoconstrictive agents, or conversion to hysterectomy. The mortality rate after

TABLE 4 | The rates or estimated cases about myomectomy in HIRA-NIS 2009-2018.

	Rate or incidence	Estimated cases in South Korea
Myomectomy	14.6 ± 0.1[a]	191,514 ± 1,251
Mortality in myomectomy	1.3 ± 0.8[b]	10 ± 10
Conversion from myomectomy to hysterectomy	2.9 ± 1.1[c]	56.2 ± 21.3
VTE in myomectomy	5.7 ± 1.6[d]	17.7 ± 12.6
DVT in myomectomy	4.4 ± 1.4[d]	10 ± 10
PE in myomectomy	2.5 ± 1[d]	7.7 ± 7.7

DVT, deep vein thrombosis; HIRA, health insurance review and assessment service; NIS, national inpatients sample; PE, pulmonary embolism; VTE, venous thromboembolism. Data were expressed as mean values ± standard error.

[a] *The rate of myomectomy per 10,000 women.*

[b] *The rate of death per 10,000 myomectomy women.*

[c] *The conversion rate from myomectomy to hysterectomy per 10,000 myomectomy women.*

[d] *The rate of disease per 10,000 myomectomy women.*

myomectomy dropped to <1% in the 1950's (6) and was no longer higher than that after hysterectomy (6). In addition, there was no difference in complication rates between those who underwent myomectomy and hysterectomy (21).

Although myomectomy is a common operation in the field of gynecology, there are very few studies on the mortality associated with myomectomy. Therefore, we performed this study to investigate the current mortality rate of myomectomy in the era of advanced surgical skills and improved anesthesiology. In the Republic of Korea, where national health insurance is provided, most myomectomy data are acquired through the HIRA database. Therefore, we studied the mortality rate of myomectomy using the health insurance claims data. We also determined the VTE rate and conversion rate to hysterectomy. In the future, it is necessary to compare the current mortality rates of hysterectomy and myomectomy.

VTE has long been recognized as a possible complication and a leading cause of death in patients undergoing pelvic surgery (16). Pelvic operations are more prone to complications due to VTE than operations at other sites (16). PE is one of the most serious and common preventable cause of in-hospital deaths after surgery (22). Without thromboprophylaxis, the risk of DVT in patients undergoing major general or gynecologic surgery is 15–30%, and the risk of fatal PE is 0.2–0.9% (23). In a population of patients who selectively received prophylactic anticoagulants (38% of patients), the rate of VTE was 0.2% (24). Patients undergoing myomectomy (major surgery, defined as lasting for >30 min) are at a low-to-moderate risk of VTE and require appropriate thromboprophylaxis, whether mechanical or pharmacologic. In the Republic of Korea, the overall rates of postoperative VTE in major orthopedic, cancer, and benign surgeries were 1.24, 0.67, and 0.05%, respectively. Colorectal cancer surgeries (1.67%) and hip fracture (1.60%) were associated with the highest rates of VTE (25). Patients undergoing surgery for ovarian, colorectal, pancreatic, and esophageal cancers and major orthopedic surgery had a >20-fold increased risk of developing VTE than those undergoing benign surgery (25). Some authors have demonstrated that the rates of postoperative VTE in Asia, especially in the Republic of Korea, are lower than those in Caucasian populations (25). For this reason, thromboprophylaxis is not commonly offered in South Korea unless a major surgery (cancer-related surgery) is performed.

In our study, the incidence rates of VTE, DVT, and PE after myomectomy were 0.057, 0.044, and 0.025%, respectively, in the Korean population. The incidence of VTE was considerably lower than that in the general population worldwide and even in a population of patients who received prophylactic anticoagulants (VTE incidence rate: 0.2%). PE-related mortality was reported to fall from 3.3% (2001 to 2005) to 1.8% (2010 to 2013) in one study and from 17 to 10% in another study, (26, 27) with a decreasing trend each year. One of the 23,549 patients who underwent myomectomy between 2009 and 2018 died, and this patient did not have concomitant VTE. In Asian countries, such as South Korea, where VTE incidence is low, the contribution of VTE to the mortality rate associated with myomectomy is likely to be small. We believe that the considerably low mortality rates of myomectomy are due to the relatively low VTE rates in addition to improvements in surgical techniques and advanced anesthesiology methods in South Korea. However, the current study had a limitation when compared with other studies as there were no data about the body mass index and smoking status, which are often related to DVT.

Hysterectomy may be required intraoperatively to control bleeding. In our study, the conversion rate to hysterectomy during myomectomy was 0.029%. This is extremely low compared to that reported in previous studies. In cases of conversion to hysterectomy, the myomectomy code may have been omitted because there was no difference in reimbursement even if it was not entered. This could explain why the conversion rate to hysterectomy was very low in our study. Thus, future studies on the conversion rate to hysterectomy with different research methods for extracting data are required.

Myomectomy has been reported to temporarily reduce uterine volume and relieves symptoms in ∼80% of the patients (28). The risk of recurrence after myomectomy is approximately 27% for single leiomyomas and >50% for multiple leiomyomas (29). If the first surgery is performed for a single leiomyoma, 11% of the women require subsequent surgery, (30) if multiple leiomyomas are removed during the initial surgery, 26% require subsequent surgery.

Our study has several limitations. First, the mortality rates in this study may be lower than the actual rate because the incidence rates in this study included only those recorded in medical institutions. Therefore, deaths outside these institutions may not have been incorporated in this study. Additionally, sudden death occurring as a side effect of myomectomy is rare. Considering the narrow land area, the density of medical institutions, relatively low medical expenses, and free emergency transportation (119) provided by the county, the ratio is likely to be very low. Second, the conversion rate to hysterectomy during myomectomy may be much lower than the actual rate because the myomectomy surgical code was not included in some cases of conversion to hysterectomy. Third, our study design did not

distinguish between open and laparoscopic surgeries. However, there was only one recorded death, and the comparison of the mortality rates between laparoscopic surgery and laparotomy did not seem to be warranted. Fourth, we could not consider the risk factors, size and number of leiomyomas, surgical time etc. However, there was only one recorded death; thus, these factors were considered not significant. It is meaningful to investigate incidence rates of myomectomy-related mortality and venous thromboembolism in South Korean populations. Finally, the cause of death was unknown but was not related to cancer or trauma due to an accident.

In conclusion, we found that the mortality rate after myomectomy in South Korea is considerably lower than that reported in previous studies, especially at the turn of the 20th century. The myomectomy-related DVT rate is also lower than that reported in previous studies, especially in studies conducted in the Caucasian population. We have established that the current mortality rate after myomectomy has markedly reduced and that the incidence of DVT is low in this Asian population.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://figshare.com/articles/dataset/Myomectomy_mortality/14157521.

ETHICS STATEMENT

This retrospective chart review study involving human participants was conducted in accordance with the Ethical Standards of the Institutional and National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Institutional Review Board (IRB) of Sanggye Paik Hospital of Inje University granted an official waiver of ethical approval and informed consent (IRB approval number: SGPAIK 2020-07-006).

AUTHOR CONTRIBUTIONS

J-SY and MK: project development, data collection, statistical analysis, and manuscript writing. Both authors contributed to the article and approved the submitted version.

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REFERENCES

1. Stewart EA, Cookson CL, Gandolfo RA, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. *BJOG.* (2017) 124:1501–12. doi: 10.1111/1471-0528.14640
2. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM, et al. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. *Am J Obstet Gynecol.* (2003) 188:100–7. doi: 10.1067/mob.2003.99
3. Giuliani E, As-Sanie S, Marsh EE. Epidemiology and management of uterine fibroids. *Int J Gynecol Obstet*. (2020) 149:3–9. doi: 10.1002/ijgo.13102
4. Rubin IC. Progress in myomectomyl. *Am J Obstet Gynecol.* (1942) 44:196–212. doi: 10.1016/S0002-9378(42)90588-X
5. Speert H. *Obstetrics and Gynecology in America: A History*. Chicago, Ill; American College of Obstetrics and Gynecology (1980).
6. Rubin IC. Uterine fibroma and sterility. *Clin Obstet Gynecol.* (1958) 19:501–18. doi: 10.1097/00003081-195806000-00023
7. Bonney V. A clamp forceps for controlling haemorrhage when performing myomectomy. *J Obstet Gynaecol Br Emp*. (1953) 30:447–9. doi: 10.1111/j.1471-0528.1923.tb06661.x
8. Bonney V. The technique and results of myomectomy. *Lancet.* (1931) 217:171–7. doi: 10.1016/S0140-6736(00)40479-4
9. Hutchins FL Jr. Abdominal myomectomy as a treatment for symptomatic uterine fibroids. *Obstet Gynecol Clin North Am*. (1995) 22:781–9. doi: 10.1016/S0889-8545(21)00664-1
10. Iverson RE Jr, Chelmow D, Strohbehn K, Waldman L, Evantash EG. Relative morbidity of abdominal hysterectomy and myomectomy for management of uterine leiomyomas. *Obstet Gynecol.* (1966) 88:415–9. doi: 10.1016/0029-7844(96)00218-9
11. LaMorte AI, Lalwani S, Diamond MP. Morbidity associated with abdominal myomectomy. *Obstet Gynecol.* (1993) 82:897–900.
12. Viswanathan M, Hartmann K, McKoy N, Stuart G, Rankins N, Thieda P, et al. Management of uterine fibroids: an update of the evidence. *Evid Rep Technol Assess (Full Rep).* (2007) 154:1–122.
13. Olufowobi O, Sharif K, Papaionnou S, Neelakantan D, Mohammed H, Afnan M. Are the anticipated benefits of myomectomy achieved in women of reproductive age? a 5-year review of the results at a UK tertiary hospital. *J Obstet Gynaecol*. (2004) 24:434–40. doi: 10.1080/01443610410001685600
14. Dubuisson JB, Chapron C, Fauconnier A, Kreiker G. Laparoscopic myomectomy and myolysis. *Curr Opin Obstet Gynecol.* (1997) 9:233–8. doi: 10.1097/00001703-199708000-00004
15. Tsuji S, Takahashi K, Imaoka I, Sugimura K, Miyazaki K, Noda Y. MRI evaluation of the uterine structure after myomectomy. *Gynecol Obstet Invest*. (2006) 1:106–10. doi: 10.1159/000089144
16. Jeffcoate TN, Tindall VR. Venous thrombosis and embolism in obstetrics and gynaecology. *Aust N Z J Obstet Gynaecol.* (1965) 5:119–30. doi: 10.1111/j.1479-828X.1965.tb00304.x
17. Kim L, Kim J-A, Kim S. A guide for the utilization of health insurance review and assessment service national patient samples. *Epidemiol Health*. (2014) 36:e2014008. doi: 10.4178/epih/e2014008
18. Yuk J-S, Kim LY, Shin J-Y, Choi DY, Kim TY, Lee JH. A national population based study of the incidence of adnexal torsion in the Republic of Korea. *Int J Gynaecol Obstet*. (2015) 129:169–70. doi: 10.1016/j.ijgo.2014.11.027
19. Yuk J-S, Ji HY, Shin J-Y, Kim LY, Kim S-H, Lee JH. Comparison of survival outcomes in women with unsuspected uterine malignancy diagnosed after laparotomic versus laparoscopic myomectomy: a national, population-based study. *Ann Surg Oncol*. (2016) 23:1287–93. doi: 10.1245/s10434-015-4976-3
20. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol.* (2011) 173:676–82. doi: 10.1093/aje/kwq433
21. Pundir J, Walawalkar R, Seshadri S, Khalaf Y, El-Toukhy T. Perioperative morbidity associated with abdominal myomectomy compared with total abdominal hysterectomy for uterine fibroids. *J Obstet Gynaecol*. (2013) 33:655–62 doi: 10.3109/01443615.2013.816661
22. Martino MA, Borges E, Williamson E, Siegfried S, Cantor AB, Lancaster J, et al. Pulmonary embolism after major abdominal surgery in gynecologic oncology. *Obstet Gynecol.* (2006) 7:666–71. doi: 10.1097/01.AOG.0000200046.28199.ae
23. Greer IA. Epidemiology, risk factors and prophylaxis of venous thromboembolism in obstetrics and gynaecology. *Baillieres Clin Obstet Gynaecol.* (1997) 11:403–30. doi: 10.1016/S0950-3552(97)80019-3

24. Mäkinen J, Johansson J, Tomás C, Tomás E, Heinonen PK, Laatikainen T, et al. Morbidity of 10 110 hysterectomies by type of approach. *Hum Reprod.* (2001) 16:1473–8. doi: 10.1093/humrep/16.7.1473
25. Yhim HY, Jang MJ, Bang SM, Kim KH, Kim YK, Nam SH, et al. Incidence of venous thromboembolism following major surgery in Korea: from the health insurance review and assessment service database. *J Thromb Haemost.* (2014) 12:1035–43. doi: 10.1111/jth.12611
26. Konstantinides. Trends in incidence versus case fatality rates of pulmonary embolism: good news or bad news? *Thromb Haemost*. (2016) 115:233–5. doi: 10.1160/th15-10-0832
27. Jiménez D, de Miguel-Díez J, Guijarro R, Trujillo-Santos J, Otero R, Barba R, et al. Trends in the management and outcomes of acute pulmonary embolism: analysis from the RIETE registry. *J Am Coll Cardiol*. (2016) 67:162–70. doi: 10.1016/j.jacc.2015.10.060
28. Broder MS, Goodwin S, Chen G, Tang LJ, Costantino MM, Nguyen MH, et al. Comparison of long-term outcomes of myomectomy and uterine artery embolization. *Obstet Gynecol*. (2002) 100:864–8. doi: 10.1016/S0029-7844(02)02182-8
29. Kotani Y, Tobiume T, Fujishima R, Shigeta M, Takaya H, Nakai H, et al. Recurrence of uterine myoma after myomectomy: open myomectomy versus laparoscopic myomectomy. *J Obstet Gynaecol Res.* (2018) 44:298–302. doi: 10.1111/jog.13519
30. Maloue L. Myomectomy: recurrence after removal of solitary and multiple myomas. *Obstet Gynecol.* (1969) 34:200–3.

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SYSTEMATIC REVIEW
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The Prevalence and Risk Factors for Severe Maternal Morbidities: A Systematic Review and Meta-Analysis

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Introduction: Maternal mortality and severe maternal morbidity remain major public health problems globally. Understanding their risk factors may result in better treatment solutions and preventive measures for maternal health. This review aims to identify the prevalence and risk factors of severe maternal morbidity (SMM) and maternal near miss (MNM).

Methods: A systematic review and meta-analysis was conducted to assess the prevalence and risk factors of SMM and MNM. The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. A systematic search was performed in the MEDLINE (PubMed), CINAHL (EBSCOhost), and Science Direct databases for articles published between 2011 and 2020.

Results: Twenty-four of the 44 studies included were assessed as being of good quality and having a low risk of bias. The prevalence of SMM and MNM was 2.45% (95% CI: 2.03, 2.88) and 1.68% (95% CI: 1.42, 1.95), respectively. The risk factors for SMM included history of cesarean section (OR [95% CI]: 1.63 [1.43, 1.87]), young maternal age (OR [95% CI]: 0.71 [0.60, 0.83]), singleton pregnancy (OR [95% CI]: 0.42 [0.32, 0.55]), vaginal delivery (OR [95% CI]: 0.11 [0.02, 0.47]), coexisting medical conditions (OR [95% CI]: 1.51 [1.28, 1.78]), and preterm gestation (OR [95% CI]: 0.14 [0.08, 0.23]). The sole risk factor for MNM was a history of cesarean section (OR [95% CI]: 2.68 [1.41, 5.10]).

Conclusions: Maternal age, coexisting medical conditions, history of abortion and cesarean delivery, gestational age, parity, and mode of delivery are associated with SMM and MNM. This helps us better understand the risk factors and their strength of association with SMM and MNM. Thus, initiatives such as educational programs, campaigns, and early detection of risk factors are recommended. Proper follow-up is important to monitor the progression of maternal health during the antenatal and postnatal periods.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021226137, identifier: CRD42021226137.

Keywords: severe maternal morbidity, maternal near miss, prevalence, risk factor, meta-analysis

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INTRODUCTION

Severe maternal morbidity (SMM) refers to "potentially life-threatening conditions during pregnancy, childbirth or after pregnancy, from which maternal near miss (MNM) cases would emerge" (1, 2). The standard definition and internationally accepted identification criteria for SMM by the World Health Organization (WHO) Working Group on Maternal Mortality Morbidity Classifications (1, 2) incorporate clinical disorders (hemorrhagic, hypertensive, and other systemic disorders) and severe management indicators to assess the severity of SMM and to strengthen the ability of health care professionals to detect SMM (1).

However, maternal mortality and SMM remain major public health problems for global healthcare systems despite substantial progress (3). Between 1990 and 2015, the global maternal mortality ratio (MMR) declined by 44% but failed to meet the 75% reduction set by Millennium Development Goal 5. Sustainable Development Goal 3 aims to ensure healthy living, promote well-being for people of all ages, and reduce global MMR to <70 per 100,000 live births by 2030. The average reduction of 7.5% each year between 2016 and 2030 is more than three times the 2.3% annual rate of decline observed globally between 1990 and 2015.

Prior to 2011, the literature varied in its definitions and criteria used to classify SMM and MNM cases. In a review, the prevalence of SMM based on various disease-specific, management-based, and organ system dysfunction-based criteria ranged from 0.04 to 15% (4). Meanwhile, the prevalence according to organ-based dysfunction using the Mantel criteria and emergency hysterectomy was 0.42 and 0.039%, respectively. With a 98.3% I^2 value for the Mantel-based criteria and 95.5% for the emergency hysterectomy criteria, the heterogeneity among studies was large and significant (4).

While maternal mortality has been commonly used as a benchmark for maternal health status, there is evidence that it is just the "tip of the iceberg" for adverse maternal outcomes (5, 6). The SMM literature has revealed several contributing factors. Employment status (7), low household income (8), history of abortion (8), multiple births (9), and inadequate antenatal care (8) were documented as contributing factors for SMM. However, mixed findings were reported for the factors of age (10–12), race (9, 13), educational level (8, 13), co-existing medical conditions (14), parity (15), gestational period (10), mode of delivery (12, 16), previous cesarean section (14), and pre-pregnancy body mass index (9, 14).

Determining the pooled prevalence of SMM at a global level gives a better indication of its severity than discrete primary studies. The identification of factors associated with SMM allows a clearer understanding of the issue and serves as a basis for appropriate preventive strategies to be established. This pertains to primary prevention at the institutional, provider, and client levels, such as screening or preventive that could potentially avoid death or severe morbidity from a disorder. Therefore, to inform clinical policy and enhance patient care, planning beyond maternal mortality and direct, focused evaluation of the strength of each risk factor's association with SMM is required. This systematic review aims to ascertain the prevalence and risk factors of SMM based on the WHO standard definition and criteria (1). The evidence, effect estimates, and strength of statistical association between SMM and its risk factors will be summarized in this review.

METHODS

Study Design and Search Strategy

To determine the prevalence and risk factors, researchers conducted a systematic review and meta-analysis of studies on SMM. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**Figure 1**).

A systematic search was performed in the MEDLINE (PubMed), CINAHL (EBSCOhost), and Science Direct databases for articles published between 2011 and 2020 inclusive. The search was done using the following Medical Subject Headings (MeSH) and generic free-text search terms as follows: ((Prevalence [MeSH Terms]) OR (risk factors[MeSH Terms])) AND (severe maternal morbidity[Text Word])) OR (maternal near miss[Text Word])) OR (potentially life-threatening[Text Word])) OR (maternal complications[Text Word])) OR (severe acute maternal morbidity[Text Word])) OR (pregnancy complications[Text Word])) AND (("2011" [Date - Publication]: "2022" [Date - Publication])) The search terms were flexible and tailored to the various electronic databases. All studies published starting from 2011 were retrieved to assess their eligibility for inclusion in this study. The search was limited to full-text articles written in English. The reference lists of the included studies were cross-checked to locate additional potentially acceptable studies.

Eligibility Criteria

The main inclusion criterion was the reporting of prevalence or risk factors of SMM. Studies that were written in English, published in 2011 or later, had cross-sectional, case-control, or cohort designs, and were conducted in the community or health institutions were included. Case series/reports, conference papers, proceedings, abstract-only articles, editorial reviews, letters of communications, commentaries, systematic reviews, and qualitative studies were excluded.

Study Selection and Screening

All records identified using our search strategy were exported to the EndNote X8 (Clarivate Analytics). Duplicate articles were removed. Two independent reviewers (MKHR, NMN) screened the titles and abstracts of the identified articles. The full texts of eligible studies were obtained and thoroughly read to assess their suitability for the meta-analysis. A consensus discussion was held in the event of a conflict between the two reviewers, and a third reviewer was consulted. The search method is presented in the PRISMA flow chart showing the number of studies that were included and excluded, along with reasons for exclusion (**Figure 1**). The primary outcomes of this study were the prevalence and risk factors of SMM.

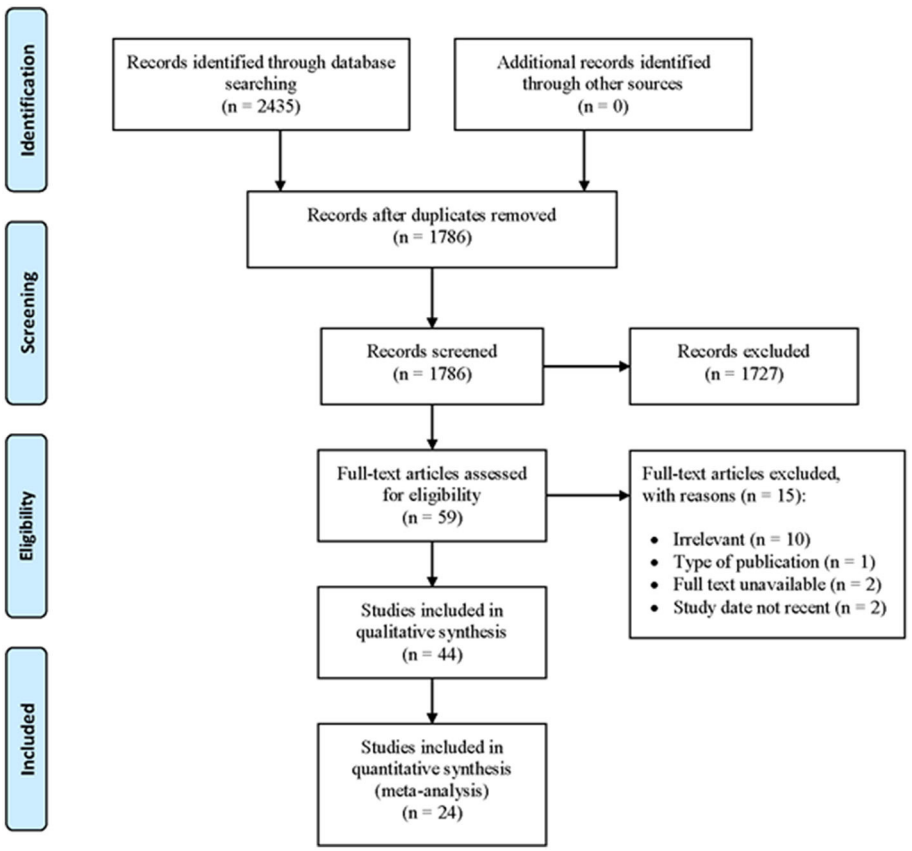

FIGURE 1 | PRISMA flow chart.

Quality Assessment and Bias

A critical appraisal was done to assess data quality using the Joanna Briggs Institute Meta-Analysis for cross-sectional, case-control, and cohort studies (17). Independent bias assessments were carried out by two reviewers. When more than 70% of the responses were "yes," moderate when 50–69% of the answers were "yes," and high when <50% of the answers were "yes," the risk of bias was rated low. Studies that showed a high or moderate risk of bias were excluded from the review.

Data Extraction

Two reviewers independently extracted data into Microsoft Excel (Microsoft Office Professional Plus 2016). The data included the name of the first author, publication year, study location, study design, setting, study population, sample size, SMM definition, prevalence, risk factors, and data for calculation of effect estimates. The data for risk factors included sociodemographic characteristics, medical and gynecological histories, and past and present obstetric performance.

Result Synthesis and Statistical Analysis

Outcomes were reported using odds ratios (ORs) and 95% confidence intervals (CIs). The analysis was performed with the Review Manager software (v.5.4; Nordic Cochrane Centre, Copenhagen, Denmark). A random-effects model was used to pool data. The I^2 statistic was used to assess heterogeneity, which was stratified as follows: 0–40%, might not be important; 30–60%, moderate heterogeneity; 50–90% substantial heterogeneity; and 75–100%, considerable heterogeneity (18). Funnel plots and Egger's test were used to assess publication bias if indicated, and a $p < 0.05$ was declared as statistically significant.

RESULTS

Characteristics of the Included Studies

A total of 2,435 articles were retrieved through an electronic search using the aforementioned search terms, of which 1,786 were eligible for the title and abstract assessment after removing 649 duplicate records. Of the 1,786 articles screened for eligibility, 1,727 were excluded after evaluating their titles and abstracts. A total of 59 articles underwent full-text assessment for eligibility, of which 15 were excluded due to irrelevancy ($n = 10$), not suitable type of publication ($n = 1$), unavailability of full text ($n = 2$), and not recent ($n = 2$) (**Figure 1**).

In this review, 44 articles underwent quality assessment, of which 24 with good quality and low risk of bias were included

and the remaining poor-quality articles excluded. Nineteen studies were cross-sectional, two were case-control, and three were cohort. A variety of countries were represented in this systematic review and meta-analysis. The smallest sample size was 262 women, and the largest was 3,162,303 (**Table 1**). The source of funding of included articles was tabulated in the **Supplementary File**.

Severe Maternal Morbidity

We observed significant variations in the prevalence of SMM in this review (**Figure 2**). The lowest reported prevalence of SMM was 0.53% (19), and the highest was 6.78% (23). Eight articles were included, with the overall pooled prevalence of SMM at 2.45% (95% CI: 2.03, 2.88). Egger's test showed statistically insignificant publication bias ($P = 0.162$).

TABLE 1 | Summary of research articles included in the systemic review and meta-analysis for SMM and MNM ($n = 24$).

No.	References	Publication year	Study area (region)	Study design	Sample size	SMM	MNM	Prevalence of SMM (%)
1	Lindquist et al. (19)	2015	Victoria, Australia	Case-control	211,060	1,119	N/A	0.53
2	Hitti et al. (20)	2018	University of Washington Medical Center	Cross-sectional	7,025	284	N/A	4.04
3	Dzakpasu et al. (21)	2019	Canada	Cross-sectional	1,418,545	22,799	N/A	1.61
4	Das et al. (22)	2014	Eastern India	Cross-sectional	6,100	99	N/A	1.62
5	Galvão et al. (23)	2020	Sergipe, Northern Brazil	Cross-sectional	16,243	1,102	77	6.78
6	Zhang et al. (24)	2020	Hebei, China	Cross-sectional	289,859	289,589	N/A	99.91
7	Norhayati et al. (12)	2016	Kelantan, Malaysia	Cross-sectional	23,422	352	N/A	1.50
8	Aoyama et al. (25)	2019	Canada	Cohort	3,162,303	54,219	N/A	1.72
9	Bashour et al. (26)	2015	Middle Eastern countries	Cross-sectional	9,063	N/A	71	0.78
10	Dessalegn et al. (27)	2020	Ethiopia	Case-control	321	0	80	24.92
11	Nansubuga et al. (28)	2013	Uganda	Cross-sectional	1,557	0	434	27.87
12	Rosendo et al. (29)	2017	Brazil	Cross-sectional	848	34	174	20.52
13	Chikadaya et al. (30)	2018	Zimbabwe	Cross-sectional	11,871	0	123	1.04
14	Rathod et al. (31)	2016	India	Cohort	21,992	0	161	0.73
15	Verschueren et al. (32)	2020	Suriname	Cohort	9,114	0	71	0.78
16	Iwuh et al. (33)	2014	Cape Town, South Africa	Cross-sectional	19,222	0	112	0.58
17	Dias et al. (34)	2014	Brazil	Cross-sectional	9,114	0	23,747	1.02
18	Domingues et al. (35)	2016	Brazil	Cross-sectional	19,222	0	243	1.02
19	Heemelaar et al. (36)	2020	Namibia	Cross-sectional	2,325,394	0	298	0.80
20	Mbachu et al. (37)	2017	Southern Nigeria	Cross-sectional	262	0	52	19.85
21	Ps et al. (38)	2013	Manipal University, India	Cross-sectional	7,390	0	131	1.77
22	Dile et al. (39)	2015	Ethiopia	Cross-sectional	806	0	188	23.33
23	Jayaratnam et al. (40)	2019	Timor Leste	Cross-sectional	4,702	0	39	0.83
24	Owolabi et al. (41)	2018	Kenya	Cross-sectional	182,571	0	1,278	0.70

N/A, Not available; SMM, severe maternal morbidity; MNM, maternal near miss.

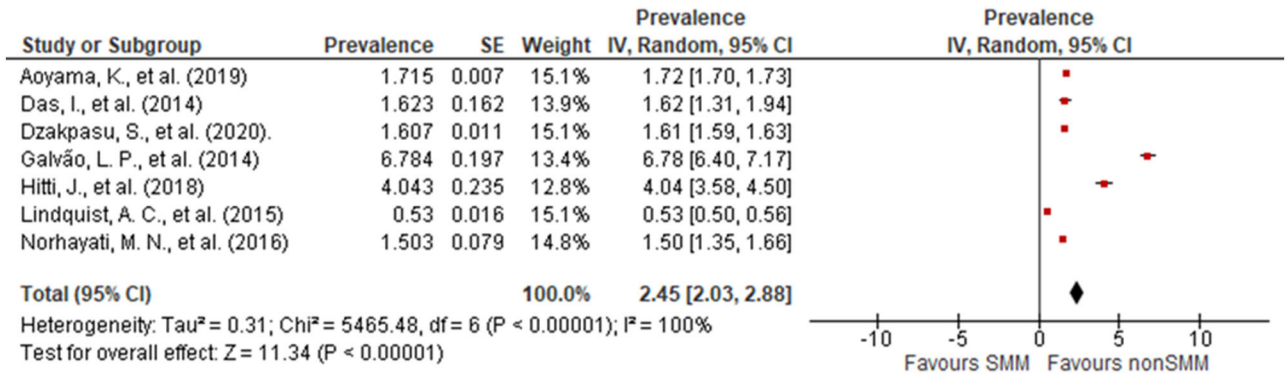

FIGURE 2 | Forest plot depicting the prevalence of severe maternal morbidity.

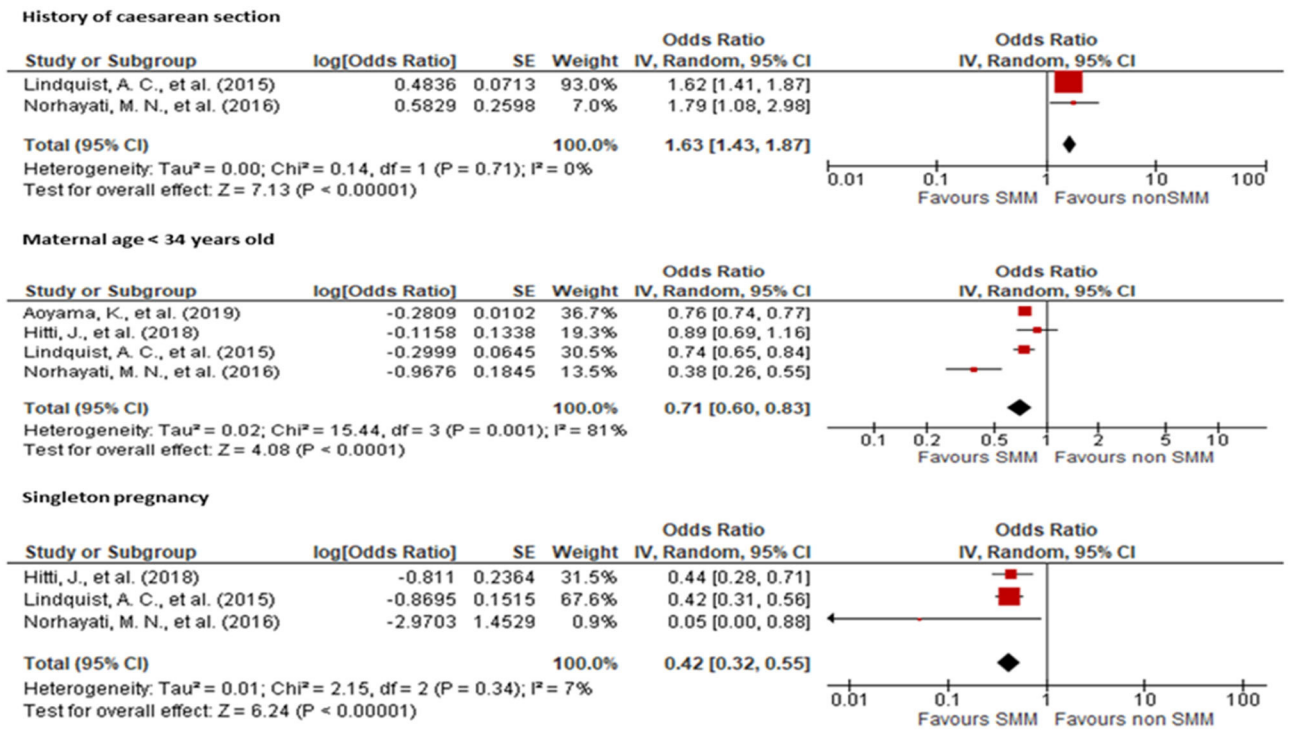

FIGURE 3 | Forest plot showing the association of history of cesarean section, maternal age, and singleton pregnancy with severe maternal morbidity.

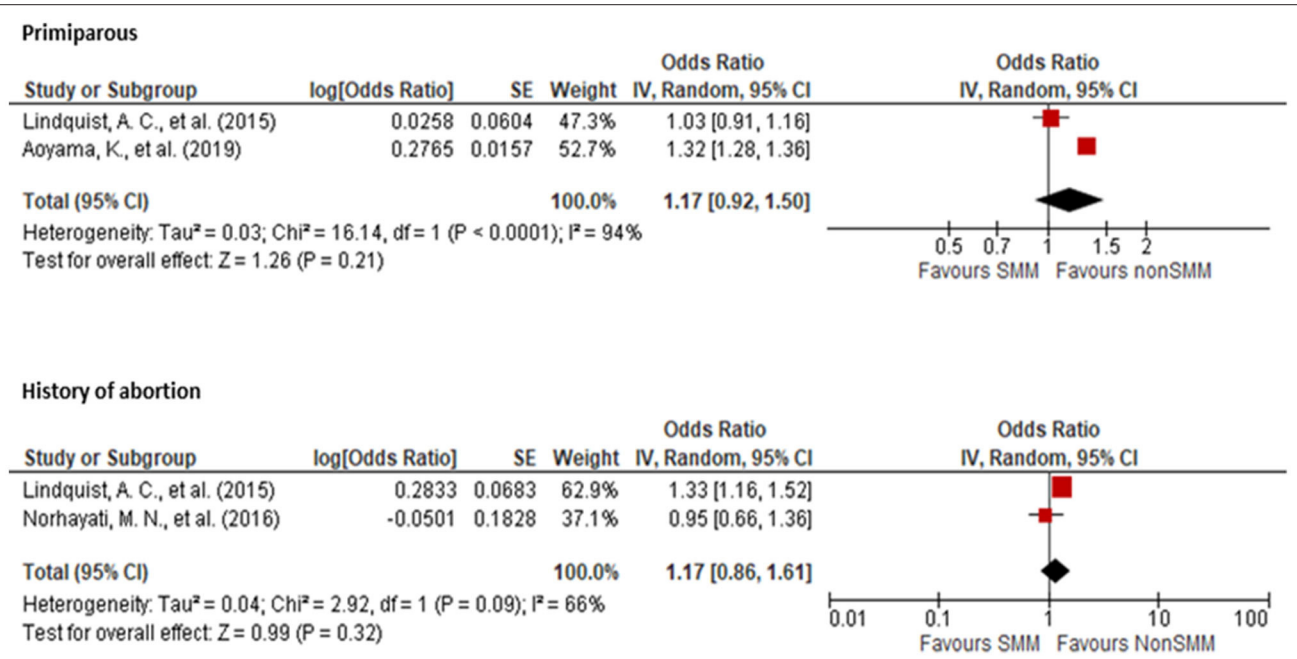

FIGURE 4 | Forest plot showing the association of parity and history of abortion with severe maternal morbidity.

Various factors such as age, parity, history of cesarean section, previous history of abortion, singleton pregnancy, and coexisting medical conditions were evaluated for their association with SMM. Two studies (12, 19) reported an association between a history of cesarean section and SMM with an OR of 1.63 (95% CI: 1.43, 1.87) when compared to women with only a history of

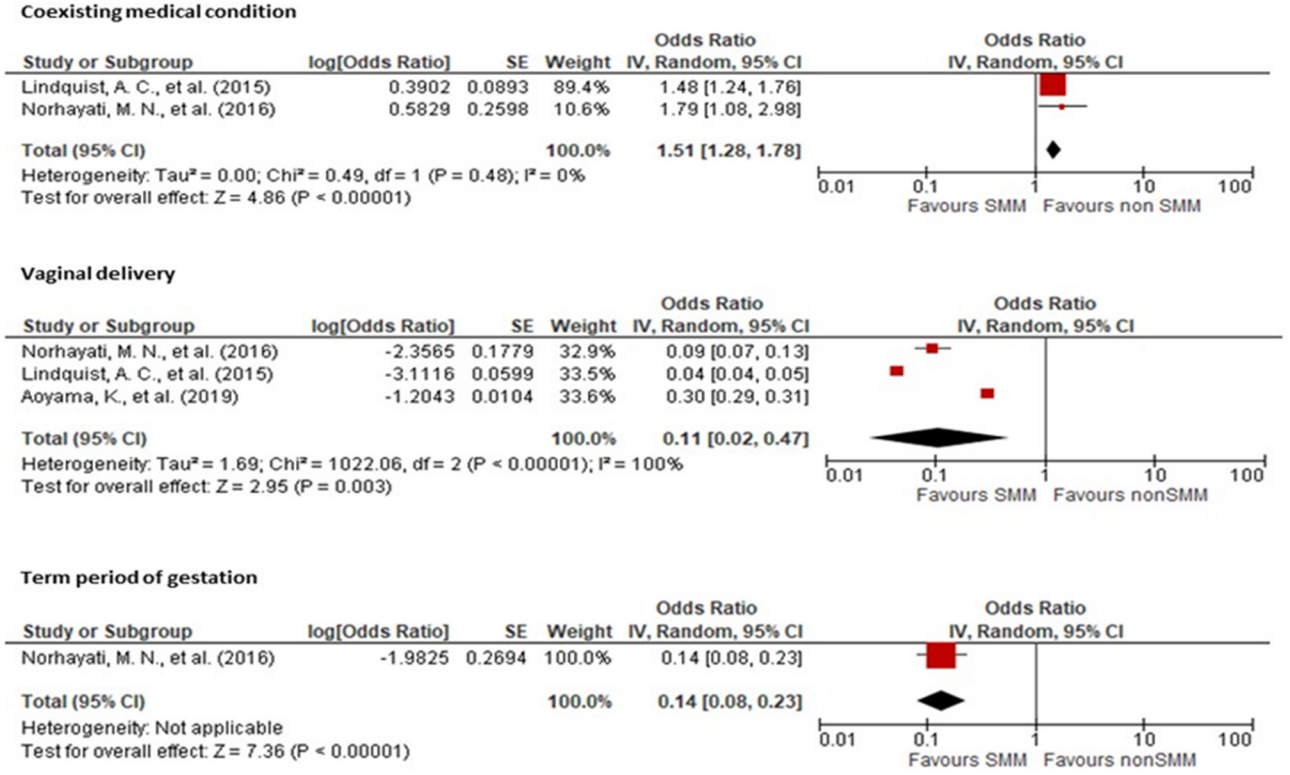

FIGURE 5 | Forest plot showing the association of history of coexisting medical conditions, vaginal delivery, and gestational period with severe maternal morbidity.

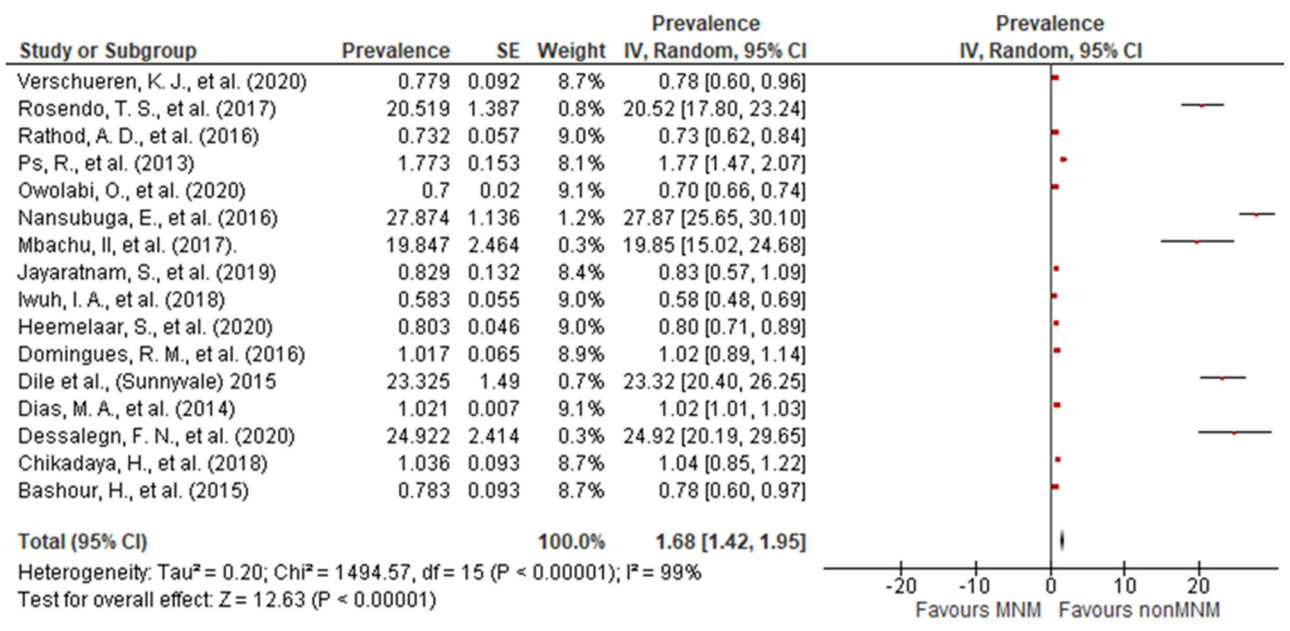

FIGURE 6 | Forest plot depicting the prevalence of maternal near miss.

vaginal delivery. Four studies (12, 19, 20, 25) showed a significant association between young maternal age and SMM with an OR of 0.71 (95% CI: 0.60, 0.83) when compared with older women. Additionally, three studies (12, 19, 20) showed a significant

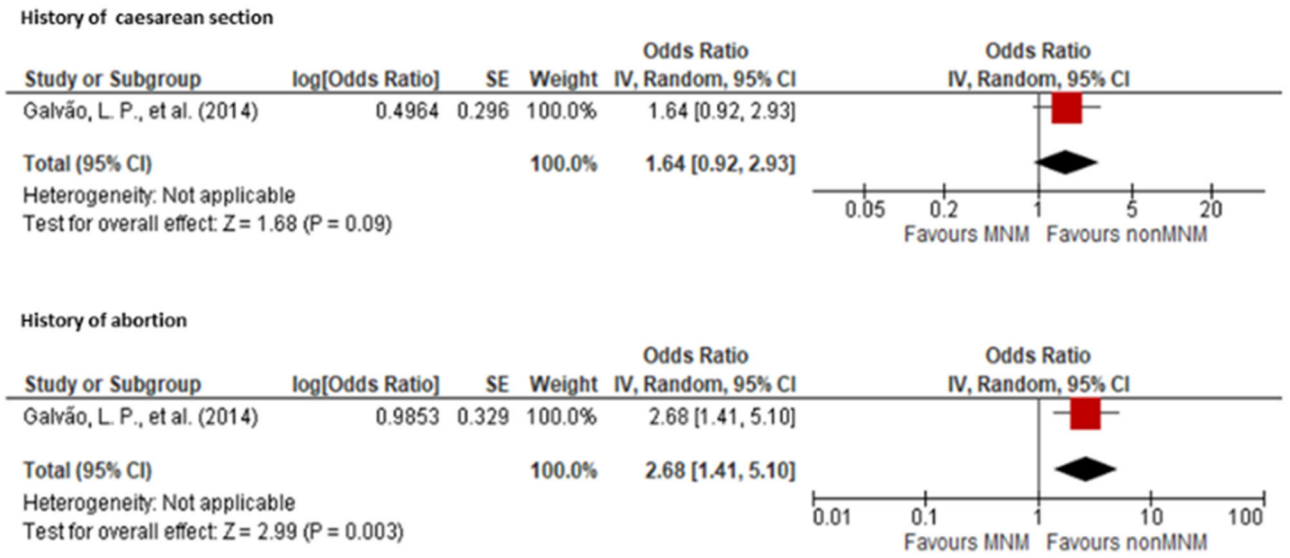

FIGURE 7 | Forest plot showing the association of history of cesarean section and abortion with maternal near miss.

association between singleton pregnancies and SMM with an OR of 0.42 (95% CI: 0.32, 0.55) when compared to twin pregnancies (**Figure 3**).

Two studies (19, 25) showed no association between parity and SMM occurrence with an OR of 1.17 for primiparous women (95% CI: 0.92, 1.50) when compared to multiparous women. Likewise, two studies (12, 19) showed no association between history of abortion and SMM occurrence with an OR of 1.17 (95% CI: 0.86, 1.61) (**Figure 4**) when compared to women without a history of abortion.

Two studies (12, 19) showed a significant association between coexisting medical conditions and SMM with an OR of 1.51 (95% CI: 1.28, 1.78) when compared to mothers without medical conditions. Three studies (12, 19, 25) showed an association between vaginal delivery and SMM with an OR of 0.11 (95% CI: 0.02, 0.47) when compared to cesarean delivery. Lastly, one study showed an association between full-term delivery and SMM with an OR of 0.14 (95% CI: 0.08, 0.23) when compared to pre-term delivery (**Figure 5**).

Maternal Near Miss

Sixteen articles were included in the estimation of the pooled prevalence of MNM. A wide variance in the prevalence of MNM was observed. The lowest reported prevalence was 0.58% (33) and the highest was 27.87% (28). The overall pooled prevalence of MNM was 1.68% (95% CI: 1.42, 1.95) (**Figure 6**).

One study (23) reported an association between a history of cesarean section and MNM with an OR of 2.68 (95% CI: 1.41, 5.10) compared to women without a history of cesarean section. Additionally, the same study (23) showed an association between a history of abortion and MNM with an OR of 1.64 (95% CI: 0.92, 2.93) when compared to women with no history of abortion (**Figure 7**).

DISCUSSION

In our analysis, the worldwide prevalence of SMM and MNM was 2.45 and 1.68%, respectively. The risk factors of history of cesarean section, advanced maternal age, multiple pregnancies, co-existing medical conditions, and cesarean birth were associated with SMM, while the sole reported risk factor for MNM was a history of cesarean section.

Older maternal age has been associated with a greater likelihood of having pre-existing medical conditions, a higher risk of obstetric complications, maternal morbidity, and an increased risk of progression from SMM to death (42). In our review, it can be concluded that advanced maternal age increases the risk of SMM. Contrary to the results of other reviews, we found that maternal morbidity was higher in mothers at both ends of the age spectrum, such as those of age >35 years and adolescents (43).

According to a review (43), national estimates from vital registration in the United States suggest that adolescents have a lower MMR than women of age >20 years. The same review also reported statistics from the United Kingdom showing that the MMR for women of age under 20 years is slightly higher than that of women of age 20–24 years but lower than that of women of age >25 years. Conversely, data from Australia suggest that the MMR for women of age under 20 years is higher than those of all other age groups apart from women of age >40 years. Evidence from both developing and developed countries also suggests that risks are greater for younger adolescents, with girls of age 15 years or younger having higher mortality rates than older adolescents. In most countries, adolescent births are concentrated among poorer, less educated women, which further compounds their disadvantaged situation by disrupting school attendance and limiting future livelihood opportunities.

In terms of physiological risk, the evidence is somewhat conflicting. Still, some evidence suggests that young women are at increased risk of several direct causes of maternal mortality, such as eclampsia, and indirect causes, such as obstructed labor. A study in Latin America also showed increased risks of hemorrhage and sepsis in young women, particularly those under 16 years of age (43).

According to a report by the Centers for Disease Control and Prevention, the MMR in the United States increased gradually with increasing maternal age and particularly in women older than 35 years, specifically, a 3.5-fold increase in MMR. This increased rate of maternal mortality is mostly attributed to comorbidities and coexisting medical conditions, such as metabolic syndrome, past and current cancer, cardiovascular, renal, and autoimmune diseases, which are more prevalent among older pregnant women. For instance, hypertension and Type II diabetes are more common in older women, and women older than 35 years have a 2- to 4-fold higher risk of having hypertension compared to women aged 30–34 years (44).

Women with a prior cesarean delivery had almost two times the risk (CI: 1.93, 2.23) of SMM compared to those without a prior cesarean delivery. Prior cesarean delivery is known to be associated with preeclampsia, placenta previa, placenta accreta, placental abruption, uterine rupture, postpartum infection, transfusion, and admission to the intensive care unit (14). The risks of placenta previa and morbidly adherent placenta in subsequent pregnancies increased markedly with an increasing number of prior cesarean sections. Compared with those without a history of cesarean section, pregnant women with a history of cesarean section were significantly more likely to experience uterine rupture, morbidly adherent placenta, MNM, severe maternal outcomes, and placenta previa. Uterine rupture during pregnancy and delivery is one of the most devastating obstetric complications, as it frequently results in life-threatening maternal and fetal compromises (45).

According to the 2018 annual report by the National Perinatal Epidemiology Center of Ireland, 45.4% of women who experienced an SMM in 2016 were nulliparous (46). The SMM rate for multiparous women was 6.46 per 1,000, 32% higher than that of primiparous women. However, nulliparous women had the highest SMM of 7.66 per 1,000 births, 56% higher than primiparous women at 4.91 per 1,000 births.

A French study found that the risk for SMM was significantly higher for unplanned cesarean deliveries at all maternal ages. In contrast, the planned delivery mode analysis showed an increased risk of SMM associated with planned cesarean delivery compared with planned vaginal delivery in only women aged 35 years and older (42).

According to a secondary analysis by the WHO Multicountry Survey on Maternal and Newborn Health (WHOMCS), a cross-sectional study performed in 29 countries, it was found that twin pregnancies had a higher risk of contributing to SMM and mortality in all regions (47). Using the new WHO diagnostic criteria for severe maternal conditions, another recent WHOMCS study identified that twin pregnancies doubled the risk of SMM, tripled the risk of MNM, and increased the risk of maternal death 4-fold when compared to singleton pregnancies. The current review found a higher occurrence of preterm deliveries in SMM, which correlates with the underlying etiology of the women's medical conditions.

According to the WHO, maternal deaths have been described as the tip of the iceberg and maternal morbidity as the base (5). For every woman who dies from pregnancy-related reasons, another 20 to 30 women suffer from acute or chronic morbidity, frequently with long-term consequences that impair their ability to function normally. Women's physical, mental, and sexual health, as well as their ability to perform in particular areas (e.g., cognition, mobility, and social involvement), body image, and socioeconomic position, are all affected by these consequences. Maternal morbidity, like maternal mortality, is expected to be the highest in low- and middle-income nations, particularly among the poorest women. There are no proper standardized results on the implications of SMM. However, it is well-known that it can lead to short- and long-term consequences, which are preventable.

The studies in the current review underwent quality assessment, and only good-quality studies with a low risk of bias were included. There were only a few studies that compared women with and without maternal complications, which did not allow us to identify population risk factors. The heterogeneity in the outcomes ranged from low to high, possibly due to the participants' sociodemographic characteristics. However, subgroup analysis was not possible because of the limited number of studies that had substantial heterogeneity. We involved only three databases for searching. However, MEDLINE is the most extensive database for social and medical sciences and the inclusion of 24 papers is strong enough to conclude the outcome. Moreover, we have displayed the cumulative effect estimates in forest plots that consolidate the findings.

CONCLUSIONS

Notably, identifying the risk factors for severe maternal morbidity and maternal near miss is pertinent to prevent maternal death. Quantifying the strength of association of the risk factors and surveillance of the presence of these factors at primary and tertiary care levels helps to identify the interventions required that can be performed during antenatal care and childbirth. Initiatives such as educational programs, campaigns, and early detection of risk factors contributing to SMM and MNM are recommended. Proper follow-up is important to monitor the progression of maternal health during the antenatal and postnatal periods. We recommend additional studies comparing women with and without SMM and MNM using the WHO definition and criteria.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

NHNH, MNN, and ISB: conceptualization, methodology, and visualization. MNN and NHNH: validation, resources, and data curation. MNN and HRMK: formal analysis and writing of original draft preparation. HRMK: investigation. NHNH, MNN, ISB, and HRMK: writing of review and editing. NHNH: project administration. All authors have read and agreed to the published version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.861028/full#supplementary-material

REFERENCES

1. WHO. *Evaluating the Quality of Care for Severe Pregnancy Complications: The WHO Near-Miss Approach for Maternal Health*. Geneva: World Health Organization (2011).
2. Say L, Souza JP, Pattinson RC. Maternal near miss–towards a standard tool for monitoring quality of maternal health care. *Best Pract Res Clin Obstet Gynaecol.* (2009) 23:287–96. doi: 10.1016/j.bpobgyn.2009.01.007
3. WHO. *Trends in Maternal Mortality: 1990 to 2015: Estimates by WHO, UNICEF, UNFPA, World Bank Group and the United Nations Population Division*. Geneva: World Health Organization (2015).
4. Tuncalp O, Hindin MJ, Souza JP, Chou D, Say L. The prevalence of maternal near miss: A systematic review. *BJOG.* (2012) 119:653–61. doi: 10.1111/j.1471-0528.2012.03294.x
5. Firoz T, Chou D, von Dadelszen P, Agrawal P, Vanderkruik R, Tunçalp O, et al. Measuring maternal health: focus on maternal morbidity. *Bull World Health Organ.* (2013) 91:794–6. doi: 10.2471/BLT.13.117564
6. King JC. Maternal mortality in the United States–why is it important and what are we doing about it? *Semin Perinatol.* (2012) 36:14–8. doi: 10.1053/j.semperi.2011.09.004
7. Van Hanegem N, Miltenburg AS, Zwart JJ, Bloemenkamp KW, Van Roosmalen J. Severe acute maternal morbidity in asylum seekers: a two-year nationwide cohort study in the Netherlands. *Acta Obstet Gynecol Scand.* (2011) 90:1010–6. doi: 10.1111/j.1600-0412.2011.01140.x
8. de Moraes AP, Barreto SM, Passos VM, Golino PS, Costa JE, Vasconcelos MX. Severe maternal morbidity: a case-control study in Maranhao, Brazil. *Reprod Health.* (2013) 10:11. doi: 10.1186/1742-4755-10-11
9. Lindquist A, Knight M, Kurinczuk JJ. Variation in severe maternal morbidity according to socioeconomic position: a UK national case-control study. *BMJ Open.* (2013) 3:6. doi: 10.1136/bmjopen-2013-002742
10. Liu S, Joseph KS, Hutcheon JA, Bartholomew S, León JA, Walker M, et al. Gestational age-specific severe maternal morbidity associated with labor induction. *Am J Obstet Gynecol.* (2013) 209:209.e1-8. doi: 10.1016/j.ajog.2013.05.033
11. van Mello NM, Zietse CS, Mol F, Zwart JJ, van Roosmalen J, Bloemenkamp KW, et al. Severe maternal morbidity in ectopic pregnancy is not associated with maternal factors but may be associated with quality of care. *Fertil Steril.* (2012) 97:623–9. doi: 10.1016/j.fertnstert.2011.12.021
12. Norhayati MN, Nik Hazlina NH, Aniza AA, Sulaiman Z. Factors associated with severe maternal morbidity in Kelantan, Malaysia: A comparative cross-sectional study. *BMC Pregnancy Childbirth.* (2016) 16:185. doi: 10.1186/s12884-016-0980-2
13. Oliveira FC, Jr., Costa ML, Cecatti JG, Pinto e Silva JL, Surita FG. Maternal morbidity and near miss associated with maternal age: the innovative approach of the 2006 Brazilian demographic health survey. *Clinics.* (2013) 68:922–7. doi: 10.6061/clinics/2013(07)06
14. Gray KE, Wallace ER, Nelson KR, Reed SD, Schiff MA. Population-based study of risk factors for severe maternal morbidity. *Paediatr Perinat Epidemiol.* (2012) 26:506–14. doi: 10.1111/ppe.12011
15. Roost M, Altamirano VC, Liljestrand J, Essen B. Does antenatal care facilitate utilization of emergency obstetric care? A case-referent study of near-miss morbidity in Bolivia. *Acta Obstet Gynecol Scand.* (2010) 89:335–42. doi: 10.3109/00016340903511050
16. van Dillen J, Zwart JJ, Schutte J, Bloemenkamp KW, van Roosmalen J. Severe acute maternal morbidity and mode of delivery in the Netherlands. *Acta Obstet Gynecol Scand.* (2010) 89:1460–5. doi: 10.3109/00016349.2010.519018
17. Aromataris E, Munn Z. *JBI Manual for Evidence Synthesis*. The Joanna Briggs Institute. Adelaide (2020). doi: 10.46658/JBIMES-20-01
18. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. *Cochrane Handbook for Systematic Reviews of Interventions version 6.1* (updated September 2020). Cochrane (2020). doi: 10.1002/9781119536604
19. Lindquist AC, Kurinczuk JJ, Wallace EM, Oats J, Knight M. Risk factors for maternal morbidity in Victoria, Australia: a population-based study. *BMJ Open.* (2015) 5:e007903. doi: 10.1136/bmjopen-2015-007903
20. Hitti J, Sienas L, Walker S, Benedetti TJ, Easterling T. Contribution of hypertension to severe maternal morbidity. *Am J Obstet Gynecol.* (2018) 219:405.e1-405. doi: 10.1016/j.ajog.2018.07.002
21. Dzakpasu S, Deb-Rinker P, Arbour L, Darling EK, Kramer MS, Liu S, et al. Severe maternal morbidity surveillance: Monitoring pregnant women at high risk for prolonged hospitalisation and death. *Paediatr Perinat Epidemiol.* (2020) 34:427–439. doi: 10.1111/ppe.12574
22. Das I, Datta M, Samanta S, Mahapatra B, Mukherjee P. A cross-sectional study on post-partum severe acute maternal morbidity and maternal deaths in a Tertiary Level Teaching Hospital of Eastern India. *Int J Women Health Reproduct Sci.* (2014) 2:113–8. doi: 10.15296/ijwhr.2014.18
23. Galvão LP, Alvim-Pereira F, de Mendonça CM, Menezes FE, Góis KA, Ribeiro RF, et al., et al. The prevalence of severe maternal morbidity and near miss and associated factors in Sergipe, Northeast Brazil. *BMC Pregnancy Childbirth.* (2014) 14:25. doi: 10.1186/1471-2393-14-25
24. Zhang T, Wang H, Wang X, Yang Y, Zhang Y, Tang Z, et al. The adverse maternal and perinatal outcomes of adolescent pregnancy: a cross sectional study in Hebei, China. *BMC Pregnancy Childbirth.* (2020) 20:339. doi: 10.1186/s12884-020-03022-7
25. Aoyama K, Pinto R, Ray JG, Hill AD, Scales DC, Lapinsky SE, et al. Association of maternal age with severe maternal morbidity and mortality in Canada. *JAMA network open.* (2019) 2:e199875. doi: 10.1001/jamanetworkopen.2019.9875
26. Bashour H, Saad-Haddad G, DeJong J, Ramadan MC, Hassan S, Breebaart M, et al. A cross sectional study of maternal "near-miss" cases in major public hospitals in Egypt, Lebanon, Palestine and Syria. *BMC Pregnancy Childbirth.* (2015) 15:296. doi: 10.1186/s12884-015-0733-7
27. Dessalegn FN, Astawesegn FH, Hankalo NC. Factors associated with maternal near miss among women admitted in West Arsi Zone Public Hospitals, Ethiopia: unmatched case-control study. *J Pregnancy.* (2020) 2020:6029160. doi: 10.1155/2020/6029160
28. Nansubuga E, Ayiga N, Moyer CA. Prevalence of maternal near miss and community-based risk factors in Central Uganda. *Int J Gynaecol Obstet.* (2016) 135:214–20. doi: 10.1016/j.ijgo.2016.05.009
29. Rosendo TS, Roncalli AG, Azevedo GD. Prevalence of maternal morbidity and its association with socioeconomic factors: a population-based survey of a city in Northeastern Brazil. *Rev Bras Ginecol Obstet.* (2017) 39:587–95. doi: 10.1055/s-0037-1606246

30. Chikadaya H, Madziyire MG, Munjanja SP. Incidence of maternal near miss in the public health sector of Harare, Zimbabwe: a prospective descriptive study. *BMC Pregnancy Childbirth.* (2018) 18:458. doi: 10.1186/s12884-018-2092-7
31. Rathod AD, Chavan RP, Bhagat V, Pajai S, Padmawar A, Thool P. Analysis of near-miss and maternal mortality at tertiary referral centre of rural India. *J Obstet Gynaecol India.* (2016) 66:295–300. doi: 10.1007/s13224-016-0902-2
32. Verschueren KJ, Kodan LR, Paidin RR, Samijadi SM, Paidin RR, Rijken MJ, et al. Applicability of the WHO maternal near-miss tool: a nationwide surveillance study in Suriname. *J Glob Health.* (2020) 10:020429. doi: 10.7189/jogh.10.020429
33. Iwuh IA, Fawcus S, Schoeman L. Maternal near-miss audit in the Metro West maternity service, Cape Town, South Africa: a retrospective observational study. *S Afr Med J.* (2018) 108:171–5. doi: 10.7196/SAMJ.2018.v108i3.12876
34. Dias MA, Domingues RM, Schilithz AO, Nakamura-Pereira M, Diniz CS, Brum IR, et al. Incidence of maternal near miss in hospital childbirth and postpartum: data from the Birth in Brazil study. *Cad Saude Publica.* (2014) 30(Suppl. 1):S1–12. doi: 10.1590/0102-311X00154213
35. Domingues RM, Dias MA, Schilithz AO, Leal MD. Factors associated with maternal near miss in childbirth and the postpartum period: findings from the birth in Brazil National Survey, 2011-2012. *Reprod Health.* (2016) 13:115. doi: 10.1186/s12978-016-0232-y
36. Heemelaar S, Josef M, Diener Z, Chipeio M, Stekelenburg J, van den Akker T, et al. Maternal near-miss surveillance, Namibia. *Bull World Health Organ.* (2020) 98:548–57. doi: 10.2471/BLT.20.251371
37. Mbachu, II, Ezeama C, Osuagwu K, Umeononihu OS, Obiannika C, et al. A cross sectional study of maternal near miss and mortality at a rural tertiary centre in southern Nigeria. *BMC Pregnancy Childbirth.* (2017) 17:251. doi: 10.1186/s12884-017-1436-z
38. Ps R, Verma S, Rai L, Kumar P, Pai MV, Shetty J. "Near miss" obstetric events and maternal deaths in a tertiary care hospital: an audit. *J Pregnancy.* (2013) 2013:393758. doi: 10.1155/2013/393758
39. Dile M, Seyum T. Proportion of maternal near misses and associated factors in referral hospitals of Amhara regional state, Northwest Ethiopia: institution based cross sectional study. *Gynecol Obstet.* (2015) 5:2161. doi: 10.4172/2161-0932.1000308
40. Jayaratnam S, Soares M, Jennings B, Thapa AP, Woods C. Maternal mortality and 'near miss' morbidity at a tertiary hospital in Timor-Leste. *Aust N Z J Obstet Gynaecol.* (2019) 59:567–72. doi: 10.1111/ajo.12940
41. Owolabi O, Riley T, Juma K, Mutua M, Pleasure ZH, Amo-Adjei J, et al. Incidence of maternal near-miss in Kenya in 2018: findings from a nationally representative cross-sectional study in 54 referral hospitals. *Sci Rep.* (2020) 10:15181. doi: 10.1038/s41598-020-72144-x
42. Korb D, Goffinet F, Seco A, Chevret S, Deneux-Tharaux C. Risk of severe maternal morbidity associated with cesarean delivery and the role of maternal age: a population-based propensity score analysis. *Can Med Assoc J.* (2019) 191:E352–60. doi: 10.1503/cmaj.181067
43. Nove A, Matthews Z, Neal S, Camacho AV. Maternal mortality in adolescents compared with women of other ages: evidence from 144 countries. *Lancet Global Health.* (2014) 2:e155–64. doi: 10.1016/S2214-109X(13)70179-7
44. Attali E, Yogev Y. The impact of advanced maternal age on pregnancy outcome. *Best Pract Res Clin Obstet Gynaecol.* 70:2–9. doi: 10.1016/j.bpobgyn.2020.06.006
45. Kietpeerakool C, Lumbiganon P, Laopaiboon M, Rattanakanokchai S, Vogel JP, Gülmezoglu AM. Pregnancy outcomes of women with previous caesarean sections: secondary analysis of World Health Organization Multicountry Survey on Maternal and Newborn Health. *Sci Rep.* (2019) 9:9748. doi: 10.1038/s41598-019-46153-4
46. Leitao S. *Severe Maternal Morbidity in Ireland.* (2018).
47. Santana DS, Silveira C, Costa ML, Souza RT, Surita FG, Souza JP, et al. Perinatal outcomes in twin pregnancies complicated by maternal morbidity: evidence from the WHO Multicountry Survey on Maternal and Newborn Health. *BMC Pregnancy Childbirth.* (2018) 18:449. doi: 10.1186/s12884-018-2082-9

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REVIEW
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The Role of Human Epididymis Protein 4 in the Diagnosis and Prognosis of Diseases: An Umbrella Review of Systematic Reviews and Meta-Analyses of Observational Studies

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Background: The application of human epididymis protein 4 (HE4) in diverse health diseases, especially in cancers, has been extensively studied in recent decades. To summarize the existing evidence of the aforementioned topic, we conducted an umbrella review to systematically evaluate the reliability and strength of evidence regarding the role of HE4 in the diagnostic and prognostic estimate of diverse diseases.

Methods: Electronic searches in PubMed, Web of Science, and Embase databases were conducted from inception to September 16, 2021, for meta-analyses, which focus on the role of HE4 in the diagnosis and prognosis of diseases. This study protocol has been registered at PROSPERO (CRD42021284737). We collected the meta-analysis effect size of sensitivity, specificity, positive predictive value, and negative predictive value from diagnostic studies and gathered the hazard ratio (*HR*) of disease-free survival, overall survival, and progression-free survival from prognostic studies. For each systematic review and meta-analysis, we used a measurable tool for evaluating systematic reviews and meta-analysis (AMSTAR) to evaluate the methodological quality. Additionally, we assessed the quality of evidence on estimating the ability of HE4 in the diagnosis and prognosis of diverse diseases by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guideline.

Results: Overall, 20 meta-analyses including a total of 331 primary studies of different diseases were examined, mainly including ovarian cancer (OC) (n = 9), endometrial cancer (EC) (n = 6), and lung cancer (LC) (n = 4). The methodological qualities of all studies were rated as moderate (45%) or high (55%) by the AMSTAR. According to the GRADE, the certainties of 18 diagnostic pieces of evidence (9 for sensitivity and 9 for specificity) were rated as moderate (34%), low (33%), and very low (33%). Moreover,

outcomes from prognosis studies showed evidence (1 for disease-free survival) with high certainty in regard to cancers (such as EC, OC, and LC) with the remaining three being moderate.

Conclusion: This umbrella review suggested that HE4 was a favored biomarker in the prognosis of cancers, which was supported by high certainty of evidence. Additionally, HE4 could provide a suitable method for the diagnosis of EC, OC, and LC with moderate certainty evidence. Further large prospective cohort studies are needed to better elucidate the diagnostic and prognostic role of HE4 in diseases.

Keywords: diagnosis, GRADE, human epididymis protein 4, prognosis, umbrella review

INTRODUCTION

The existence or quantitative change of biomarkers can indicate the nature of the diseases and contribute to a clear understanding of the progress of the diseases (1). Biomarker-disease relationships have been extensively investigated. Compared with other diagnostic methods, serum biomarkers, such as carcinoembryonic antigen (2) and squamous cell carcinoma antigen (3) take priority due to their low inspection cost and non-invasiveness, which is an essential step for the screening, diagnosis, classification, and prognosis of diverse diseases. Carbohydrate antigen 125 (CA125) levels are widely used for the diagnosis and prognosis of diseases (4, 5), but human epididymis protein 4 (HE4) has a higher true positive rate and true negative rate than CA125, so the clinical application of HE4 is wider than that of CA125. HE4 is a secretory glycoprotein, transcribed and translated from the whey acidic protein 4-disulfide core domain 2 genes (6). HE4 was known as one of the most promising novel serum biomarkers for the diagnosis, prognosis, and monitoring of diverse diseases, and its ability on disease diagnosis was approved and supported by Food and Drug Administration (7, 8). HE4 is considered as a potential biomarker for ovarian cancer (OC) because it shows higher specificity and diagnostic accuracy than other biomarkers (9). The functions of HE4 in the field of biomarkers were found in 2003 (10). Considering the two well-researched protein co-expression genes near HE4, secretory leukocyte protease inhibitor and P13, which are demonstrated to have angiogenesis regulation, cell growth, cell migration, immune, antimicrobial, and anti-HIV functions (11, 12).

Previous epidemiological studies have investigated the diagnostic role of HE4 in some diseases, such as OC (13, 14), lung cancer (LC) (15), renal fibrosis (16), breast cancer (17), and endometrial carcinoma (EC) (18). For example, the results of a meta-analysis showed that HE4 had higher specificity (0.84 vs. 0.57) and similar sensitivity (0.79 vs. 0.81) than CA125 for differentiating malignant from benign pelvic mass disease (19), similar findings could be observed in those meta-analyses (7, 20, 21). However, a meta-analysis demonstrated that HE4 was no better than CA125 for OC prediction (22). Due to the high disease heterogeneity and risk of bias, there is no consensus on the accuracy of HE4 in different diseases. On the other hand, the prognostic role of HE4 expression in diseases has also been reported (23–26). However, the findings from these studies remain controversial. For example, Kalapotharakos et al. (23) reported that the serum level of HE4 was a prognostic marker for overall survival (OS) among Sweden women with epithelial OC. In addition, a previous study (25) reported that 2-year OS was not associated with HE4 levels (positive vs. negative). The disparity in these studies is probably attributed to different kinds of diseases, histological types of the same disease, the proportion of the usual population, and methods/instruments for the measurement of HE4 levels. Therefore, we sought a method to evaluate the diagnostic value (sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio) and prognostic value [OS, disease-free survival (DFS), and progression-free survival (PFS)] of HE4 in diverse diseases.

Umbrella reviews could find the disparity, analyze the reason, and summarize the information of a specific topic. In the umbrella review, the strength and credibility of associations can be assessed using standardized methods, such as evaluating bias or grading the evidence (27). Umbrella reviews can provide an overall examination of the role of HE4 in the diagnosis and prognosis of diseases, and compare and contrast the results of published systematic reviews. Hence, we conducted an umbrella review to consolidate the existing evidence to estimate the ability of HE4 in the diagnosis and prognosis of diverse diseases.

METHODS

Literature Search and Eligibility Criteria

We performed an umbrella review, which was the systematic collection and assessment of multiple systematic reviews and meta-analyses about the role of HE4 in the diagnosis and prognosis of diseases. The report of this umbrella review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group (28). Our protocol has been registered in PROSPERO (CRD42021284737). PubMed, Web of Science, and Embase databases were searched from inception to September 16, 2021, for related systematic reviews and meta-analyses. In addition, we hand-searched the reference lists of eligible articles to prevent omissions. The present search strategy used the following keywords: "(human epididymis 4 OR HE4 protein OR human epididymis secretory protein 4 OR wap 4-disulfide core domain proteins 2 OR whey acidic protein four disulfide core protein

2) AND (meta-analysis OR systematic overview OR systematic review)" (**Supplementary Appendix 1**).

Inclusion and Exclusion Criteria

Two authors (Sun ML and Li YZ) screened all records independently. Differences were resolved through consensus with the third author (Gong TT). The inclusion criteria were as follows: (1) published systematic reviews and the meta-analyses of observational studies in English; (2) articles assessing the role of HE4 in the diagnosis and prognosis of diseases; (3) studies providing critical data [diagnosis (sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio) and prognosis (PFS, DFS, OS, disease-specific survival, mortality, and progression/recurrence)]. This topic defined exposure as HE4 and outcome as the diagnosis and prognosis of diverse diseases. When two or more systematic reviews and meta-analyses examined the exact same exposures and outcomes, we included the larger or largest number of original studies to avoid duplicate assessments of the same topic (29).

We excluded articles if they met the following criteria: (1) narrative reviews, systematic reviews, and meta-analyses that involved fewer than three original studies; (2) articles that did not report necessary study-specific data (30–32); (3) studies exploring genetics or experiments in animals, *in vitro*, and *in vivo*; (4) full texts that were not available. For each eligible systematic review and meta-analyses, we collected all the exposure and outcome of the study we were interested in, such as subgroup analysis and dose-response analysis.

Data Extraction

Relevant data from each included systematic review and meta-analysis were extracted by two investigators (Sun ML and Li YZ) independently. The final decision was reached by a third investigator (Gong TT) when in case of discrepancies. From each eligible systematic review and meta-analysis, we recorded the first author name, publication year, journal, exposure, effect sizes, number of studies, and outcomes. For the information of the original diagnostic study, we further extracted the first author, publication year, cutoff value, case number, total population, and adjusted estimates (sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio). For the primary studies on prognosis, we extracted event numbers, total populations, comparisons, and effect size [hazard ratio (*HR*)]. If necessary, we would search for information from primary studies to find the missing data.

Evaluation of the Quality of Included Meta-Analyses

The quality of each eligible systematic review and meta-analyses was evaluated based on a measurement tool for evaluating systematic reviews and meta-analyses (AMSTAR) (33). The evaluations were performed independently by two researchers (Sun ML and Li YZ) and determined by a third researcher (Gong TT) when differences occurred. The AMSTAR tool is an 11-item questionnaire that asks reviewers to answer yes, no, cannot answer, or not applicable (33). If an item of the criteria is met with "yes," one point will be awarded. The final total score of 11-items can measure the methodological quality of systematic reviews and meta-analyses. The AMSTAR score was graded as high (8–11), moderate (4–7), and low (0–3) quality (33).

Grading of the Evidence

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) principles to evaluate the credibility of evidence from the eligible systematic reviews and meta-analyses (34–36). Each body of evidence was evaluated independently by two authors (Sun ML and Li YZ), and the third author (Gong TT) made the decision when differences arose. There were four levels of evidence through the GRADE tool: high, moderate, low, and very-low quality (37–40). For the studies of diagnostic test accuracy, a body of evidence begins with high certainty (34). Moreover, there was no sufficient guidance available on the application of the three GRADE criteria for upgrading evidence related to diagnostic test accuracy studies (35), thus we downgraded the evidence on the basis of prespecified criteria. The GRADE method proposes 5 factors rating down certainty in the evidence, such as the risk of bias, inconsistency, indirectness, imprecision, and publication bias (35, 41). Besides, for prognostic studies, the initial quality of evidence was high. We downgraded the quality of the evidence (risk of bias, inconsistency, indirectness, imprecision, and publication bias) and upgraded the quality (large effect, dose response, and plausible residual confounding) (41).

RESULTS

Study Selection

Overall, the search retrieved 270 articles from three databases (**Figure 1**). After the removal of duplicates, 163 articles were identified. Then after screening the titles and abstracts, 109 articles were excluded. Subsequently, a further 34 articles were excluded for the following reasons: 13 presented insufficient data, 6 did not conduct meta-analysis, 4 explored outcomes that we were not interested in, 4 published not in English, the full text of 3 articles were not available, 2 published duplicated reports, 1 explored exposure that we were not interested in, and 1 conducted less than three original studies. Ultimately, 20 studies (7, 8, 15, 19–22, 42–54) were eligible to be included in the main analysis.

Diagnostic Meta-Analysis

As reported in **Table 1**, 250 primary studies of 17 meta-analyses were included in the 16 articles for diagnosis (7, 15, 19–22, 42, 43, 45–50, 52, 53). These sixteen articles were published between 2012 and 2021. The studies enrolled in the meta-analyses were all diagnostic accuracy tests, and the median number of original studies per meta-analysis was 12 (range from 4 to 45). The number of participants ranged from 891 to 10,671, and the number of cases exceeded 1,000 in 10 meta-analyses. The median cutoff value of HE4 ranged from 19 to 82 pmol/L. HE4 had the highest diagnostic value in OC (48) with an area under

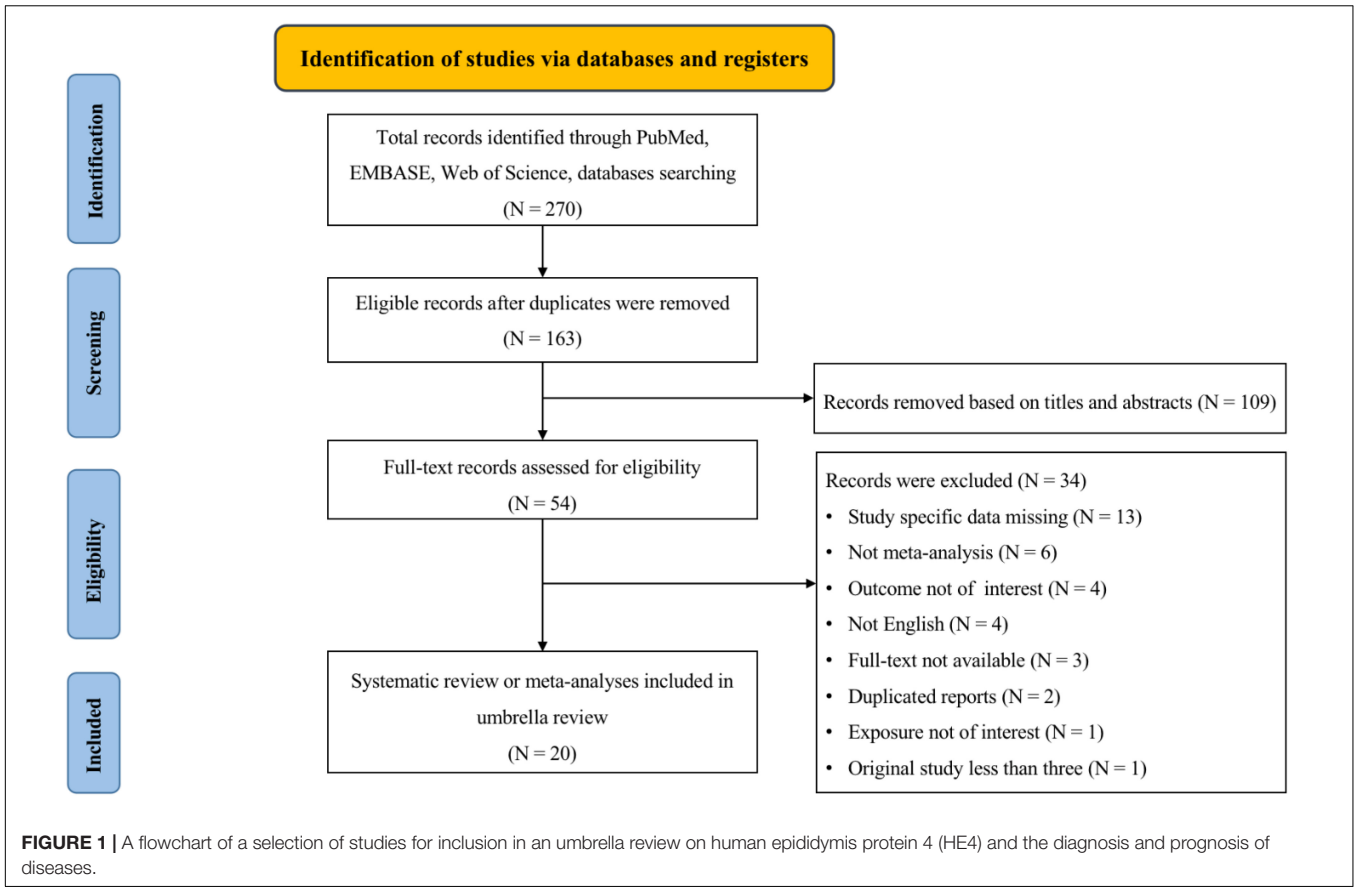

FIGURE 1 | A flowchart of a selection of studies for inclusion in an umbrella review on human epididymis protein 4 (HE4) and the diagnosis and prognosis of diseases.

the curve (AUC) of 0.96 [95% confidence interval (*CI*) = 0.95–0.98], and the lowest diagnostic value in EC (46) with an AUC of 0.75 (95% *CI* = 0.81–0.87). The numbers of meta-analysis evaluating the role of HE4 expression in the diagnosis of OC, EC, LC, EOC, and malignant pelvic mass were seven, five, three, one, and one, respectively. Furthermore, twelve and five meta-analyses systematically evaluated the quality of the included studies according to the Quality Assessment of Diagnostic Studies version 2 (QUADAS-2) tool and the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool, respectively.

Prognostic Meta-Analysis

Table 2 showed the nine meta-analyses that involved 81 original studies in four articles for prognosis (8, 44, 51, 54). These 4 articles were published between 2017 and 2020. Each meta-analysis combined 3–23 original cohort study estimates, with a median of 8. The number of participants ranged from 484 to 3,564. The lowest number of events in the meta-analyses was 63 and the highest number was 1,051. The types of outcomes in these meta-analyses included EC, OC, LC, and gastric cancer (GC). Of the nine meta-analyses, four, two, and three meta-analyses assessed the association between HE4 expression and OS, DFS, and PFS, respectively. Among nine meta-analyses, only four conducted the quality assessment for individual studies by the Newcastle-Ottawa Quality Assessment Scale (NOS).

The Methodological Quality of the Meta-Analyses

Among the 20 articles (both for diagnosis and prognosis) included in our umbrella review, 11 (55%) articles were rated as high quality and nine (45%) were defined as a moderate quality based on the AMSTAR criteria (**Supplementary Figure 1**). The common flaws were that gray literature was not considered in the literature search (85%), and the list of excluded studies was not presented (100%).

Grading of Evidence

In total, eighteen and four pieces of evidence met the conditions of the GRADE, which were from nine diagnostic articles (7, 15, 20, 21, 42, 43, 48, 52, 53) and two prognostic articles (8, 44), respectively. Due to the lack of the quality of assessment and bias publication, eighteen pieces of evidence were eventually evaluated by the GRADE assessment (**Table 3**). No evidence in diagnosis was rated as high evidence, whereas six of the pieces of evidence were supported by moderate. In addition, six pieces of evidence presented low evidence, and the others were supported by very-low evidence.

Only four pieces of evidence were graded by GRADE in the umbrella review, and only one association between HE4 expression and DFS was supported by high evidence (**Table 4**). Moreover, the association between HE4 and PFS/OS presented

TABLE 1 | Main characteristics of the included systematic reviews or meta-analysis that evaluate the role of HE4 in the diagnosis of diseases.

Outcome	References	effect size	No. of studies	No. of population	No. of cases	Cut-off (pmol/L), MD	AUC	Quality of assessment
Endometrial cancer	Liu et al. (46)	SE, SP, PLR, NLR, DOR	17	3,167	1,807	74	0.75	QUADAS-2
	Chen et al. (43)	SE, SP, DOR	8	1,832	1,129	70	0.77	QUADAS
	Bie et al. (49)	SE, SP, DOR	6	1,551	791	64	0.83	QUADAS-2
	Hu et al. (7)	SE, SP, DOR	21	4,623	2,229	75	0.78	QUADAS-2
	Li et al. (21)	SE, SP	12	3,150	1,442	77	0.88	QUADAS
Ovarian cancer	Jia et al. (52)	SE, SP, PLR, NLR, DOR	7	986	413	19	0.93	QUADAS-2
	Ferraro et al. (20)	SE, SP, PLR, NLR	13	3,471	1,200	74	N/A	QUADAS-2
	Yu et al. (47)	SE, SP, PLR, NLR	12	2,607	779	72	0.95	QUADAS
	Yang et al. (48)	SE, SP, PLR, NLR	31	7,045	2,112	70	0.96	QUADAS-2
	Huang et al. (53)	SE, SP	18	4,673	1,369	72	0.91	QUADAS-2
	Macedo et al. (50)	SE, SP	45	10,671	3,946	74	0.92	QUADAS
	Li et al. (22)	SE, SP	5	891	388	74[a]	0.95	QUADAS-2
Epithelial ovarian cancer	Li et al. (22)	SE, SP	4	916	265	70[a]	0.95	QUADAS-2
Malignant pelvic mass	Olsen et al. (19)	SE, SP	7	1,403	433	72	N/A	QUADAS-2
Lung cancer	Cheng et al. (42)	SE, SP, PLR, NLR, DOR	7	1,245	715	75	0.86	QUADAS
	He et al. (15)	SE, SP, PLR, NLR	21	3,599	1,893	82	0.86	QUADAS-2
	Yan et al. (45)	SE, SP	16	3,202	1,756	77	0.86	QUADAS-2

DOR, diagnostic odds ratio; HE4, human epididymis protein; MD, median; NLR negative likelihood ratio; N/A, not available; PLR, positive likelihood ratio; QUADAS, Quality Assessment of Diagnostic Studies tool; QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies version 2 tool; SE, sensitivity; SP, specificity.
[a] *The unit is PM in the systematic review conducted by Li et al. (22).*

moderate evidence (n = 3). There was no association indicating low or very-low evidence.

DISCUSSION

Principal Findings

In this umbrella review, we provided an overview of the role of HE4 in the diagnosis and prognosis of diverse diseases using the AMSTAR tool and GRADE guidelines. In the study exploring the diagnostic role of HE4, six associations (outcomes of OC, EC, and LC) were supported by moderate evidence, and all of them had serious limitations of inconsistency in the evaluation by GRADE guideline. For the prognostic studies, there was only one evidence of HE4 performing its action in the clinical setting as a suitable biomarker with high certainty while the remaining three associations were moderate. The key findings echo the scientific question we raised at the outset of the present study, whether HE4 could be a useful biomarker for disease diagnosis and prognosis.

Explanation Findings From Prognostic Meta-Analyses

According to the criteria of the GRADE guideline, there was one high-quality evidence, Dai et al. (44) conducted a meta-analysis and reported that the HE4 level can provide a useful prognostic biomarker (only for DFS) for patients with cancers (987 patients with EC, 211 patients with LC, and 98 patients with OC). The prognostic effect of HE4 on the disease was mainly focused on OC, but a systematic review suggested that the prognostic role of HE4 in other types of cancers needed more endeavor than before (55). Previous articles or meta-analyses suggested that OC (23, 56), EC (57), LC (58), and GC (59) patients with a high concentration of HE4 have shorter survival or more likely metastasis than those with low concentrations. However, to the best of our knowledge, our umbrella review is the first to present the evidence from previous systematic reviews and meta-analyses regarding the roles of HE4 in the diagnosis and prognosis of diverse diseases. Besides, we found that the prognosis had a higher quality level of evidence than the diagnosis. Of note, the risk of bias was the main reason for the discrepancy in overall certainty between diagnosis and prognosis. We inferred that the QUADAS/QUADAS-2 scale used for diagnosis was more rigorous than the NOS scale used for prognosis study (most included cohort studies). However, considering the different stages of different study designs, we suggested the following framework of Whiting when conducting a quality assessment (60).

In addition, the meta-analysis conducted by Dai et al. provided three different pieces of evidence (high certainty evidence for DFS, moderate certainty evidence for OS and PFS). One possible explanation for the lower certainty evidence for OS and PFS is that they both have publication bias. Publication bias was an

TABLE 2 | Main characteristics of the included systematic reviews or meta-analysis that evaluate the role of HE4 in the prognosis of diseases.

Outcomes	References	Disease type	Level of comparison	Effect size, HR	No. of studies	No. of population	No. of events	Quality of assessment
Overall survival	He et al. (54)	EC	High vs. low	2.71 (1.28, 4.15)	5	755	206	N/A
	Dai et al. (44)	EC, OC, LC, GC		2.15 (1.77, 2.62)	23	3,564	1,051	NOS
	Yuan et al. (51)	OC		1.91 (1.40, 2.61)	9	1,152	367	N/A
	Zhong et al. (8)	LC		1.73 (1.19, 2.52)	7	1,312	378	NOS
Disease-free survival	He et al. (54)	EC		2.00 (1.16, 2.84)	5	971	94	N/A
	Dai et al. (44)	EC, OC, LC, GC		2.50 (1.86, 3.37)	8	1,307	133	NOS
Progression-free survival	He et al. (54)	EC		2.81 (0.72, 4.90)	3	484	63	N/A
	Dai et a.l (44)	EC, OC, LC, GC		1.27 (1.11, 1.45)	10	1,272	389	NOS
	Yuan et al. (51)	OC		1.38 (1.13, 1.69)	11	1,102	462	N/A

EC, endometrial cancer; GC, gastric cancer; HE4, human epididymis protein; HR, hazard ratio; LC, lung cancer; MOOSE, Meta-analysis of Observational Studies in Epidemiology guidelines; NOS, Newcastle-Ottawa Quality Assessment Scale; N/A, not available; OC, ovarian cancer.

important factor leading to different quality levels measured by GRADE guidelines, and asymmetry of funnel plots was found in these two pieces of evidence from the same meta-analysis (44), which may arise from the low possibility of publication for studies with negative results. We graded the quality of evidence for the prognostic effect of HE4 only in LC as moderate (downgraded for inconsistency, I^2 is 81%) The heterogeneity could be explained by ethnicity. Zhong et al. concluded that HE4 was associated with OS only in Asian populations but not in Caucasian patients (8).

Explanation Findings From the Diagnostic Meta-Analysis

Our study found that HE4 played a potential role in the diagnosis of OC (20, 48, 52, 53) that was consistent with previous meta-analyses (9, 61). For example, the article reported a high pooled specificity (92%) for HE4, and the AUC of HE4 was higher than that of CA125, with values of 0.89 and 0.85, respectively (61). Besides, Ferraro et al. conducted a study and showed a similar result, and they found HE4 seems to be superior to CA125 in the terms of diagnostic performance (diagnostic sensitivity, specificity, positive likelihood ratios, and negative likelihood ratios) of patients with OC (20). There was sufficient evidence for HE4 is overexpressed in OC, which can reinforce the confidence of our result. The increased level of HE4 can help to improve the specificity for the diagnosis of OC. Dochez et al. reported a specificity of 90.4% for HE4, and the AUC was higher than CA125 alone, with the values of 0.91 and 0.83, respectively (62). Additionally, a study including 762 Korean patients showed that HE4 could be used for differentiating benign gynecological diseases and OC (9). The potential regulatory mechanism of HE4 in the cancer invasion and metastasis of OC could be attributed to the activation of MAPK and FOCAL signaling pathways (63). HE4 participates in the metastasis of OC by regulating the expression of extracellular matrix components, such as LAMC2 and LAMB3 (64).

Of all the certainties of evidence for the association, 50% was very low. We evaluated the quality of evidence on OC through GRADE, and most pieces of evidence were downgraded because of inconsistency ($I^2 > 50\%$), risk of bias (20, 48, 52), and publication bias (20, 48). Specifically, some meta-analyses had a high risk of bias for patient selection, index test (52), and reference standards (48). The difference between these two studies (48, 52) may be attributed to the number of publications (7 vs. 31) and sample type (urine vs. serum). Moreover, the methodological quality of six published meta-analyses by the AMSTAR was moderate, whereas for the remaining three meta-analyses, the methodological quality high. All these nine meta-analyses did not pay attention to the status of publication, such as searching gray literature, which included all languages or screening the references of the included articles. Considering that the gray literature in the search strategy and inclusion criteria can help to reduce the publication bias (65), we encouraged the authors of systematic analysis to search the gray literature.

In addition, the present umbrella review demonstrated that HE4 could play a probable role in the diagnosis of EC, and our results were in line with the previous systematic review and

TABLE 3 | The results of GRADE assessment of the evidence certainty on the association between the diagnostic accuracy of HE4 and diverse diseases.

Outcome	References	Outcomes rated	Downgrade factors					Certainty of the evidence
			Risk of bias	Imprecision	Inconsistency	Indirectness	Publication bias	
Endometrial cancer	Chen et al. (43)	SE	No serious	No serious	Serious limitation[b]	Serious limitation[d]	No serious	⊕⊕○○ low
		SP	No serious	No serious	Serious limitation[b]	Serious limitation[d]	No serious	⊕⊕○○ low
	Hu et al. (7)	SE	No serious	No serious	Serious limitation[b]	No serious	Serious limitation[e]	⊕⊕○○ low
		SP	No serious	No serious	Serious limitation[b]	No serious	Serious limitation[e]	⊕⊕○○ low
	Li et al. (21)	SE	No serious	No serious	Serious limitation[b]	No serious	No serious	⊕⊕⊕○ moderate
		SP	No serious	No serious	Serious limitation[b]	No serious	No serious	⊕⊕⊕○ moderate
Ovarian cancer	Jia et al. (52)	SE	Serious limitation[a]	No serious	Serious limitation[b]	No serious	No serious	⊕⊕○○ low
		SP	Serious limitation[a]	No serious	Serious limitation[b]	No serious	No serious	⊕⊕○○ low
	Ferraro et al. (20)	SE	Serious limitation[a]	No serious	Serious limitation[c]	No serious	Serious limitation[e]	⊕○○○ very low
		SP	Serious limitation[a]	No serious	Serious limitation[b]	No serious	Serious limitation[e]	⊕○○○ very low
	Yang et al. (48)	SE	Serious limitation[a]	No serious	Serious limitation[b]	No serious	Serious limitation[e]	⊕○○○ very low
		SP	Serious limitation[a]	No serious	Serious limitation[b]	No serious	Serious limitation[e]	⊕○○○ very low
	Huang et al. (53)	SE	No serious	No serious	Serious limitation[c]	No serious	No serious	⊕⊕⊕○ moderate
		SP	No serious	No serious	Serious limitation[b]	No serious	No serious	⊕⊕⊕○ moderate
Lung cancer	Cheng et al. (42)	SE	No serious	No serious	Serious limitation [b]	No serious	No serious	⊕⊕⊕○ moderate
		SP	No serious	No serious	Serious limitation[c]	No serious	No serious	⊕⊕⊕○ moderate
	He et al. (15)	SE	Serious limitation[a]	No serious	Serious limitation[b]	Serious limitation[d]	No serious	⊕○○○ very low
		SP	Serious limitation[a]	No serious	Serious limitation[b]	Serious limitation[d]	No serious	⊕○○○ very low

SE, sensitivity; SP, specificity.

[a]*Downgraded by one level for the risk of bias: this domain was downgraded by 1 level because the Quality Assessment of Diagnostic Accuracy Studies version 2 tool.*

[b]*Downgraded by only one level for inconsistency: substantial heterogeneity is seen between studies ($I^2 > 75\%$), whereas heterogeneity was mainly explained.*

[c]*Downgraded by one level for inconsistency: substantial heterogeneity is seen between studies ($50\% < I^2 <= 75\%$).*

[d]*Downgraded by one level for indirectness: the concentration of HE4 measured by different test methods.*

[e]*Downgraded by one level for publication bias: asymmetry on funnel plot, the value of p of Deek's test < 0.1.*

TABLE 4 | The results of GRADE assessment of the evidence certainty on the association between HE4 and diverse diseases in prognosis.

Outcome	References	Downgrade factors					Upgrade factors			Certainty of the evidence
		Risk of bias	Imprecision	Inconsistency	Indirectness	Publication bias	Large effect	Dose-response	Plausible confounding	
OS†	Dai et al. (44)	Not serious	Not serious	Serious limitation[a]	Not serious	Serious limitation[c]	Yes[d]	No	Would Not Reduce Effect	⊕⊕⊕◯ moderate
OS‡	Zhong et al. (8)	Not serious	Not serious	Serious limitation[b]	Not serious	Not serious	No	No	Would Not Reduce Effect	⊕⊕⊕◯ moderate
DFS*	Dai et al. (44)	Not serious	Not serious	Not serious	Not serious	Not serious	Yes[d]	No	Would Not Reduce Effect	⊕⊕⊕⊕ high
PFS*	Dai et al. (44)	Not serious	Not serious	Not serious	Not serious	Serious limitation[c]	No	No	Would Not Reduce Effect	⊕⊕⊕◯ moderate

DFS, disease-free survival; OS, overall survival; PFS, progression-free survival.

†Prognosis of cancers, such as EC, OC, LC, and GC.

**Prognosis of cancers, such as EC, OC, and LC.*

‡Overall survival of LC.

[a]Downgraded by one level for inconsistency: substantial heterogeneity is seen between studies ($I^2 > 50\%$).

[b]Downgraded by only one level for inconsistency: substantial heterogeneity is seen between studies ($I^2 > 75\%$), whereas heterogeneity was mainly explained.

[c]Downgraded by one level for publication bias: asymmetry on funnel plot, the p of Egger's test or Begg's test < 0.05.

[d]Upgraded by only one level for large effect: because of the large magnitude of effect (HR > 2.0).

meta-analysis (21, 32). For example, the meta-analysis identified 12 articles dealing with HE4 and the diagnosis of EC and found that the sensitivity of 0.71 (95% *CI*: 0.56–0.82) and specificity of 0.87 (95% *CI*: 0.80–0.92) (21). Besides, one meta-analysis stated that HE4 is generally a better biomarker than CA125 in EC diagnosis by its higher sensitivity than CA125, and the author suggested that the combination of CA125 and HE4 may enhance the diagnostic sensitivity for patients with EC (43). Besides, the serum HE4 level in patients with EC was enhanced compared with that in benign patients (57, 66). The overexpression of HE4 was associated with cell proliferation, colony formation in soft agar, and the Matrigel invasion of EC cells (67). In addition, the level of HE4 was correlated with the depth of myometrial invasion, which was an important factor in the risk stratification or metastasis of EC (68).

Using GRADE guidelines, the six pieces of evidence from three meta-analyses were all downgraded by one level for inconsistency. The heterogeneity in most meta-analyses may be attributed to the population, intervention, controls, study design, threshold bias, and publication country (21, 50). Of note, we evaluated the indirectness using the test method for HE4 level [electrochemiluminescence (ECLIA) vs. ELISA] (69). Among the eight primary studies included in the meta-analysis (43), three studies used ELISA (26, 70, 71), whereas one study tested the HE4 level by ECLIA (72). Therefore, an indirectness of evidence existed. Moreover, the proportion of high methodological quality of meta-analyses evaluated by the AMSTAR was approximately 50% (3/6). All six meta-analyses did not show a study list of inclusion and exclusion, through which other scientists could repeat the study and confirm the authenticity of these results. Therefore, we encouraged the authors of meta-analyses to provide not only a list of included studies but also an exclusion study list.

We observed that the high expression of HE4 was associated with LC. However, the diagnostic effect of HE4 on LC has been limited. There were some results from other studies consistent with our conclusion (8, 42, 73). For example, an original study found that serum HE4 levels in patients with any histological type of LC (adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and small cell lung carcinoma) were significantly increased compared with those in the control group (73). Thus, the overexpression of HE4 suggested a scientific basis for its potential diagnostic ability in LC. In addition, Cheng et al. conducted a meta-analysis of seven studies and found that the AUC was 0.856 for HE4 for patients with LC (42). In contrast, an original study found that the association between squamous cells LC was weak at 10% (74). The exact biological mechanisms of HE4 expression in LC were limited. One possible explanation was the effect of smoking, which may be correlated with lung chronic inflammation and HE4 levels (14, 75).

For diagnostic studies, the pieces of evidence (sensitivity and specificity) from a meta-analysis were both downgraded for the risk of bias (15). The methodological quality of most primary studies in the meta-analysis (15) was low using QUADAS-2, especially in the patient selection domain (5/21 were high risk, 3/21 were low risk with the remaining were unclear risk of bias). In the evaluation of LC by the AMSTAR, 75% of the

meta-analyses exploring the function of HE4 in LC have high methodological quality. Remarkably, none of those meta-analyses display a CRD number that was registered on PROSPERO. Considering the advantages of prospective registration, such as study design, conduct procedure, and report results (76), we encouraged the author of meta-analyses to register before conducting a new project.

Study Strengths

For strengths, to our knowledge, this is the first umbrella review to provide the most comprehensive critical appraisal of previously published systematic reviews and meta-analyses about the role of HE4 in the diagnosis and prognosis of diverse diseases. The methodological quality of the included systematic reviews and meta-analyses and the strength and credibility of associations were assessed by a unified method. At first, umbrella review is the review of existing systematic reviews and meta-analyses (27). Compared with an individual systematic review and/or meta-analysis, an umbrella review has a higher level of evidence, which can better promote clinical practice. Second, the quality of the included meta-analyses was moderate or high, which was evaluated by the AMSTAR tool. Articles in our umbrella review were partially or almost fully consistent with the standards of methodological quality, thereby suggesting the outcome of the role of HE4 in the diagnosis and prognosis of diseases with a high degree of credibility.

Study Limitations

However, several caveats should be considered. For the present umbrella reviews, we only included the most recently published original studies, systematic reviews, and meta-analyses. First, meta-analyses published after our study and had yet to be assessed through meta-analyses will have an impact on our results. This limitation is shared by all umbrella reviews addressing clinical research. Second, the quality of this umbrella review depends on the quality of the articles included in the study. Some factors may have affected the strength and validity of evidence in meta-analyses, such as study design, sample size, and adjustment for confounders. For the original studies, the methods for assessing HE4 and the sample source were inconsistent, which might increase the risk of bias. However, we have assessed included meta-analyses by the AMSTAR tool to ensure their quality. After evaluation, the methodological quality was high or moderate. Third, the number of meta-analyses included in the umbrella review is limited, especially only four pieces of evidence from the prognostic meta-analysis. Given this limitation, we need to interpret the results of the present study with caution. Fourth, some studies failed to meet the requirements of the GRADE and cannot be evaluated. We did not reanalyze all the data, and the data were extracted from the original literature. Therefore, we encourage the remaining authors of the secondary study to comply with the protocol (28). Finally, most of the evidence from diagnosis and prognosis assessed by GRADE is moderate, low, and very low, and only one association was rated as high. It is important for us to interpret the results with caution. The low- and very low-quality evidence of the association between the role of HE4 in the diagnosis and the prognosis of diseases could only provide direction for future study.

CONCLUSION

In summary, the high certainty evidence of HE4 was present for its prognostic role in cancers. HE4 could provide a suitable method for the diagnosis of diseases with moderate certainty evidence. We suggested that clinicians could use HE4 as a biomarker related to the diagnosis and prognosis of EC, OC, and LC in clinical work, so as to improve the understanding of disease diagnosis, efficacy, recurrence, outcome, and prognosis of patients. Considering that other diseases remain uncertain and inadequate, further studies are needed to better elucidate the diagnostic and prognostic role of HE4 in the future.

AUTHOR CONTRIBUTIONS

BL, Q-JW, and T-TG contributed to the study design. M-LS, Y-ZL, and X-YL collected the data and analyzed the data. M-LS, Z-YY, BL, Y-ZL, X-YL, F-HL, Y-FW, Z-YW, Q-JW, and T-TG wrote the first draft of the manuscript and edited the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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REFERENCES

1. Henry NL, Hayes DF. Cancer biomarkers. *Mol Oncol.* (2012) 6:140–6.

2. Saito G, Sadahiro S, Kamata H, Miyakita H, Okada K, Tanaka A, et al. Monitoring of serum carcinoembryonic antigen levels after curative resection of colon cancer: cutoff values determined according to preoperative levels enhance the diagnostic accuracy for recurrence. *Oncology.* (2017) 92:276–82.

3. Rudin CM, Mauer A, Smakal M, Juergens R, Spelda S, Wertheim M, et al. Phase I/II study of pemetrexed with or without ABT-751 in advanced or metastatic non-small-cell lung cancer. *J Clin Oncol.* (2011) 29:1075–82. doi: 10.1200/JCO.2010.32.5944
4. Stiekema A, Lok C, Korse CM, van Driel WJ, van der Noort V, Kenter GG, et al. Serum HE4 is correlated to prognostic factors and survival in patients with endometrial cancer. *Virchows Arch.* (2017) 470:655–64. doi: 10.1007/s00428-017-2115-1
5. Abdalla N, Pazura M, Slomka A, Piorkowski R, Sawicki W, Cendrowski K. The role of HE4 and CA125 in differentiation between malignant and non-malignant endometrial pathologies. *Ginekol Pol.* (2016) 87:781–6. doi: 10.5603/GP.2016.0088
6. Kirchhoff C, Habben I, Ivell R, Krull N. A major human epididymis-specific cDNA en-codes a protein with sequence homology to extracellular proteinase inhibitors. *Biol Reprod.* (1991) 45:350–7. doi: 10.1095/biolreprod45.2.350
7. Hu L, Du S, Guo W, Chen D, Li Y. Comparison of serum human epididymis protein 4 and carbohydrate antigen 125 as markers in endometrial cancer: a meta-analysis. *Int J Gynecol Cancer.* (2016) 26:331–40. doi: 10.1097/igc.0000000000000621
8. Zhong H, Qian Y, Fang S, Yang L, Li L, Gu W. HE4 expression in lung cancer, a meta-analysis. *Clinica Chimica Acta.* (2017) 470:109–14. doi: 10.1016/j.cca.2017.05.007
9. Kim B, Park Y, Kim B, Ahn HJ, Lee K, Chung JE, et al. Diagnostic performance of CA 125, HE4, and risk of ovarian malignancy algorithm for ovarian cancer. *J Clin Lab Anal.* (2019) 33:e22624. doi: 10.1002/jcla.22624
10. Hellström I, Raycraft J, Hayden-Ledbetter M, Ledbetter JA, Schummer M, McIntosh M, et al. The HE4 (WFDC2) protein is a biomarker for ovarian carcinoma. *Cancer Res.* (2003) 63:3695–700.
11. Chen Y, Huang L, Wang S, Liu T, Wu Y, Li J, et al. WAP four-disulfide core domain protein 2 promotes metastasis of human ovarian cancer by regulation of metastasis-associated genes. *J Ovarian Res.* (2017) 10:40. doi: 10.1186/s13048-017-0329-0
12. Chen Y, Huang L, Wang S, Li J, Li M, Wu Y, et al. WFDC2 contributes to epithelial-mesenchymal transition (EMT) by activating AKT signaling pathway and regulating MMP-2 expression. *Cancer Manag Res.* (2019) 11:2415–24. doi: 10.2147/CMAR.S192950
13. Moore RG, Brown AK, Miller MC, Skates S, Allard WJ, Verch T, et al. The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass. *Gynecol Oncol.* (2008) 108:402–8. doi: 10.1016/j.ygyno.2007.10.017
14. Gasiorowska E, Kluz T, Lipski D, Warchoł W, Tykarski A, Nowak-Markwitz E. Human epididymis protein 4 (HE4) reference limits in polish population of healthy women, pregnant women, and women with benign ovarian tumors. *Dis Markers.* (2019) 2019:3890906. doi: 10.1155/2019/3890906
15. He Y, Li L, Tang J, Yi L, Zhao Y, Zhang H, et al. HE4 as a biomarker for diagnosis of lung cancer: a meta-analysis. *Medicine.* (2019) 98:e17198. doi: 10.1097/MD.0000000000017198
16. Chen P, Yang Q, Li X, Qin Y. Potential association between elevated serum human epididymis protein 4 and renal fibrosis: a systemic review and meta-analysis. *Medicine.* (2017) 96:e7824. doi: 10.1097/MD.0000000000007824
17. Gündüz UR, Gunaldi M, Isiksacan N, Gündüz S, Okuturlar Y, Kocoglu H. A new marker for breast cancer diagnosis, human epididymis protein 4: a preliminary study. *Mol Clin Oncol.* (2016) 5:355–60. doi: 10.3892/mco.2016.919
18. Montagnana M, Benati M, Danese E, Giudici S, Perfranceschi M, Ruzzenenete O, et al. Aberrant MicroRNA expression in patients with endometrial cancer. *Int J Gynecol Cancer.* (2017) 27:459–66. doi: 10.1097/IGC.0000000000000913
19. Olsen M, Lof P, Stiekema A, van den Broek D, Wilthagen EA, Bossuyt PM, et al. The diagnostic accuracy of human epididymis protein 4 (HE4) for discriminating between benign and malignant pelvic masses: a systematic review and meta-analysis. *Acta Obstet Gynecol Scan.* (2021) 100:1788–99.
20. Ferraro S, Braga F, Lanzoni M, Boracchi P, Biganzoli EM, Panteghini M. Serum human epididymis protein 4 vs. carbohydrate antigen 125 for ovarian cancer diagnosis: a systematic review. *J Clin Pathol.* (2013) 66:273–81. doi: 10.1136/jclinpath-2012-201031
21. Li J, Wang X, Qu W, Wang J, Jiang S. Comparison of serum human epididymis protein 4 and CA125 on endometrial cancer detection: a meta-analysis. *Clin Chim Acta.* (2019) 488:215–20. doi: 10.1016/j.cca.2018.11.011
22. Li F, Tie R, Chang K, Wang F, Deng S, Lu W, et al. Does risk for ovarian malignancy algorithm excel human epididymis protein 4 and CA125 in predicting epithelial ovarian cancer: a meta-analysis. *BMC Cancer.* (2012) 12:258. doi: 10.1186/1471-2407-12-258
23. Kalapotharakos G, Asciutto C, Henic E, Casslén B, Borgfeldt C. High preoperative blood levels of HE4 predicts poor prognosis in patients with ovarian cancer. *J Ovarian Res.* (2012) 5:20. doi: 10.1186/1757-2215-5-20
24. Wang X, Fan Y, Wang J, Wang H, Liu W. Evaluating the expression and diagnostic value of human epididymis protein 4 (HE4) in small cell lung cancer. *Tumour Biol.* (2014) 35:6847–53. doi: 10.1007/s13277-014-1943-8
25. Nagy BJ, Bhattoa HP, Steiber Z, Csobán M, Szilasi M, Méhes G, et al. Serum human epididymis protein 4 (HE4) as a tumor marker in men with lung cancer. *Clin Chem Lab Med.* (2014) 52:1639–48. doi: 10.1515/cclm-2014-0041
26. Liu X, Zhao F, Hu L, Sun Y. Value of detection of serum human epididymis secretory protein 4 and carbohydrate antigen 125 in diagnosis of early endometrial cancer of dif-ferent pathological subtypes. *Oncotargets Ther.* (2015) 8:1239–43. doi: 10.2147/OTT.S81853
27. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: Methodological development, conduct and reporting of an umbrella review approach. *Int J Evid Based Healthc.* (2015) 13:132–40. doi: 10.1097/XEB.0000000000000055
28. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ.* (2009) 339:b2700. doi: 10.1136/bmj.b2700
29. Raglan O, Kalliala I, Markozannes G, Cividini S, Gunter MJ, Nautiyal J, et al. Risk factors for endometrial cancer: an umbrella review of the literature. *Int J Cancer.* (2019) 145:1719–30. doi: 10.1002/ijc.31961
30. Karlsen NS, Karlsen MA, Høgdall CK, Høgdall EVS. HE4 tissue expression and serum HE4 levels in healthy individuals and patients with benign or malignant tumors: a systematic review. *Cancer Epidemiol Biomarkers Prev.* (2014) 23:2285–95. doi: 10.1158/1055-9965.EPI-14-0447
31. Dai H, Hu F, Ding Y. Diagnostic value of serum human epididymis protein 4 and cancer antigen 125 in the patients with ovarian carcinoma: a protocol for systematic review and meta-analysis. *Medicine.* (2021) 100:e25981. doi: 10.1097/MD.0000000000025981
32. Degez M, Caillon H, Chauviré-Drouard A, Leroy M, Lair D, Winer N, et al. Endometrial cancer: a systematic review of HE4, REM and REM-B. *Clinica chimica acta.* (2021) 515:27–36. doi: 10.1016/j.cca.2020.12.029
33. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol.* (2007) 7:10. doi: 10.1186/1471-2288-7-10
34. Schünemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ.* (2008) 336:1106–10. doi: 10.1136/bmj.39500.677199.ae
35. Gopalakrishna G, Mustafa RA, Davenport C, Scholten RJPM, Hyde C, Brozek J, et al. Applying grading of recommendations assessment, development and evaluation (GRADE) to diagnostic tests was challenging but doable. *J Clin Epidemiol.* (2014) 67:760–8. doi: 10.1016/j.jclinepi.2014.01.006
36. Foroutan F, Guyatt G, Zuk V, Vandvik PO, Alba AC, Mustafa R, et al. GRADE guidelines 28: use of GRADE for the assessment of evidence about prognostic factors: rating certainty in identification of groups of patients with different absolute risks. *J Clin Epidemiol.* (2020) 121:62–70. doi: 10.1016/j.jclinepi.2019.12.023
37. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol.* (2011) 64:401–6. doi: 10.1016/j.jclinepi.2010.07.015
38. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epi-demiol.* (2011) 64:383–94. doi: 10.1016/j.jclinepi.2010.04.026
39. Brunetti M, Shemilt I, Pregno S, Vale L, Oxman AD, Lord J, et al. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. *J Clin Epi-demiol.* (2013) 66:140–50.
40. Chiavaroli L, Viguiliouk E, Nishi SK, Blanco Mejia S, Raheliæ D, Kahleová H, et al. DASH dietary pattern and cardiometabolic outcomes: an umbrella

review of systematic reviews and meta-analyses. *Nutrients.* (2019) 11:338. doi: 10.3390/nu11020338
41. Tan J, Li L, Huang X, Yang C, Liang X, Zhao Y, et al. Associations between gastro-oesophageal reflux disease and a range of diseases: an umbrella review of systematic reviews and meta-analyses. *BMJ Open.* (2020) 10:e38450. doi: 10.1136/bmjopen-2020-038450
42. Cheng D, Sun Y, He H. The diagnostic accuracy of HE4 in lung cancer: a meta-analysis. *Dis Markers.* (2015) 2015:352670. doi: 10.1155/2015/352670
43. Chen Y, Ren YL, Li N, Yi XF, Wang HY. Serum human epididymis protein 4 vs. Carbohydrate antigen 125 and their combination for endometrial cancer diagnosis: a meta-analysis. *Eur Rev Med Pharmaco.* (2016) 20:1974–85.
44. Dai C, Zheng Y, Li Y, Tian T, Wang M, Xu P, et al. Prognostic values of HE4 expression in patients with cancer: a meta-analysis. *Cancer Manag Res.* (2018) 10:4491–500. doi: 10.2147/CMAR.S178345
45. Yan L, Hu Z. Diagnostic accuracy of human epididymis secretory protein 4 for lung cancer: a systematic review and meta-analysis. *J Thorac Dis.* (2019) 11:2737–44. doi: 10.21037/jtd.2019.06.72
46. Liu J, Han L, Sun Q, Li Y, Niyazi M. Meta-analysis of the diagnostic accuracy of HE4 for endometrial carcinoma. *Eur J Obstet Gynecol Reprod Biol.* (2020) 252:404–11. doi: 10.1016/j.ejogrb.2020.07.015
47. Yu S, Yang H, Xie S, Bao Y. Diagnostic value of HE4 for ovarian cancer: a meta-analysis. *Clin Chem Lab Med.* (2012) 50:1439–46.
48. Yang Z, Wei C, Luo Z, Li L. Clinical value of serum human epididymis protein 4 assay in the diagnosis of ovarian cancer: a meta-analysis. *Oncotargets Ther.* (2013) 6:957–66. doi: 10.2147/OTT.S45681
49. Bie Y, Zhang Z. Diagnostic value of serum HE4 in endometrial cancer: a meta-analysis. *World J Surg Oncol.* (2014) 12:169. doi: 10.1186/1477-7819-12-169
50. Macedo ACL, Da Rosa MI, Lumertz S, Medeiros LR. Accuracy of serum human epididymis protein 4 in ovarian cancer diagnosis: a systematic review and meta-analysis. *Int J Gynecol Cancer.* (2014) 24:1222–31. doi: 10.1097/IGC.0000000000000192
51. Yuan C, Li R, Yan S, Kong B. Prognostic value of HE4 in patients with ovarian cancer. *Clin Chem Lab Med.* (2018) 56:1026–34. doi: 10.1515/cclm-2017-1176
52. Jia M, Deng J, Cheng X, Yan Z, Li Q, Xing Y, et al. Diagnostic accuracy of urine HE4 in patients with ovarian cancer: a meta-analysis. *Oncotarget.* (2017) 8:9660–71. doi: 10.18632/oncotarget.14173
53. Huang J, Chen J, Huang Q. Diagnostic value of HE4 in ovarian cancer: a meta-analysis. *Eur J Obstet Gynecol Reprod Biol.* (2018) 231:35–42. doi: 10.1016/j.ejogrb.2018.10.008
54. He Y, Wang J, Ma C, Kang Y. Role of human epididymis protein 4 (HE4) in determining survival of patients with endometrial cancer: a meta-analysis. *Technol Cancer Res T.* (2020) 19:1079239308. doi: 10.1177/1533033820971660
55. Kumarasamy C, Madhav MR, Sabarimurugan S, Lakhotiya K, Pandey V, Priyadharshini T, et al. Diagnostic and prognostic role of HE4 expression in multiple carcinomas: a protocol for systematic review and meta-analysis. *Medicine.* (2019) 98:e15336. doi: 10.1097/MD.0000000000015336
56. Rong Y, Li L. Early clearance of serum HE4 and CA125 in predicting platinum sensitivity and prognosis in epithelial ovarian cancer. *J Ovarian Res.* (2021) 14:2. doi: 10.1186/s13048-020-00759-9
57. Lan T, Mu C, Wang Z, Wang Y, Li Y, Mai Y, et al. Diagnostic and prognostic values of serum EpCAM, TGM2, and HE4 levels in endometrial cancer. *Front Oncol.* (2020) 10:1697. doi: 10.3389/fonc.2020.01697
58. Lamy P, Plassot C, Pujol J. Serum HE4: an independent prognostic factor in non-small cell lung cancer. *PLoS One.* (2015) 10:e128836. doi: 10.1371/journal.pone.0128836
59. Guo Y, Wang J, Lu H, Li X, Song W, Zhang X, et al. The human epididymis protein 4 acts as a prognostic factor and promotes progression of gastric cancer. *Tumour biol.* (2015) 36:2457–64. doi: 10.1007/s13277-014-2858-0
60. Whiting P, Wolff R, Mallett S, Simera I, Savoviæ J. A proposed framework for developing quality assessment tools. *System Rev.* (2017) 6:204. doi: 10.1186/s13643-017-0604-6
61. Zhen S, Bian L, Chang L, Gao X. Comparison of serum human epididymis protein 4 and carbohydrate antigen 125 as markers in ovarian cancer: a meta-analysis. *Mol clin oncol.* (2014) 2:559–66. doi: 10.3892/mco.2014.279
62. Dochez V, Randet M, Renaudeau C, Dimet J, Le Thuaut A, Winer N, et al. Efficacy of HE4, CA125, risk of malignancy index and risk of ovarian malignancy index to detect ovarian cancer in women with presumed benign ovarian tumours: a prospective, multicentre trial. *J Clin Med.* (2019) 8:1784. doi: 10.3390/jcm8111784
63. Zhuang H, Tan M, Liu J, Hu Z, Liu D, Gao J, et al. Human epididymis protein 4 in association with annexin II promotes invasion and metastasis of ovarian cancer cells. *Mol Cancer.* (2014) 13:243. doi: 10.1186/1476-4598-13-243
64. Ribeiro JR, Gaudet HM, Khan M, Schorl C, James NE, Oliver MT, et al. Human epididymis protein 4 promotes events associated with metastatic ovarian cancer via regulation of the extracelluar matrix. *Front Oncol.* (2017) 7:332. doi: 10.3389/fonc.2017.00332
65. Mele B, Van S, Holroyd-Leduc J, Ismail Z, Pringsheim T, Goodarzi Z. Diagnosis, treatment and management of apathy in Parkinson's disease: a scoping review. *BMJ Open.* (2020) 10:e37632. doi: 10.1136/bmjopen-2020-037632
66. Antonsen SL, Høgdall E, Christensen IJ, Lydolph M, Tabor A, Loft Jakobsen A, et al. HE4 and CA125 levels in the preoperative assessment of endometrial cancer patients: a prospective multicenter study (ENDOMET). *Acta Obstet Gyn Scan.* (2013) 92:1313–22. doi: 10.1111/aogs.12235
67. Li J, Chen H, Mariani A, Chen D, Klatt E, Podratz K, et al. HE4 (WFDC2) promotes tumor growth in endometrial cancer cell lines. *Int J Mol Sci.* (2013) 14:6026–43. doi: 10.3390/ijms14036026
68. Moore RG, Miller CM, Brown AK, Robison K, Steinhoff M, Lambert-Messerlian G. Utility of tumor marker HE4 to predict depth of myometrial invasion in endometrioid adenocarcinoma of the uterus. *Int J Gynecol Cancer.* (2011) 21:1185–90. doi: 10.1097/IGC.0b013e3182229ad8
69. Bolton JS, Chaudhury S, Dutta S, Gregory S, Locke E, Pierson T, et al. Comparison of ELISA with electro-chemiluminescence technology for the qualitative and quantitative assessment of serological responses to vaccination. *Malar J.* (2020) 19:159. doi: 10.1186/s12936-020-03225-5
70. Bignotti E, Ragnoli M, Zanotti L, Calza S, Falchetti M, Lonardi S, et al. Diagnostic and prognostic impact of serum HE4 detection in endometrial carcinoma patients. *Brit J Cancer.* (2011) 104:1418–25. doi: 10.1038/bjc.2011.109
71. Angioli R, Plotti F, Capriglione S, Montera R, Damiani P, Ricciardi R, et al. The role of novel biomarker HE4 in endometrial cancer: a case control prospective study. *Tumour Biol.* (2013) 34:571–6. doi: 10.1007/s13277-012-0583-0
72. Omer B, Genc S, Takmaz O, Dirican A, Kusku-Kiraz Z, Berkman S, et al. The diagnostic role of human epididymis protein 4 and serum amyloid-A in early-stage endometrial cancer patients. *Tumour Biol.* (2013) 34:2645–50. doi: 10.1007/s13277-013-0814-z
73. Choi SI, Jang MA, Jeon BR, Shin HB, Lee YK, Lee YW. Clinical usefulness of human epididymis protein 4 in lung cancer. *Ann Lab Med.* (2017) 37:526–30. doi: 10.3343/alm.2017.37.6.526
74. Celik B, Bulut T. Human epididymis protein 4 may not be a reliable screening biomarker for detecting lung carcinoma patients. *Biomed Rep.* (2017) 7:297–300. doi: 10.3892/br.2017.971
75. Bolstad N, Øijordsbakken M, Nustad K, Bjerner J. Human epididymis protein 4 refer-ence limits and natural variation in a Nordic reference population. *Tumour biol.* (2012) 33:141–8. doi: 10.1007/s13277-011-0256-4
76. Ge L, Tian J, Li Y, Pan J, Li G, Wei D, et al. Association between prospective registra-tion and overall reporting and methodological quality of systematic reviews: a meta-epidemiological study. *J Clin Epidemiol.* (2018) 93:45–55. doi: 10.1016/j.jclinepi.2017.10.012

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Intrauterine Perfusion of Autologous Platelet-Rich Plasma Before Frozen-Thawed Embryo Transfer Improves the Clinical Pregnancy Rate of Women With Recurrent Implantation Failure

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Objective: To evaluate whether the intrauterine perfusion of platelet-rich plasma (PRP) before frozen-thawed embryo transfer (FET) improves the pregnancy outcomes of patients with repeated implantation failure (RIF).

Methods: This retrospective study included 288 infertile women with RIF after undergoing *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment from October 1, 2019, to January 1, 2021, at Qingdao Women and Children's Hospital. Patients were divided into two groups according to whether they received PRP intrauterine perfusion before embryo transfer in FET cycles. 138 women were in the PRP group, 150 women were in the control group. The primary outcome measure was live birth rates and the secondary outcome were clinical pregnancy, positive β hCG, miscarriage and implantation rates.

Results: No significant differences in baseline demographic and clinical characteristics were observed between the two groups. Overall, significantly more women in the PRP group than in the control group achieved a live birth rate (41 women; 29.71% vs. 27 women; 18%) and a clinical pregnancy (50 women; 36.23% vs. 37 women; 24.67%). The PRP group had a higher implantation rate and lower spontaneous miscarriage rate than the control group, but these differences were not statistically significant. No pregnancy outcome difference between two groups in PCOS patients with RIF.

Conclusion: Our results showed that intrauterine perfusion of PRP before embryo transfer in FET cycles can significantly increase the live birth and clinical pregnancy rates in patients with RIF.

Keywords: platelet-rich plasma (PRP), frozen-thawed embryo transfer (FET), intrauterine perfusion, live birth rate, clinical pregnancy rate (CPR)

INTRODUCTION

In the context of *in vitro* fertilization-embryo transfer (IVF-ET), RIF refers to patients for whom implantation fails after repeated transfers of morphologically good-quality embryos into a normal uterus (1). Despite great progress in the application of IVF-ET to infertile couples, recurrent implantation failure (RIF) following embryo transfer (ET) continues to be a major problem affecting about 10% of women causing great psychological and economic burden to individuals and their families (2, 3), New strategies to improve the pregnancy likelihoods are urgently needed for these patients.

The successful implantation depends on embryo quality and endometrial receptivity. Endometrial receptivity is a complex process that involves the participation of and regulation by many molecules, including cytokines, growth factors, adhesion molecules, and cytoskeletal proteins, among other factors (4). Patients with RIF are in most due to endometrial receptivity disorders. numerous studies have investigated ways to improve endometrial receptivity, and the methods examined have included low-dose aspirin therapy, intrauterine infusion of human chorionic gonadotrophin (HCG) or colony cell-stimulating factor (CSF), endometrial injury and so like (5–8), however, the optimal technique remains unclear.

PRP is an autologous blood-derived concentrate of platelets from peripheral blood with a considerable concentration of growth factors and cytokines. Since its introduction in 1970, PRP has been widely used as a form of regenerative treatment in multiple medical fields, such as sports medicine, maxillofacial surgery and cosmetology. Studies in recent years have shown great promise in reproduction fields. Many studies have demonstrated that autologous PRP can regenerate and thicken the thin endometrium and decrease the likelihood of implantation failure leading to good pregnancy outcomes (9–11), however the patient's heterogeneity and small sample size of the subjects led to different research results, therefore this research analyzed the use of PRP before embryo transfer in RIF patients of frozen thawed cycles and its efficacy in this population.

MATERIALS AND METHODS

Study Design

This retrospective study was carried at reproductive center of Qingdao Women and Children's Hospital. We retrospectively analyzed the records of 410 patients with history of RIF underwent FET in Qingdao Women and Children's Hospital from October 1, 2019, to January 1, 2021. 138 patients (screened from 168 patients) who received PRP intrauterine perfusion before embryo transfer in frozen thawed cycles were collected, 150 patients (screened from 242 patients) with history of RIF did not receive PRP intrauterine perfusion as the control group. We excluded 122 patients who did not meet the criteria and had incomplete data. No repeat treatment cycle for all patients. Clinicians and this PRP intrauterine treatment study were authorized by the ethics committee of Qingdao Women and Children's Hospital. Informed consent was obtained from all patients with PRP intrauterine perfusion on endometrial transformation day, follow-up was complete in all patients.

Patient Enrolment Criteria

Patients aged 23 to 40 years who had three or more consecutive failed embryo implantations with good-quality embryos (at least 6 cleavage-stage embryos or three blastocysts) were included in the study (12). The exclusion criteria were an abnormal karyotype from either partner, evidence of uterine defects, ultrasonographic evidence of hydrosalpinx, infections, endocrine problems, coagulation defects or autoimmune defects.

Endometrial preparation for frozen-thawed cycle included hormone replacement treatment (HRT) protocol (estrogen-progesterone cycle, EP) and natural cycle (NC). PRP intrauterine perfusion was performed 48–72 h before embryo transfer. One or two good quality embryos were transferred. The rates of live birth, clinical pregnancy, positive-hCG, miscarriages and implantation will be assessed. Serum β-hCG was measured *14* days after embryo transfer and was considered positive for β- hCG level $\geq$ 5IU. Clinical pregnancy was confirmed by transvaginal ultrasonography 30 days after embryo transfer.

Plate-Rich Plasma Preparation and Intrauterine Perfusion

Twenty milliliters of peripheral blood were collected from each patient and centrifuged at 500 × g for 10 min at 18°C. After centrifugation, three layers were visible, namely, the serum, platelets and red blood cells. The serum and platelets were transferred to another tube and centrifuged at 500 × g for another 10 min at 18°C. The supernatant was discarded, the remaining 1 mL PRP was infused into the uterine cavity using artificial insemination catheter 2 days before embryo transfer (13). The mean number of platelets in PRP was 1513.45 ± 322.18 × 10^9/L (Automated Hematology Analyzer sysmex xs-500i, Sysmex Corporation, Kobe, Japan). All perfusions were prepared and performed by a single operator.

Statistical Analysis

All statistical analyses were performed using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). Student's *t*-test was used for comparisons of continuous variables between the groups. The chi-squared test or Fisher's exact test, where appropriate, was used for comparisons of categorical variables. The results are presented as the mean ± standard deviation (SD). Statistical significance was set at a probability (P) value < 0.05.

RESULTS

A total of 288 patients with an RIF history were included in this study; 138 patients undergoing intrauterine PRP perfusion before embryo transfer in frozen-thawed cycles were included in the PRP group, and the remaining 150 women who were not undergoing PRP perfusion were included in the control group. The mean age was 35.7 ± 4.6 years, the mean duration of infertility was 7.8 ± 3.7 years and the mean number of history embryo transfer cycles was 3.72 ± 1.09 and the control was 3.67

TABLE 1 | Baseline characteristics of the participants with RIF patients.

	PRP group ($n = 138$)	Control group ($n = 150$)	*P*-value
Demographic characteristics			
Female age (years), mean ± SD	34.92 ± 4.80	34.93 ± 4.87	0.986
Male age (years), mean ± SD	35.83 ± 5.72	36.71 ± 6.65	0.232
BMI (kg/m^2), mean ± SD	24.08 ± 3.65	24.81 ± 3.90	0.103
FSH (IU/ml), mean ± SD	6.69 ± 1.50	6.45 ± 1.47	0.172
AMH (ng/ml), mean ± SD	2.38 ± 2.45	2.40 ± 3.03	0.951
Infertility duration, mean ± SD	4.35 ± 3.29	4.28 ± 3.74	0.867
Number of history ET cycles	3.72 ± 1.09	3.67 ± 0.98	0.682
Type of infertility			
Primary infertility, *n* (%)	75/138 (54.35)	78/150	0.159
Secondary infertility, *n* (%)	63/138 (45.65)	72/150	0.159
Diagnosis of infertility			
Tubal factor, *n* (%)	44/138 (31.89)	49/150	0.821
Male factor, *n* (%)	41/138 (29.71)	44/150	0.944
PCOS, *n* (%)	29/138 (21.01)	38/150	0.386
Other causes, *n* (%)	20/138 (14.49)	19/150	0.219

The values are expressed as the mean ± SD.

TABLE 2 | Clinical characteristics of the participants with RIF patients.

	PRP group ($n = 138$)	Control group ($n = 150$)	*P*-value
Endometrial thickness, mean ± SD (Endometrial conversion day)	980 ± 2.27	10.06 ± 2.16	0.320
Number of embryo transfers, mean ± SD	1.48 ± 0.50	1.40 ± 0.50	0.176
Number of blastocysts, *n* (%)	60/138 (43.48)	62/150 (41.33)	0.713
Number of cleavage-stage embryos, n (%)	78/138 (57.78)	88/150 (58.67)	0.713
Positive β hCG rates, *n* (%)	62/138 (44.93)*	45/150 (30.00%)	<0.01*
Implantation rate, *n* (%)	56/206 (27.18)	37/210 (17.62)	0.067
Biochemical pregnancies, *n* (%)	12/138 (8.70)	8/150 (6.67)	0.156
Clinical pregnancies, *n* (%)	50/138 (36.23)*	37/150 (24.67)	0.040*
Spontaneous miscarriages, *n* (%)	9/50 (18.00)	10/37 (27.03)	0.454
Live births, *n* (%)	41/138 (29.71)*	27/150 (14)	<0.01*

**Indicate significant differences between the two groups.*

± 0.98. No local or systemic side effects relating to the use of PRP perfusion were reported (**Table 1**).

Regarding the patients' baseline demographic characteristics, we found no differences between the two groups in age, body mass index (BMI), duration of infertility, number of history cycles transferred or infertility diagnosis between the two groups. There were also no differences in cycle characteristics, such as endometrial thickness, number of days embryo transfer, or number of blastocysts or cleavage-stage embryos transferred between the two groups (**Table 2**).

To evaluate whether PRP improves the reproductive outcomes of patients with RIF, we first calculated the live birth rates and the clinical pregnancy rates in two groups. In our study, there were 41 live birth in the PRP intrauterine perfusion group (41/138) and 27 in the control group (27/150), the live birth rate was significantly higher in the PRP group (29.71%) than in the control group 18% ($P < 0.01$). Additionally, the clinical pregnancy rate was also higher in the PRP group 36.23% than in the control group 24.67% ($P = 0.040$). Further analysis of the secondary outcomes showed that the Positive β hCG rates is significantly higher in PRP group 44.93% (62/138) than the control group 28.66% ($P < 0.01$). None of other secondary outcome indices were significantly different between the two groups, that the implantation rates were 27.18% and 17.62% ($P = 0.067$), respectively; that the biochemical pregnancy rates were 7.97% and 6.675 ($P = 0.156$), respectively; and that the miscarriage rates were 18.0% and 27.03% ($P = 0.454$), respectively (**Table 2**). There is also no in clinical pregnancy and live birth rate difference between PRP group and control group in RIF PCOS patients (**Table 2**).

DISCUSSION

This retrospective cohort study was performed to evaluate the pregnancy outcomes of RIF patients who underwent PRP intrauterine perfusion before embryo transfer and compare these results to a cohort of RIF patients who were not treated with PRP. We found there is significant different in live birth and clinical pregnancy rates, we have also found there is significantly different in positive β-hCG rates, no significantly difference were found in the implantation rates and miscarriages.

Yajie Chang, Sunita R, Tandulwadkar, and Eftekhar have demonstrated that autologous PRP intrauterine perfusion could expanded the thin endometrium and increase the clinical pregnancy and implantation rates in FET cycles (15–17), they think that PRP could regenerate and improve the endometrium receptivity leading to good pregnancy outcomes. Hakan Coksuer also found that PRP intrauterine perfusion could thicken the endometrium leading to good endometrial lining and optimal pregnancy outcomes in RIF patients (18). Xiaohan Wang and colleagues found that PRP significantly stimulated the growth, migration and adhesion of endometrial mesenchymal stem cells, these effects are probably because it contains or stimulates several growth factors such as transforming growth factor, Platelet-derived growth factor, vascular endothelial growth factor, insulin like growth factor, epithelial growth factor and bioactive-cytokines (14). However, these majority of studies had small sample cases, most less than 50 patients and almost all fewer than 100 patients. the live birth rate was not reported in most studies. Our study is relatively larger sample size of 238 patients, we found no difference in endometrium thickness between groups, the live birth rate, clinical pregnancy, positive β-HCG rates are higher than the control group, the results are consistent with the literature. We think those biological factors may acts in most by improving and triggering endometrial receptivity through the improvement of cell proliferation, vascularization, anti-inflammatory properties, rather than expanded endometrial growth.

However, contradictory views on the usefulness of PRP perfusion treatment in IVF reproductive medicine persists. Tehraninejad and Allahveisi found that the pregnancy outcomes,

namely, the clinical and ongoing pregnancy rates, live birth rates were similar between the PRP intrauterine infusion group and the control group in RIF patients of FET cycles (10, 11). The reason for the inconsistency between our results and those of others might be attributable to the different subject cohorts, different definitions of RIF and wide variety of *PRP* preparation protocols. The PRP in our study contains leukocytes in addition to the platelets and plasma, it is categorized as leucocyte-poor PRP, not pure PRP. leukocytes might be also a source of several growth factors and cytokines (19). The concentrations of platelets and leukocytes obtained in PRP preparation depending on how the blood sample was treated, which may in turn impact the amount of various types of growth factors playing a key part in the treatment.

To date, only a few RCT studies on intrauterine infusion of PRP have been performed in the reproductive field. Eftekhar and Nazari suggested that PRP could expand the thin endometrium and improve clinical pregnancy outcomes (17, 20), while Allahveisi's study concluded that intrauterine infusion of PRP did not improve pregnancy outcomes in patients with recurrent implantation failure (11). Design of placebo in the control group was inconsistent across studies. The intrauterine perfusion of PRP is associated with the potential effect of the endometrial injury, is it possible the beneficial effect is due to the endometrial injury of the catheter? So we should design studies carefully, especially RCTs, larger scales, the standard PRP preparation procedure and the strict indication of the PRP treatment should be all considered.

Another notable point is that PRP intrauterine perfusion did not improve pregnancy outcomes in RIF PCOS patients. There is no significant difference between the two groups. This might be caused by the small sample size in this study. Besides, PCOS is a special group where obesity, insulin resistance, abnormal glucose metabolism and metabolic syndrome may alter the competence of oocytes, embryos and endometrium (21). Palomba's comprehensive review shows that among several interventions to improve endometrial receptivity in women with PCOS, only lifestyle modification, metformin and bariatric surgery have the scientific evidence for clinical benefit (22).

The strength of this study is that we included a large sample of RIF patients with the PRP intervention before embryo transfer in our reproductive center, which allows us to draw a conclusion on the efficacy of this strategy. The main drawback of this study was retrospective and its non-randomized design. The findings provide evidence for future randomized, controlled trials with large sample size in this field. One further prospective and high-quality randomized controlled trial is ongoing in our center to identify subpopulations that would benefit most from PRP therapy.

In summary, we analyzed the effect of intrauterine PRP treatment before embryo transfer in patients with RIF and found that the PRP intervention improved the live birth rate and clinical pregnancy rate.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Qingdao Women and Children's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YX took part in the first draft and preparation of the manuscript. JF, XL, PX, and RM collected material and data. CH contributed to the concept, design and preparation of the manuscript. All authors were involved in the study conception and design and read and approved the final manuscript.

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REFERENCES

1. Coughlan C, Ledger W, Wang Q, Liu F, Demirol A, Gurgan T, et al. Recurrent implantation failure: definition and management. *Reprod Biomed Online.* (2014) 28:14–38. doi: 10.1016/j.rbmo.2013.08.01
2. Busnelli A, Reschini M, Cardellicchio L, Vegetti W, Somigliana E, Vercellini P. How common is real repeated implantation failure? An indirect estimate of the prevalence. *Reprod Biomed Online.* (2020) 40:91–7. doi: 10.1016/j.rbmo.2019.10.014
3. Simon A, Laufer N. Assessment and treatment of repeated implantation failure (RIF). *J Assist Reprod Genet.* (2012) 29:1227–39. doi: 10.1007/s10815-012-9861-4
4. Dey SK, Lim H, Das SK, Reese J, Paria BC, Daikoku T, et al. Molecular cues to implantation. *Endocr Rev.* (2004) 25:341–73. doi: 10.1210/er.2003-0020
5. Blois SM, Klapp BF, Barrientos G. Decidualization and angiogenesis in early pregnancy: unravelling the functions of DC and NK cells. *J Reprod Immunol.* (2011) 88:86–92. doi: 10.1016/j.jri.2010.11.002
6. Volovsky MHM, Maclachlan VB. Intrauterine human chorionic gonadotropin (HCG) infusion prior to embryo transfer (ET) may be detrimental to pregnancy rate. *Fertility Sterility.* (2016) 106:e52. doi: 10.1016/j.jaad.2019.07.024
7. Vlachadis N, Tsamadias V, Economou E. Aspirin to improve IVF unexplained implantation rates: time for an individualized approach. *Reprod Biomed Online.* (2014) 28:133. doi: 10.1016/j.rbmo.2013.09.007
8. Kunicki M, Lukaszuk K, Woclawek-Potocka I, Liss J, Kulwikowska P, Szczyptańska J. Evaluation of granulocyte colony-stimulating factor effects on treatment-resistant thin endometrium in women undergoing *in vitro* fertilization. *Biomed Res Int.* (2014) 2014:913235. doi: 10.1155/2014/913235
9. Coksuer H, Akdemir Y, Ulas Barut M. Improved *in vitro* fertilization success and pregnancy outcome with autologous platelet-rich plasma treatment in

unexplained infertility patients that had repeated implantation failure history. *Gynecol Endocrinol.* (2019) 35:815–8. doi: 10.1080/09513590.2019.1597344
10. Tehraninejad ES, Kashani NG, Hosseini A, Tarafdari A. Autologous platelet-rich plasma infusion does not improve pregnancy outcomes in frozen embryo transfer cycles in women with history of repeated implantation failure without thin endometrium. *J Obstet Gynaecol Res.* (2021) 47:147–51. doi: 10.1111/jog.14445
11. Allahveisi A, Seyedoshohadaei F, Rezaei M, Bazrafshan N, Rahimi K. The effect of platelet-rich plasma on the achievement of pregnancy during frozen embryo transfer in women with a history of failed implantation. *Heliyon*. (2020) 6:e03577. doi: 10.1016/j.heliyon2020.e03577
12. Simon A, Laufer N. Repeated implantation failure: clinical approach. *Fertil Steril.* (2012) 97:1039–43. doi: 10.1016/j.fertnstert.2012.03.010
13. Cengiz IF, Oliveira JM, Reis RL. PRP Therapy. *Adv Exp Med Biol.* (2018) 1059:241–53. doi: 10.1007/978-3-319-76735-2_11
14. Wang X, Liu L, Mou S, Zhao H, Fang J, Xiang Y, et al. Investigation of platelet-rich plasma in increasing proliferation and migration of endometrial mesenchymal stem cells and improving pregnancy outcome of patients with thin endometrium. *J Cell Biochem*. (2018). doi: 10.1002/jcb.28014
15. Chang Y, Li J, Wei LN, Pang J, Chen J, Liang X. Autologous platelet-rich plasma infusion improves clinical pregnancy rate in frozen embryo transfer cycles for women with thin endometrium. *Medicine.* (2019) 98:e14062. doi: 10.1097/MD.0000000000014062
16. Tandulwadkar SR, Naralkar MV, Surana AD, Selvakarthick M, Kharat AH. Autologous intrauterine platelet-rich plasma instillation for suboptimal endometrium in frozen embryo transfer cycles: a pilot study. *J Hum Reprod Sci*. (2017) 10:208–2. doi: 10.4103/jhrs.JHRS_28_17
17. Eftekhar M, Neghab N, Naghshineh E, Khani P. Can autologous platelet rich plasma expand endometrial thickness and improve pregnancy rate during frozen-thawed embryo transfer cycle? A randomized clinical trial Taiwan. *J Obstet Gynecol.* (2018) 57:810–3. doi: 10.1016/j.tjog.2018.10.007
18. Coksuer H, Akdemir Y, Ulas Barut M. Improved *in vitro* fertilization success and pregnancy outcome with autologous platelet-rich plasma treatment in unexplained infertility patients that had repeated implantation failure history. *Gynecol Endocrinol.* (2019) 35:815–8. doi: 10.1080/095135902019.1597344
19. Cerza F, Carnì S, Carcangiu A, Di Vavo I, Schiavilla V, Pecora A, et al. Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. *Am J Sports Med.* (2012) 40:2822–7. doi: 10.1177/03635465124 61902
20. Nazari L, Salehpour S, Hoseini S, Zadehmodarres S, Azargashb E. Effects of autologous platelet-rich plasma on endometrial expansion in patients undergoing frozen-thawed embryo transfer: a double-blind RCT. *Int J Reprod Biomed.* (2019) 17:443–8. doi: 10.18502/ijrm.v17i6. 4816
21. Palomba S. Is fertility reduced in ovulatory women with polycystic ovary syndrome? An opinion paper. *Hum Reprod.* (2021) 36:2421–8. doi: 10.1093/humrep/deab181
22. Palomba S, Piltonen TT, Giudice LC. Endometrial function in women with polycystic ovary syndrome: a comprehensive review. *Hum Reprod Update.* (2021) 27:584–618. doi: 10.1093/humupd/dmaa051

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Differential Effects of Intrauterine Balloon Tamponade Indications on Postpartum Hemorrhage Outcomes

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Objective: To determine whether the indication of intrauterine balloon tamponade (IUBT) was associated with postpartum hemorrhage (PPH) outcomes.

Methods: Patients with PPH who underwent IUBT between January 2013 and November 2021 were included in a cohort study. PPH outcomes in patients who had IUBT for indications of uterine atony were compared to those who had IUBT for indications of placental site bleeding. PPH outcomes included uterine artery embolization (UAE) or hysterectomy after IUBT, estimated blood loss (EBL) after balloon placement, and blood transfusion. Statistical analysis was performed using multivariate logistic regression.

Results: IUBT was performed on 603 cases, with 121 (20.1%) undergoing it for placental site bleeding and 482 (79.9%) for uterine atony. In general, IUBT was a reliable treatment for PPH, but the specific efficacy varied depending on the indication for placement. After controlling for confounding variables, compared to the indication of uterine atony, the indication of placental site bleeding increased the risk of transfusion of ≥4 units of PRBCs (aOR 2.47, 95%CI 1.32–3.98), EBL ≥ 300 ml after IUBT (aOR 3.78, 95%CI 2.22–5.33), and UAE or hysterectomy (aOR 2.52, 95%CI 1.20–6.01), respectively. Other factors associated with adverse PPH outcomes were lower antenatal hemoglobin, higher IUBT volume, longer duration of IUBT and larger shock index values.

Conclusions: IUBT was less effective in treating PPH patients with indications of placental site bleeding than with indications of uterine atony. Follow-up monitoring of PPH patients with placental site bleeding should be intensified.

Keywords: postpartum hemorrhage, placental site bleeding, uterine atony, intrauterine balloon tamponade, blood transfusion, estimated blood loss, uterine artery embolization, hysterectomy

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INTRODUCTION

Postpartum hemorrhage (PPH) remains the primary source of maternal morbidity and mortality worldwide, accounting for nearly a third of all maternal deaths (1, 2). The number of elderly pregnant women and parous women in China has increased dramatically since the implementation of the two-child policy in 2005 (3). Accordingly, the proportion of patients with PPH has also increased, which poses a great challenge for postpartum management (4).

PPH requires multistep treatment. Invasive second-line management, such as intrauterine suture, uterine artery embolization (UAE), and uterine vessel ligation, may be attempted after a first-line treatment, such as uterotonics, has failed (5, 6). If none of these options is viable, a hysterectomy can be performed as a life-saving procedure (7). However, the adverse effects on fertility associated with invasive procedures and hysterectomy prevent their use from being the preferred method.

Intrauterine balloon tamponade (IUBT) was first used to treat PPH by Bakri et al. (8) in 1992, and numerous studies have confirmed the efficacy of IUBT in treating PPH while avoiding the problem of reduced fertility due to invasive procedures (9–11). Despite its widespread use today, IUBT is still largely empirical and devoid of standardization. Specifically, to the best of the authors' knowledge, the relationship between IUBT placement indications and PPH–related outcomes remains unidentified.

Thus, we examined up to 9 years of total cases at the institution to investigate the effect of different IUBT indications on PPH outcomes as well as other factors associated with PPH outcomes. We hypothesized that women with IUBT indications of placental site bleeding would have worse PPH outcomes than women with IUBT indications of uterine atony.

MATERIALS AND METHODS

Study Design and Patients

This is a cohort study conducted at the International Peace Maternal and Child Health Hospital (IPMCH), affiliated with Shanghai Jiao Tong University. The clinical data of all women who had IUBT for severe PPH at the institution between January 2013 and November 2021 were analyzed retrospectively. According to the International Federation of Gynecology and Obstetrics (FIGO) guidelines, a total estimated blood loss (EBL) $\geq$ 1,000 ml was defined as severe PPH, with specific values recorded in the critical care record form of the hospital electronic medical record. IUBT is the main option for the rescue of refractory postpartum hemorrhage (ineffectiveness of combined uterine massage with uterotonics) in the study institution. Intrauterine suture or B-Lynch suture may have been performed to stop bleeding prior to IUBT for cesarean delivery. The indications for IUBT are determined by the obstetrician and include uterine atony and placental site bleeding. If the obstetrician documented the indication as uterine atony or if the medical record described the cause of bleeding as softness of the lower uterine segment or softness of the uterine global, the main indication was defined as uterine atony. If the documented indication was placental site bleeding, or if the main description in the medical record was about placental

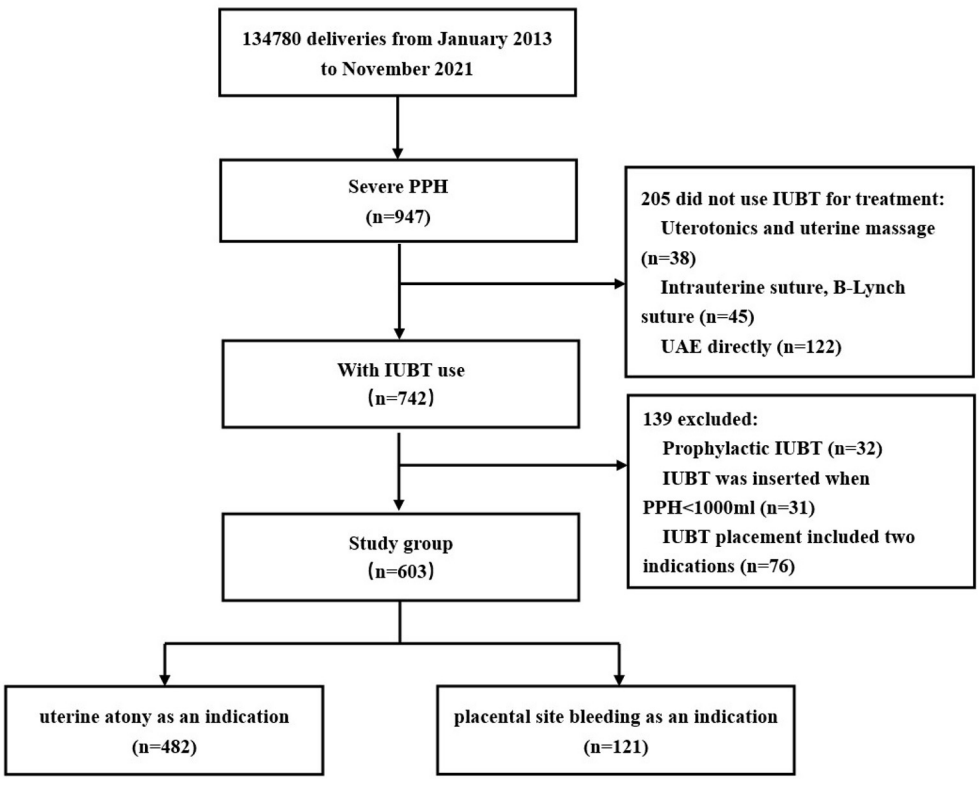

FIGURE 1 | Flowchart. IUBT, intrauterine balloon tamponade; PPH, postpartum hemorrhage; UAE, uterine artery embolization.

TABLE 1 | Demographic, obstetric, and IUBT-related data were grouped according to IUBT indications.

	Uterine atony (n = 482)	Placental site bleeding (n = 121)	*P*-value
Maternal age (years)	32.5 ± 4.5	33.4 ± 4.7	0.143
Pre-pregnancy BMI (kg/m^2)	23.4 ± 4.1	23.7 ± 4.3	0.312
Nulliparous	275 (57.1)	51(42.1)	0.004
Multiple gestation	110 (22.8)	22 (18.2)	0.325
Premature birth	29 (6.0)	18 (14.9)	0.002
Induction of labor	195 (40.5)	25 (20.7)	< 0.001
History of PPH	49 (10.2)	11(9.1)	0.741
Antenatal hemoglobin (mg/dl)	11.5 ± 1.4	11.6 ± 1.5	0.883
Delivery mode			
Cesarean	213 (44.2)	50 (42.1)	0.569
Vaginal	269 (55.8)	71 (57.9)	
Surgical hemostatic before IUBT			
None	330 (68.4)	79 (65.3)	0.154
Intrauterine suture	130 (27.0)	31 (25.6)	
B-Lynch suture	22 (4.6)	11 (9.1)	
Uterotonics before UBT			
0 or 1	43 (8.9)	21 (17.4)	0.009
≥2	439 (91.1)	100 (82.6)	
Time from birth to IUBT (min)	45 (15–80)	45 (15–75)	0.082
Duration of IUBT (h)	18.3 ± 5.6	18.7 ± 8.5	0.442
IUBT volume (ml)			
<250	24 (5.0)	8 (6.6)	0.371
250–350	432 (89.6)	103 (85.1)	
≥350	26 (5.4)	10 (8.3)	
Postpartum SI			
<1	30 (6.2)	13 (10.7)	0.145
1–1.4	340 (70.6)	86 (71.1)	
≥1.5	112 (23.2)	22 (18.2)	

The values are given in the form of a number (percentage) or mean ± SD or median and interquartile range.
The Chi-square test were used for categorical variables. The independent sample t-tests or Mann-Whitney U-tests were used for continuous variables.
BMI, body mass index; IUBT, intrauterine balloon tamponade; PPH, postpartum hemorrhage.

TABLE 2 | Outcomes of women with PPH treated by IUBT due to uterine atony or placental site bleeding.

	Uterine atony (n = 482)	Placental site bleeding (n = 121)	*P*-value
Transfusion of ≥4 units of PRBCs			
Yes	81 (16.8)	42 (34.7)	<0.001
No	401 (83.2)	79 (65.3)	
EBL ≥ 300 ml after IUBT			
Yes	99 (20.5)	53(43.8)	<0.001
No	383 (79.5)	68(56.2)	
UAE or hysterectomy			
Yes	17 (3.5)	10 (8.3)	0.029
No	465 (96.5)	111 (91.7)	

The values are given in the form of a number (percentage).
The Chi-square test were used for categorical variables.
CI, confidence interval; EBL, estimated blood loss; IUBT, intrauterine balloon tamponade; OR, odds ratio; PPH, postpartum hemorrhage; PRBCs, packed red blood cell; UAE, uterine artery embolization.

abnormalities (placental invasion, or placenta residue), or if the bleeding point was clearly indicated to be located in the placental bed, the main indication was defined as placental site bleeding.

We created a subset cohort of eligible women who performed IUBT based on the following exclusion criteria: underwent IUBT due to placental site bleeding combined with uterine atony, IUBT was inserted when PPH < 1,000 ml, and performed prophylactic IUBT due to high-risk delivery factors (e.g., central placenta previa, coagulation disorders, uterine malformation, etc.).

IUBT Placement and Removal

The IUBT device used in the institution was the Bakri balloon (Bakri Medical, Bloomington, USA). According to the cervical opening, the IUBT balloon was inserted through the cesarean incision or vagina. When the IUBT balloon was inserted through the cesarean incision, a volume of saline was first flushed in based on the operator's estimated size of the uterine cavity to prevent dislodgement during the operation. After suturing the incision, saline was flushed again in under ultrasound guidance until the blood flow through the device catheter was reduced significantly. When the IUBT balloon was inserted through the vagina, a one-time flush of saline is applied to the balloon if the ultrasound observes that the balloon is in the correct position. After the operation, a large piece of gauze approximately 10 cm wide was filled into the vagina to prevent the balloon from falling out of its normal position. The time of IUBT placement and the total volume of saline flushed into the balloon are recorded. After IUBT, the patients were monitored in the monitoring ward for a period of time, which included blood pressure, heart rate, and other vital signs, as well as assessment of ongoing blood loss. The duration of IUBT was decided by the physician based on the patient's condition and EBL and usually takes no more than 24 h. Prior to the IUBT balloon removal, 20 U of oxytocin was administered intravenously. During the procedure, 50 mL of saline was withdrawn from the IUBT balloon every 15 min with assisted uterine massage, and the balloon and vaginal gauze were withdrawn if there was no active bleeding.

Data Collection

All study data was obtained from electronic cases. Demographic and obstetric data included maternal age at delivery (years), pre-pregnancy BMI (kg/m^2), nulliparous (yes, no), multiple gestation (yes, no), premature birth (yes, no), induction of labor (yes, no), history of PPH (yes, no), antenatal hemoglobin (g/dl), delivery mode (cesarean, vaginal). IUBT-related data included: surgical hemostasis before IUBT (none, intrauterine suture, B-Lynch suture), uterotonics before IUBT (0 or 1, ≥2), time from birth to IUBT (min), IUBT volume (<250, 250–349, ≥350 ml), duration of IUBT (hours), postpartum shock index (SI; calculated as the ratio of heart rate to systolic blood pressure) (<1, 1–1.4, ≥1.5).

TABLE 3 | Risk factors for the prevalence of transfusion ≥ 4 units of PRBCs.

	Univariate		Multivariate	
	OR (95% CI)	***P*-value**	**aOR (95% CI)**	***P*-value**
IUBT indications				
Uterine atony	Reference	–	Reference	–
Placental site bleeding	2.63 (1.69–4.10)	<0.001	2.47 (1.32–3.98)	<0.001
Maternal age	1.03 (0.94–1.05)	0.791	–	–
Multiple gestation	1.56 (0.82–2.89)	0.411	–	–
Antenatal hemoglobin(mg/dl)	0.62 (0.41–0.87)	0.023	0.60 (0.41-0.83)	0.019
Delivery mode				
Vaginal	Reference	–	–	–
Cesarean	1.03 (0.74–1.44)	0.792	–	–
Time from birth to IUBT (min)	1.02 (0.91–1.03)	0.834	–	–
Duration of IUBT (h)	1.13 (0.66-1.87)	0.079	–	–
IUBT volume (ml)				
250–350	Reference	–	Reference	–
<250	1.28 (0.81–1.88)	0.523	–	–
≥350	3.58 (1.88–6.79)	< 0.001	3.43 (1.76–6.52)	< 0.001
Postpartum SI				
<1	Reference	–	Reference	–
1–1.4	1.69 (1.10–2.32)	0.011	1.72 (1.28–2.57)	0.009
≥1.5	3.27 (1.82–4.55)	< 0.001	3.43 (2.22–4.89)	< 0.001

CI, confidence interval; EBL, estimated blood loss; OR, odds ratio; PRBCs, packed red blood cell; IUBT, intrauterine balloon tamponade; PPH, postpartum hemorrhage; UAE, uterine artery embolization; SI, shock index.

Outcomes

PPH outcomes included UAE or hysterectomy, EBL ≥ 300 ml after IUBT, and transfusion of ≥4 units of packed red blood cells (PRBCs). Intrauterine suture and B-Lynch suture were not included, as these measures may have been used before IUBT. UAE implemented prior to IUBT is not counted. The output from the IUBT device itself, the weight of disposable pads and drapes, and the number of blood-soaked sponges were all used to calculate EBL after IUBT. All caregivers of PPH patients have been trained in standardized bleeding estimation.

Statistical Methods

Distributions of maternal demographic, obstetric, and IUBT-related data were shown as numbers (percentages) or mean ± SD or median and interquartile range. The chi-square test was used to compare categorical variables and the independent sample *t*-tests or Mann-Whitney *U*-tests were used to compare continuous variables. Crude ratios (OR) and 95% confidence intervals were calculated for all factors studied in the analysis. Univariate and multivariate logistic regression analyses were performed to identify independent prognostic factors for each PPH outcome. We examined potential confounders for multivariate modes based on a literature review and included factors from univariate analysis with *p*-values < 0.20. The following variables were included in the multivariate logistic regression analysis: maternal age, multiple gestation, antenatal hemoglobin, delivery mode, time from birth to IUBT, IUBT volume, duration of IUBT, postpartum SI.

All data was processed using SPSS 25.0 (Windows, IBM, Armonk, NY, USA). Statistical significance was defined as *p*-values < 0.05.

Ethics

The protocol was approved by the IPMCH Ethics Committee and the requirement for informed consent was waived (GKLW 2021–55). Since our study is a retrospective cohort study, clinical trial registration is not required. All procedures followed were carried out in accordance with the Helsinki Declaration's ethical standards.

RESULTS

During the study time frame (9 years), a total of 134,780 deliveries were performed at our institution, including 742 women with IUBT for PPH, of which 139 were excluded. Finally, 603 women were included in the study, with 482 (79.9%) having uterine atony as the main indication and 121 (20.1%) having placental site bleeding as the main indication (**Figure 1**). During the study period, there were 18 women with PPH ≥ 3,000 ml, 10 of whom had uterus hysterectomy, and there were no maternal deaths due to PPH or related complications.

Maternal demographics, obstetric baseline, and IUBT-related data are presented in **Table 1**. Compared with the group with uterine atony, the group with placental site bleeding had a greater proportion of parous women (57.9 vs. 42.9%, $p = 0.004$) and premature births (14.9 vs. 6.0%, $p = 0.002$), but the rate of induction of labor was relatively low (20.7 vs. 40.5%, $p <$

TABLE 4 | Risk factors for the prevalence of EBL ≥ 300 ml after IUBT.

	Univariate		Multivariate	
	OR (95% CI)	***P*-value**	**aOR (95% CI)**	***P*-value**
IUBT indications				
Uterine atony	Reference	–	Reference	–
Placental site bleeding	3.02 (1.98–4.60)	<0.001	3.78 (2.22–5.33)	<0.001
Maternal age	0.97 (0.72–1.18)	0.329	–	–
Multiple gestation	1.67 (0.83–2.76)	0.222	–	–
Antenatal hemoglobin(mg/dl)	0.89 (0.66–1.09)	0.143	–	–
Delivery mode				
Vaginal	Reference	–	–	–
Cesarean	0.66 (0.37–1.27)	0.087	–	–
Time from birth to IUBT (min)	0.93 (0.67–1.12)	0.286	–	–
Duration of IUBT (h)	1.24 (1.03–1.78)	0.033	1.27 (1.04-1.62)	0.028
IUBT volume (ml)				
250–350	Reference	–	Reference	–
<250	1.28 (0.81–1.93)	0.412	–	–
≥350	2.26 (1.21–3.79)	0.019	2.32 (1.27–3.98)	0.013
Postpartum SI				
<1	Reference	–	–	–
1–1.4	1.24 (0.59–2.07)	0.482	–	–
≥1.5	1.58 (0.83–2.79)	0.369	–	–

CI, confidence interval; EBL, estimated blood loss; OR, odds ratio; PRBCs, packed red blood cell; IUBT, intrauterine balloon tamponade; PPH, postpartum hemorrhage; UAE, uterine artery embolization; SI, shock index.

0.002). The proportion of two or more uterotonics applied was higher in the group with uterine atony compared with the group with placental site bleeding (91.5 vs. 82.6%, $p = 0.009$). No significant differences were seen in the maternal age, pre-pregnancy BMI, multiple gestation, history of PPH, antenatal hemoglobin, delivery mode, surgical hemostatic before IUBT, time from birth to IUBT, IUBT volume, duration of IUBT, or postpartum SI between the two groups (both $p \geq 0.05$).

Univariate analysis was performed with IUBT indication as a covariate and PPH outcomes as a dependent variable. The incidence of transfusion ≥ 4 units of PRBCs was significantly higher in the group with placental site bleeding than in the group with uterine atony (34.7 vs. 16.8%, $p < 0.001$). Similar results were observed for EBL ≥ 300 ml after IUBT (43.8 vs. 20.0%, $p < 0.001$) and UAE or hysterectomy (8.3 vs. 3.5%, $p = 0.029$) (**Table 2**).

Adjusting for confounding factors by multivariate logistic regression analysis, in general, PPH outcomes were worse in those who underwent IUBT for placental site bleeding. Placental site bleeding increased the risk of transfusion ≥ 4 units of PRBCs (aOR 2.47, 95% CI 1.32–3.98), EBL ≥ 300 ml after IUBT (aOR 3.78, 95% CI 2.22–5.33), and UAE or hysterectomy (aOR 2.52, 95% CI 1.20–6.01) when compared to uterine atony. The higher antenatal hemoglobin values were negatively correlated with the incidence of transfusion ≥ 4 units of PRBCs (aOR 0.60, 95% CI 0.41–0.83) and UAE or hysterectomy (aOR 0.71, 95% CI 0.32–0.90). Different cut-off values were used to stratify the IUBT volume. We observed that the risk of transfusion ≥ 4 units of PRBCs (aOR 3.43, 95%CI 1.76–6.52) and EBL ≥ 300 ml (aOR 2.32, 95%CI 1.27–3.98) was significantly increased when IUBT volume ≥ 350 ml. Interestingly, as the prolonged duration of IUBT increased, the risk of EBL ≥ 300 ml was significantly increased (aOR 1.27, 95%CI 1.04–1.62). As in clinical practice, an SI value ≥ 1.5 was significantly associated with an increased risk of transfusion ≥ 4 units of PRBCs (aOR 3.43, 95%CI 1.76–6.52) and UAE or hysterectomy (aOR 2.29, 95%CI 1.06–4.14) (**Tables 3**–**5**).

DISCUSSION

Main Findings

This retrospective cohort study demonstrated that the therapeutic effect of IUBT for severe PPH was not the same for different indications. We also found a significant association between antenatal hemoglobin, IUBT volume, duration of IUBT, postpartum SI, and PPH outcomes.

Interpretation

We found that in PPH patients, IUBT performed in the placental site bleeding group was more likely to have adverse PPH outcomes compared to the uterine atony group. Although IUBT was originally proposed by Bakri to be used in PPH patients with placenta previa or low-lying placenta (8), the sample size was only 5, and the study efficacy was limited. Previous studies have shown that placenta accreta spectrum (PAS) was negatively associated with the success of IUBT (12, 13). According to Liu et al. (14), IUBT was only 54.8% successful in cases with previa abnormalities. Our study indicates that perhaps IUBT for

TABLE 5 | Risk factors for the prevalence of UAE or hysterectomy.

	Univariate		Multivariate	
	OR (95% CI)	***P*-value**	**aOR (95% CI)**	***P*-value**
IUBT indications				
Uterine atony	Reference	–	Reference	–
Placental site bleeding	2.46 (1.10–5.53)	0.029	2.52 (1.20–6.01)	0.023
Maternal age	1.14 (0.72–1.52)	0.721	–	–
Multiple gestation	1.22 (0.78–1.62)	0.182	–	–
Antenatal hemoglobin(mg/dl)	0.73 (0.34-0.92)	0.033	0.71 (0.32-0.90)	0.029
Delivery mode				
Vaginal	Reference	–	–	–
Cesarean	1.29 (0.92–2.04)	0.132	–	–
Time from birth to IUBT (min)	1.01 (0.65–1.99)	0.826	–	–
Duration of IUBT (h)	0.92 (0.31-1.40)	0.423	–	–
IUBT volume (ml)				
250–350	Reference	–	Reference	–
<250	0.96 (0.49–1.34)	0.780	–	–
≥350	1.11 (1.03–1.68)	0.038	1.09 (1.01–1.47)	0.043
Postpartum SI				
<1	Reference	–	Reference	–
1–1.4	1.43 (0.82–3.01)	0.108	–	–
≥1.5	2.33 (1.07–4.66)	0.032	2.29 (1.06–4.14)	0.040

CI, confidence interval; EBL, estimated blood loss; OR, odds ratio; PRBCs, packed red blood cell; IUBT, intrauterine balloon tamponade; PPH, postpartum hemorrhage; UAE, uterine artery embolization; SI, shock index.

PPH due to placental abnormalities is not the best management measure given the high incidence of adverse outcomes after placement. In cases with placental abnormalities, the placenta was often unable to detach from the uterine wall, and manual detachment may result in active bleeding due to damage to the myometrium. Whether the compression force of the balloon alone to stop bleeding can achieve the ultimate therapeutic effect remains to be further investigated. However, it is worth mentioning that IUBT is a simple and rapid way to stop bleeding. IUBT can be used as a temporary hemostatic measure until other treatment measures are prepared, even if the final treatment is ineffective.

The present study found a correlation between higher prenatal hemoglobin levels and good outcomes in PPH patients treated with IUBT, which was consistent with previous research (15). To reduce the morbidity associated with PPH, the Royal College of Obstetricians and Gynecologists published guidelines in 2016 recommending that antenatal anemia be investigated and treated appropriately (2). A higher prenatal hemoglobin value means that the mother has a greater reserve capacity for blood loss, which is an important guideline for managing PPH.

SI aids in predicting the severity of early hypovolemic states and determining the need for transfusion or surgical treatment in cases of massive blood loss (16). SI has always been equally important in determining the need for intervention in PPH, and it plays a more important role than HR and BP indicators (17). According to the findings of this study, elevated SI values are an important predictor of postpartum transfusion and the need for additional invasive procedures.

Ji et al. suggested in a retrospective cohort study of 289 individuals (15) that IUBT volume > 350 ml was associated with adverse PPH outcomes. Similar results were obtained in our study. A reasonable explanation is that a larger IUBT volume may suggest a softer uterus or require more pressure to compress the uterine cavity to stop the bleeding. The conclusion that some studies (18) have reported greater amounts of fluid required to fill the balloon and a higher rate of IUBT failure in the case of multiple and twin births validates the findings mentioned above to some extent. However, it is worth mentioning that the direct cause of the adverse PPH outcomes was the patient's underlying condition rather than the more fluid. IUBT volume can be used as a proxy when it is not possible to quantify the degree of uterine softness or the required pressure to stop bleeding in patients with PPH.

To our knowledge, no previous studies have demonstrated the impact of IUBT duration time on PPH outcomes. Although the instructions recommend placement for no longer than 24 h, various guidelines do not suggest how long IUBT placement should be retained. The present study showed a positive correlation between prolonged IUBT duration time and EBL ≥ 300 ml. Alouini (19) suggests that the additional IUBT placement time may be due to persistent uterine bleeding without other techniques to control the bleeding. We believe well-designed

prospective studies are required if precise conclusions are desired.

Strengths and Limitations

First, thanks to the high volume of deliveries at our institution, this study included 603 participants, which is a larger sample size than any previous one. Second, we refined the PPH outcomes after IUBT into EBL > 300 ml, transfusion > 4 units PRBCs, and UAE or hysterectomy, which allowed a more adequate assessment of maternal changes after IUBT. The main limitation of this study is that it is a retrospective study because PPH treatment is often performed in emergency situations and it is difficult to perform controlled trials. Bias in data quality and sample selection is difficult to avoid. Also, the etiology of PPH in patients sometimes overlaps, e.g., uterine atony may be secondary to placental abnormalities, the main cause of which depends mainly on the clinician's determination.

CONCLUSION

In this study, our data suggest that IUBT is a relatively reliable treatment for PPH, but its therapeutic efficacy varies depending on the indication for placement. Patients with PPH due to placental site bleeding should receive more attention in clinical practice. Prenatal hemoglobin and SI are good predictors of PPH outcome, and clinicians should actively correct anemia and closely monitor SI values in patients with PPH. The causal relationship between the IUBT volume, the IUBT duration time, and the PPH outcomes still needs to be corroborated by a large number of controlled trials.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by GKLW 2021–55. The Ethics Committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

This study was designed by CX, XChe, and LW, who also analyzed and interpreted the data. CX and YC gathered information and wrote the manuscript. All authors discussed the findings, contributed to the article, and signed off on the final draft.

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REFERENCES

1. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health*. (2014) 2:e323–33. doi: 10.1016/S2214-109X(14)70227-X
2. Prevention and management of postpartum hemorrhage: green-top guideline no. 52. *BJOG*. (2017) 124:e106–49. doi: 10.1111/1471-0528.14178
3. Zeng Y, Hesketh T. The effects of China's universal two-child policy. *Lancet*. (2016) 388:1930–8. doi: 10.1016/S0140-6736(16)31405-2
4. Li HT, Xue M, Hellerstein S, Cai Y, Gao Y, Zhang Y, et al. Association of China's universal two child policy with changes in births and birth related health factors: national, descriptive comparative study. *BMJ*. (2019) 366:l4680. doi: 10.1136/bmj.l4680
5. Doumouchtsis SK, Papageorghiou AT, Arulkumaran S. Systematic review of conservative management of postpartum hemorrhage: what to do when medical treatment fails. *Obstet Gynecol Surv*. (2007) 62:540–7. doi: 10.1097/01.ogx.0000271137.81361.93
6. Hayman RG, Arulkumaran S, Steer PJ. Uterine compression sutures: surgical management of postpartum hemorrhage. *Obstet Gynecol*. (2002) 99:502–6. doi: 10.1097/00006250-200203000-00022
7. Dahlke JD, Mendez-Figueroa H, Maggio L, Hauspurg AK, Sperling JD, Chauhan SP, et al. Prevention and management of postpartum hemorrhage: a comparison of 4 national guidelines. *AJOG*. (2015) 213:76.e1–10. doi: 10.1016/j.ajog.2015.02.023
8. Bakri YN, Amri A, Abdul Jabbar F. Tamponade-balloon for obstetrical bleeding. *Int J Gynaecol Obstet*. (2001) 74:139–42. doi: 10.1016/S0020-7292(01)00395-2
9. Revert M, Cottenet J, Raynal P, Cibot E, Quantin C, Rozenberg P. Intrauterine balloon tamponade for management of severe postpartum hemorrhage in a perinatal network: a prospective cohort study. *BJOG*. (2017) 124:1255–62. doi: 10.1111/1471-0528.14382
10. Kaya B, Tuten A, Daglar K, Misirlioglu M, Polat M, Yildirim Y, et al. Balloon tamponade for the management of postpartum uterine hemorrhage. *J Perinat Med*. (2014) 42:745–53. doi: 10.1515/jpm-2013-0336
11. Suarez S, Conde-Agudelo A, Borovac-Pinheiro A, Suarez-Rebling D, Eckardt M, Theron G, et al. Uterine balloon tamponade for the treatment of postpartum hemorrhage: a systematic review and meta-analysis. *Am J Obstet Gynecol*. (2020) 222:293.e1–52. doi: 10.1016/j.ajog.2019.11.1287
12. Kong CW, To WW. Prognostic factors for the use of intrauterine balloon tamponade in the management of severe postpartum hemorrhage. *Int J Gynaecol Obstet*. (2018) 142:48–53. doi: 10.1002/ijgo.12498
13. Maher MA, Abdelaziz A. Comparison between two management protocols for postpartum hemorrhage during cesarean section in placenta previa: balloon protocol versus non-balloon protocol. *J Obstet Gynaecol Res*. (2017) 43:447–55. doi: 10.1111/jog.13227
14. Liu C, Gao J, Liu J, Wang X, He J, Sun J, et al. Predictors of failed intrauterine balloon tamponade in the management of severe postpartum hemorrhage. *Front Med*. (2021) 8:656422. doi: 10.3389/fmed.2021.656422
15. Park JE, Park JK, Jo HC, Cho IA, Baek JC. The association between intrauterine balloon tamponade volume and postpartum hemorrhage outcomes. *Int J Gynaecol Obstet*. (2020) 148:325–30. doi: 10.1002/ijgo.13069
16. Jaramillo S, Barnhart K, Takacs P. Use of the shock index to predict ruptured ectopic pregnancies. *Int J Gynaecol Obstet*. (2011) 112:68. doi: 10.1016/j.ijgo.2010.08.005

17. Kohn JR, Dildy GA, Eppes CS. Shock index and delta-shock index are superior to existing maternal early warning criteria to identify postpartum hemorrhage and need for intervention. *J Matern Fetal Neonatal Med.* (2019) 32:1238–44. doi: 10.1080/14767058.2017.1402882
18. Vitthala S, Tsoumpou I, Anjum ZK, Aziz NA. Use of Bakri balloon in post-partum hemorrhage: a series of 15 cases. *Aust N Z J Obstet Gynaecol.* (2009) 49:191–4. doi: 10.1111/j.1479-828X.2009.00968.x
19. Alouini S. Excessive duration of intrauterine balloon placement. *Am J Obstet Gynecol.* (2017) 217:226. doi: 10.1016/j.ajog.2017.04.001

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Prevalence, Associated Factors, and Survival Outcomes of Small-Cell Neuroendocrine Carcinoma of the Gynecologic Tract: A Large Population-Based Analysis

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Small-cell carcinomas are highly malignant tumors with neuroendocrine function and which often occur in the lungs. Primary small-cell neuroendocrine carcinomas of the gynecologic tract are extremely rare. This study aimed to evaluate the prevalence of independent predictors related to the prognosis and overall survival of patients with small-cell neuroendocrine carcinomas of the gynecologic tract. Patients with gynecologic small-cell neuroendocrine carcinomas diagnosed between 1973 and 2015 were identified from the Surveillance, Epidemiology, and End Results database. Univariate and multivariate Cox risk regression analyses were performed to determine the independent predictors of overall survival. Overall survival was calculated using the Kaplan–Meier method, and the log-rank test was used for comparison. We included 5,15,393 eligible carcinomas in the present study; the prevalence of gynecologic small-cell neuroendocrine carcinomas was 0.121% (N = 622). Multivariate analysis indicated that advanced age, stage III and IV cancer, and no chemotherapy treatment may be predictors of poor small-cell neuroendocrine cervical carcinoma prognosis. Stage III and IV cancer and lack of surgery, radiotherapy, or chemotherapy were identified as potential predictors of poor prognosis in patients with ovarian small-cell neuroendocrine carcinoma. Kaplan–Meier analysis suggested that the median survival was 19, 11, and 12 months for cervical, ovarian, and endometrial small-cell neuroendocrine carcinomas, respectively. The 1-, 3-, and 5-year overall survival rates were as follows: 58.8, 31.4, and 26.1%, respectively, for small-cell neuroendocrine cervical carcinoma; 46.3, 23.5, and 22.0%, respectively, for ovarian small-cell neuroendocrine carcinoma; and 49.4, 29.4, and 25.9%, respectively, for endometrial small-cell neuroendocrine carcinoma. Our findings indicate that comprehensive and individualized treatment of small-cell neuroendocrine carcinomas of the gynecologic tract may prolong patient survival, although further studies are required.

Keywords: small cell carcinoma, neuroendocrine carcinoma, prevalence, prognosis, ovarian epithelial carcinoma, endometrial neoplasms, cervical carcinoma

INTRODUCTION

Small-cell carcinomas are highly malignant tumors with neuroendocrine function, often occurring in the lungs. Primary small-cell neuroendocrine carcinomas of the gynecologic tract are extremely rare; they most often occur in the cervix, followed by the ovary and endometrium (1).

While case studies and studies of single gynecological neuroendocrine cancers exist (2, 3), no large-scale studies have investigated treatment strategies and patient prognosis across different areas of the gynecologic tract. Additionally, there is currently no conventional guideline, unified treatment plan, or method for prognostic evaluation for gynecologic small-cell neuroendocrine carcinoma. This study aimed to investigate the prevalence, risk factors, and survival outcomes of gynecologic small-cell neuroendocrine carcinoma using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) dataset.

MATERIALS AND METHODS

Data Source and Patient Selections

The patients and related data were recruited and obtained from the SEER database, respectively. We enrolled patients with primary gynecologic small-cell neuroendocrine carcinoma initially diagnosed between 1973 and 2015. The site International Classification of Diseases for Oncology 3 code was 8041/3 (small-cell carcinoma), while the World Health Organization 2008 designations were restricted to cervical, ovarian, and uterine corpus. The exclusion criteria were as follows: age <18 years, diagnosis of carcinoma *in situ*, benign or borderline tumors, diagnosis at autopsy or *via* death certificate, presence of a non-primary gynecologic small-cell neuroendocrine carcinoma, missing/unknown cause of death, and miscellaneous malignant cancer. SEER*Stat 8.3.8 software[1] was used to generate case listings. The deidentified data in the SEER database are publicly available; thus, their use is exempt from review by the Shengjing Hospital Affiliated to China Medical University Institutional Review Board.

Clinical and Demographic Characteristics

We analyzed the patients' demographic data, including age at diagnosis (<45, 45–64, 65–84, ≥85 years), race (white, black, other, and unknown), marital status (single/unmarried, married, divorced/separated, widowed, and unknown), insurance status (insured, any Medicaid, uninsured, and unknown), year of diagnosis (1973–2015), tumor stage and grade (IA-IVB or unknown; well-differentiated, moderately differentiated, poorly differentiated, undifferentiated, or unknown), lymph node status (negative, positive, not examined, and unknown), number of lymph node metastases (none, 1–3, ≥4, and unknown), bone metastasis (yes, no), brain metastasis (yes, no), liver metastasis (yes, no), and lung metastasis (yes, no). Treatment patterns included surgery (yes, no), chemotherapy (yes, no), and radiotherapy (yes, no).

Statistical Analysis

The patients' clinical and demographic characteristics were compared using chi-square tests or Fisher's exact test. Categorical data are presented as numbers and percentages (N,%). Quantitative data are presented as the mean ± standard deviation. Univariate and multivariate Cox risk regression analyses were performed to determine independent predictors of overall survival. Overall survival was calculated using the Kaplan–Meier method, and the log-rank test was used for comparison. All data were analyzed using SPSS software (version 23.0; SPSS, Chicago, IL, United States). Kaplan–Meier survival curves were drawn using GraphPad Prism (GraphPad Software, San Diego, CA, United States), and *P*-values <0.05 were considered significant.

In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers upon request.

RESULTS

The prevalence of cervical small-cell neuroendocrine carcinoma was higher among married, divorced/separated, and widowed patients than among single/unmarried patients ($P = 0.001$) and among uninsured patients and those with any form of Medicaid than among insured patients ($P < 0.001$). Stages II–IV were associated with a higher prevalence than stage I ($P < 0.001$).

Additionally, diagnosis between 2004 and 2015 was associated with a higher prevalence of cervical small-cell neuroendocrine carcinoma than diagnosis before 2004 ($P < 0.001$). The prevalence was also higher for moderately differentiated, poorly differentiated, and undifferentiated tumors than for well-differentiated tumors ($P < 0.001$). Positive lymph nodes or non-examined lymph nodes were associated with a higher prevalence of cervical small-cell neuroendocrine carcinoma than negative lymph nodes ($P < 0.001$). Prevalence was also higher among patients with bone, brain, liver, and lung metastases than those without (**Table 1**).

Treatment patterns differed between the cervical small-cell neuroendocrine carcinoma and cervical cancer groups. Patients with cervical small-cell neuroendocrine carcinoma were more likely to receive adjuvant chemotherapy (77.9% vs. 29.5%; $P < 0.001$) and adjuvant radiotherapy (28.0% vs. 47.6%; $P < 0.001$) than those with cervical cancer. Additionally, patients with cervical small-cell neuroendocrine carcinoma were less likely to receive adjuvant surgery than those with cervical cancer (40.5% vs. 50.7%; $P < 0.001$; **Table 1**).

The prevalence of ovarian small-cell neuroendocrine carcinoma was higher in the ≥85-year age group than in the 45–64-year age group ($P < 0.001$) Furthermore, diagnosis between 2004 and 2015 was associated with a higher prevalence of ovarian small-cell neuroendocrine carcinoma than diagnosis prior to 2004 ($P < 0.001$). The prevalence of ovarian small-cell

[1]https://seer.cancer.gov/data/

neuroendocrine carcinoma was also higher for moderately differentiated, poorly differentiated, and undifferentiated tumors than for well-differentiated tumors ($P < 0.001$). Positive or non-examined lymph nodes were associated with a higher prevalence of ovarian small-cell neuroendocrine carcinoma than negative lymph nodes ($P = 0.049$). The prevalence was also higher among patients with bone, brain, and liver metastases than those without (**Table 1**).

TABLE 1 | Demographic and clinical characteristics of patients with small-cell neuroendocrine carcinoma of the gynecologic tract (SCNCGT) and carcinoma of the gynecologic tract (CGT).

Patient	SCNCC	CC		SCNCO	OC		SCNCE	EC	
characteristics	**N(%)**	**N (%)**	***P-value***	**N (%)**	**N (%)**	***P-value***	**N (%)**	**N (%)**	***P-value***
ALL	299(0.32)	94179(99.68)		217(0.15)	145595(99.85)		106(0.04)	275619(99.96)	
Age at diagnosis (years)			0.41			**<0.001**			0.16
<45	137(45.8)	37952(40.3)		135(62.2)	18933(13.0)		7(6.6)	19742(7.2)	
45–64	116(38.8)	36171(38.4)		36(16.6)	59788(41.1)		42(39.6)	133542(48.5)	
65–84	43(14.4)	17524(18.6)		41(18.9)	56839(39.0)		49(46.2)	110212(40.0)	
≥85	3(1.0)	2532(2.7)		5(2.3)	10035(6.9)		8(7.6)	12123(4.3)	
Race			0.094			0.685			0.169
White	211(70.6)	70994(75.4)		184(84.8)	124025(85.2)		84(79.2)	232111(84.2)	
Black	46(15.4)	13556(14.4)		14(6.5)	10856(7.5)		14(13.2)	22617(8.2)	
Other	40(13.4)	8811(9.4)		18(8.3)	10294(7.1)		8(7.6)	19395(7.0)	
Unknown	2(0.6)	818(0.8)		1(0.4)	420(0.2)		0(0.00)	1496(0.6)	
Marital status			**<0.001**			**<0.001**			**0.007**
Single/unmarried	95(31.8)	20585(21.9)		88(40.5)	23716(16.3)		17(16.0)	45214(16.4)	
Married	114(38.1)	41797(44.4)		90(41.5)	70767(48.6)		39(36.8)	141684(51.4)	
Divorced/separated	45(15.1)	13663(14.5)		18(8.3)	14925(10.3)		14(13.2)	24359(8.8)	
Widowed	32(10.7)	12564(13.3)		14(6.5)	30838(21.2)		30(28.3)	51591(18.8)	
Unknown	13(4.3)	5570(5.9)		7(3.2)	5349(3.6)		6(5.7)	12771(4.6)	
Insurance status			**<0.001**			**0.006**			**0.017**
Insured	148(49.5)	18486(19.6)		72(33.2)	41788(28.7)		32(30.2)	95130(34.5)	
Any medicaid	62(20.7)	8802(9.3)		24(11.1)	6623(4.5)		11(10.4)	12520(4.5)	
Uninsured	22(7.4)	2124(2.3)		4(1.8)	1999(1.4)		2(1.8)	3766(1.4)	
Unknown	67(22.4)	64767(68.8)		117(53.9)	95185(65.4)		60(56.6)	164203(59.6)	
Stage			**<0.001**			0.856			**<0.001**
I	61(20.4)	18441(19.6)		31(14.3)	14967(10.3)		7(6.6)	90296(32.8)	
II	16(5.4)	5298(5.6)		9(4.1)	5295(3.6)		2(1.8)	9606(3.5)	
III	90(30.1)	8129(8.6)		41(18.9)	22656(15.6)		20(18.8)	17635(6.4)	
IV	126(42.1)	8818(9.4)		53(24.4)	25284(17.4)		30(28.3)	16770(6.1)	
Unknown	6(2.0)	53493(56.8)		83(38.3)	77393(53.1)		47(44.3)	141312(51.2)	
Year of diagnosis			**<0.001**			**<0.001**			0.622
<2004	0(0.00)	52949(56.2)		81(37.3)	75539(51.9)		47(44.3)	130000(47.1)	
2004–2006	63(21.1)	10339(11.0)		29(13.4)	17170(11.8)		11(10.4)	30463(11.1)	
2007–2009	76(25.4)	10548(11.2)		42(19.4)	17708(12.2)		18(17.0)	34533(12.5)	
2010–2012	68(22.7)	10162(10.8)		28(12.9)	17522(12.0)		12(11.3)	38478(14.0)	
2013–2015	92(30.8)	10181(10.8)		37(17.0)	17656(12.1)		18(17.0)	42145(15.3)	
Grade			**<0.001**			**<0.001**			**<0.001**
Well differentiated	1(0.3)	7816(8.3)		0(0.00)	10321(7.1)		3(2.8)	93778(34.0)	
Moderately differentiated	1(0.3)	23526(25.0)		1(0.5)	18686(12.8)		1(1.0)	68926(25.0)	
Poorly differentiated	110(36.8)	24415(25.9)		47(21.7)	41580(28.5)		36(34.0)	45577(16.5)	
Undifferentiated	63(21.1)	2361(2.5)		73(33.6)	15085(10.4)		40(37.7)	14291(5.2)	
Unknown	124(41.5)	36061(38.3)		96(44.2)	59923(41.2)		26(24.5)	53047(19.2)	
Lymph nodes status			**<0.001**			**0.049**			**<0.001**
Negative	48(16.1)	20707(22.0)		49(22.6)	31304(21.5)		16(15.1)	99960(36.3)	
Positive	49(16.4)	6281(6.7)		37(17.1)	15053(10.3)		25(23.6)	16289(5.9)	

SCNCC, small-cell neuroendocrine carcinoma of the cervix; SCNCO, small-cell neuroendocrine carcinoma of the ovary; SCNCE, small-cell neuroendocrine carcinoma of the endometrium; SNNCC, small-cell neuroendocrine carcinoma of the cervix; OC, carcinoma of the ovary; EC, carcinoma of the endometrium; NA, Not available. All factors with unknown data were removed in logistic regression. Bold value means p < 0.05.

Treatment patterns differed between the ovarian small-cell neuroendocrine carcinoma and ovarian cancer groups. Patients with ovarian small-cell neuroendocrine carcinoma were more likely to receive adjuvant chemotherapy (73.7% vs. 59.6%) ($P < 0.001$) and adjuvant radiotherapy (7.40% vs. 3.1%; $P < 0.001$) than those with ovarian cancer. Additionally, the rate of adjuvant surgery was not significantly different between these groups (80.6% vs. 75.4%; $P = 0.166$) (**Table 1**).

The prevalence of endometrial small-cell neuroendocrine carcinoma was higher among married, divorced/separated, and widowed patients than among single/unmarried patients ($P = 0.007$). Stages II–IV were also associated with a higher prevalence than stage I ($P < 0.001$). Prevalence was also higher for moderately differentiated, poorly differentiated, and undifferentiated tumors than for well-differentiated tumors ($P < 0.001$). Positive or non-examined lymph nodes were associated with a higher prevalence of endometrial small-cell neuroendocrine carcinoma than negative lymph nodes ($P < 0.001$). The prevalence of endometrial small-cell neuroendocrine carcinoma was also higher among patients with brain, liver, and lung metastases than those without (**Table 1**).

Treatment patterns differed between the endometrial small-cell neuroendocrine carcinoma and endometrial cancer groups. Patients with endometrial small-cell neuroendocrine carcinoma were more likely to receive adjuvant chemotherapy than those with endometrial cancer (57.5% vs. 13.1%) ($P < 0.001$). Additionally, patients with endometrial small-cell neuroendocrine carcinoma were less likely to receive adjuvant radiotherapy (15.1% vs. 25.6%; $P < 0.001$) and adjuvant surgery (60.4% vs. 89.5%; $P < 0.001$) than those with endometrial cancer (**Table 1**).

In the univariate Cox regression analysis, age, marital status, stage, lymph node status, lymph node metastasis, bone metastasis, liver metastasis, lung metastasis, surgery, chemotherapy, and radiotherapy were positively associated with risk of cervical small-cell neuroendocrine carcinoma. Age, marital status, stage, lymph node status, lymph node metastasis, liver metastasis, surgery, chemotherapy, and radiotherapy were positively associated with risk of ovarian small-cell neuroendocrine carcinoma. Furthermore, age, stage, lymph node status, lymph node metastasis, liver metastasis, surgery, chemotherapy, and radiotherapy were positively associated with risk of endometrial small-cell neuroendocrine carcinoma (**Table 2**).

In the multivariable Cox regression analysis, risk of death significantly increased in patients with cervical small-cell neuroendocrine carcinoma diagnosed at 45–64 or 65–84 years of age (hazard ratio [HR]: 1.523; 95% confidence interval [CI]: 1.034–2.242 and HR: 2.581; 95% CI: 1.607–4.146, respectively). All patients with cervical small-cell neuroendocrine carcinoma who presented with stages III–IV had a higher death risk than those with other stages; the HRs were 1.993 (95% CI: 1.033–3.847) and 3.020 (95% CI: 1.602–5.693), respectively. Patients with cervical small-cell neuroendocrine carcinoma not treated with adjuvant chemotherapy also had a higher death risk (HR: 2.784, 95% CI: 1.902–4.075) than those who received adjuvant chemotherapy. The death risk was significantly higher in patients with ovarian small-cell neuroendocrine carcinoma diagnosed at stages III–IV than those diagnosed at other stages (III: HR: 3.512, 95% CI: 1.617–7.629; IV: HR: 3.836, 95% CI: 1.744–8.437). Patients with ovarian small-cell neuroendocrine carcinoma who were not treated with adjuvant surgery, chemotherapy, and radiotherapy also had a higher death risk than patients who received adjuvant surgery, chemotherapy, and radiotherapy, with HRs of 2.127 (95% CI: 1.103–4.101), 2.023 (95% CI: 1.152–3.551), and 5.988 (95% CI: 1.350–26.560), respectively. Moreover, patients with endometrial small-cell neuroendocrine carcinoma not treated with adjuvant surgery and chemotherapy also had a higher death risk than patients who received adjuvant surgery and chemotherapy, with HRs of 4.842 (95% CI: 1.552–15.108) and 2.102 (95% CI: 0.964–4.584), respectively (**Table 3**).

The median overall survival time was 13 months for gynecologic small-cell neuroendocrine carcinoma. Median survival times were as follows: 19 months (95% CI: 16.03–21.96) for cervical, 11 months (95% CI: 8.94–13.06) for ovarian, and 12 months (95% CI: 7.17–16.84) for endometrial small-cell neuroendocrine carcinoma (**Figure 1A**, $P = 0.032$).

In Kaplan–Meier analysis, overall survival was worse for patients with cervical small-cell neuroendocrine carcinoma with advanced age (**Figure 1B**, $P < 0.001$), those with stage III and IV diseases (**Figure 1C**, $P < 0.001$) and those who had not undergone chemotherapy (**Figure 1D**, $P = 0.0015$). Survival outcomes were worse for patients with ovarian small-cell neuroendocrine carcinoma diagnosed with stage II disease (**Figure 1E**, $P < 0.001$) and those who had not undergone surgery (**Figure 1F**, $P = 0.0015$), chemotherapy (**Figure 1G**, $P = 0.020$), or radiotherapy (**Figure 1H**, $P = 0.0015$). Furthermore, overall survival was worse for patients with endometrial small-cell neuroendocrine carcinoma who had not undergone surgery (**Figure 1I**, $P = 0.0015$) or chemotherapy (**Figure 1J**, $P = 0.038$).

DISCUSSION

Summary of Main Results

Our study showed that cervical cases were the most common type of gynecologic small-cell neuroendocrine carcinoma, followed by ovarian and endometrial cases. Women with gynecologic small-cell neuroendocrine carcinoma had poor overall survival, and long-term survival was rarely reported, with the highest survival rate observed in cervical cases. Advanced age, stage III and IV cancer, and no chemotherapy treatment were potential predictors of poor prognosis of cervical small-cell neuroendocrine carcinoma, while stage III and IV cancer and lack of surgery, radiotherapy, or chemotherapy were predictors of poor prognosis of ovarian small-cell neuroendocrine carcinoma.

Results in the Context of Published Literature

Previous studies have reported that the incidence of gynecologic small-cell neuroendocrine carcinoma is 2% (4, 5). However, our analysis of SEER data yielded an incidence of only 0.125%. Our data confirmed that women with gynecologic small-cell neuroendocrine carcinoma had poor overall survival. For all

TABLE 2 | Univariable Cox regression for analyzing the associated factors for developing small-cell neuroendocrine carcinoma of the gynecologic tract (SCNCGT).

Subject characteristics	SCNCC		SCNCO		SCNCE	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age at diagnosis (years)		**<0.001**		**<0.001**		**0.004**
<45	Reference		Reference		Reference	
45–64	2.098(1.502–2.928)	**<0.001**	0.251(0.101–0.623)	0.003	0.101(0.91–1.023)	0.007
65–84	3.486(2.308–5.265)	**<0.001**	0.279(0.105–0.740)	0.010	0.149(0.109–1.197)	0.073
≥85	3.073(0.963–9.807)	0.058	0.647(0.253–1.656)	0.364	0.329(0.147–0.739)	0.007
Race		0.152		0.875		0.213
White	Reference		Reference		Reference	
Black	1.545(1.050–2.275)	0.027	1.061(0.574–1.960)	0.850	1.684(0.921–3.079)	0.091
Other	1.254(0.826–1.903)	0.288	0.874(0.495–1.544)	0.643	0.897(0.387–2.020)	0.799
Unknown	NA	NA	NA	NA		NA
Marital status		**0.014**		**<0.001**		0.115
Single/unmarried	Reference		Reference		Reference	
Married	0.997(0.694–1.433)	0.988	1.240(0.882–1.745)	0.216	1.079(0.522–2.232)	0.836
Divorced/separated	1.293(0.831–2.012)	0.255	1.255(0.702–2.244)	0.443	0.913(0.360–2.318)	0.849
Widowed	2.025(1.259–3.259)	0.004	5.652(3.085–10.354)	0.000	1.853(0.895–3.834)	0.096
Unknown	NA	NA				
Insurance status		0.441		0.519		0.334
Insured	Reference		Reference		Reference	
Any medicaid	1.183(0.803–1.743)	0.394	1.341(0.758–2.377)	0.312	1.267(0.512–3.131)	0.609
Uninsured	1.384(0.784–2.443)	0.263	0.736(0.179–3.032)	0.671	1.455(0.883–2.398)	0.141
Unknown	NA	NA				
Stage		**<0.001**		**<0.001**		**0.001**
I	Reference		Reference		Reference	
II	1.322(0.531–3.295)	0.549	3.220(1.225–8.462)	0.018	1.119(0.428–1.508)	0.981
III	2.428(1.455–4.054)	0.001	2.751(1.460–5.185)	0.002	2.442(0.523–11.398)	0.256
IV	4.900(3.017–7.959)	**<0.001**	4.204(2.272–7.778)	**<0.001**	11.294(2.488–51.270)	0.002
Unknown	NA	NA	NA	NA	NA	NA
Year of diagnosis		0.726		0.794		0.082
<2004	NA	NA	Reference		Reference	
2004–2006	Reference		1.019(0.640–1.622)	0.936	0.900(0.434–1.865)	0.777
2007–2009	0.971(0.658–1.433)	0.883	0.975(0.646–1.471)	0.903	0.420(0.202–0.871)	0.020
2010–2012	0.844(0.560–1.272)	0.418	0.955(0.585–1.559)	0.853	0.700(0.326–1.502)	0.360
2013–2015	0.814(0.525–1.262)	0.359	0.714(0.419–1.217)	0.216	1.426(0.734–2.773)	0.295
Grade		0.325		0.269		0.223
Well differentiated	Reference		–	–	–	–
Moderately differentiated	0.389(0.24–6.307)	0.506	Reference		0.391(0.039–3.891)	0.423
Poorly differentiated	0.231(0.031–1.699)	0.150	1.183(0.711–1.968)	0.519	0.425(0.057–3.189)	0.405
Undifferentiated	0.200(0.027–1.488)	0.116	0.753(0.459–1.237)	0.263	0.507(0.068–3.781)	0.508
Unknown	NA	NA	NA	NA	NA	NA
Lymph nodes status		**<0.001**		**<0.001**		**0.003**
Negative	Reference		Reference		Reference	
Positive	1.931(1.040–3.583)	0.037	2.237(1.307–3.826)	0.003	2.562(1.056–6.218)	0.038
No examined	3.348(1.989–5.637)	**<0.001**	2.781(1.796–4.307)	**<0.001**	3.914(1.738–8.815)	0.001
Unknown	NA	NA	NA	NA	NA	NA
LN metastasis numbers		***p*<0.001**		**<0.001**		**0.002**
No	Reference		Reference		Reference	
1–3	1.241(0.607–2.537)	0.554	0.447(0.228–0.878)	0.019	0.508(0.175–1.476)	0.214
≥4	0.390(0.268–0.570)	**<0.001**	0.367(0.226–0.595)	**<0.001**	0.240(0.109–0.531)	**<0.001**
Unknown	NA	NA	NA	NA	NA	NA
Bone metastasis		**<0.001**		0.491		0.109
Yes	Reference		Reference		Reference	
No	0.369(0.198–0.688)		0.606(0.143–2.559)		0.305(0.065–1.421)	
unknown	NA	NA	NA	NA	NA	NA

(Continued)

TABLE 2 | (Continued)

Subject characteristics	SCNCC		SCNCO		SCNCE	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Brain metastasis		0.123		0.272		
Yes	Reference		Reference		–	–
No	0.346(0.084–1.421)	0.141	0.047(0.143–1.827)		–	–
Unknown	NA	NA	NA	NA	–	–
Liver metastasis		**<0.001**		**<0.001**		**0.011**
Yes	Reference		Reference		Reference	
No	3.341(1.944–5.744)		0.249(0.116–0.535)		0.269(0.091–0.796)	
Unknown	NA	NA	NA	NA	NA	NA
Lung metastasis		**0.006**		**0.007**		0.129
Yes	Reference		Reference		Reference	
No	0.400(0205–0.783.)		0.168(0.038–0.743)		0.444(0.156–1.267)	
Unknown	NA	NA	NA	NA	NA	NA
Surgery performed		***p*<0.001**		**<0.001**		**<0.001**
Surgery	Reference		Reference		Reference	
No surgery	2.308(1.675–3.179)		3.131(2.157–4.546)		0.268(0.166–0.435)	
Unknown	NA	NA	NA	NA	NA	NA
Chemotherapy		**<0.001**		**<0.001**		0.005
Yes	Reference		Reference		Reference	
No	2.170(1.550–3.037)		2.262(1.619–3.160)		0.531(0.38–0.835)	
Radiotherapy		**0.001**		**0.015**		**0.001**
Yes	Reference		Reference		Reference	
No	0.534(0.369–0.773)		2.562(1.210–5.467)		0.209(0.090–0.488)	

SCNCC, small-cell neuroendocrine carcinoma of the cervix; SCNCO, small-cell neuroendocrine carcinoma of the ovary; SCNCE, small-cell neuroendocrine carcinoma of the endometrium all factors with Unknown data were removed in logistic regression model. Bold value means p < 0.05.

women with gynecologic small-cell neuroendocrine carcinoma, the median survival time after diagnosis was only 15 months. The highest survival rate was observed among patients with cervical small-cell neuroendocrine carcinoma, who exhibited a median survival time of 19 months. The median survival times for ovarian and endometrial small-cell neuroendocrine carcinoma were 11 and 12 months, respectively. The survival rates observed in our study are extremely low when compared with those for female genital tract cancer (3). The 5-year survival rates were 26.1, 22.0, and 5.9% for cervical, ovarian, and endometrial small-cell neuroendocrine carcinoma, respectively. The morbidity and survival rates observed in our study are lower than those previously reported (1). Owing to low morbidity, imperfect treatment planning, and poor patient prognosis, early diagnosis and appropriate treatment are critical for improving patient survival.

Cervical small-cell neuroendocrine carcinoma typically presents as more advanced and with poorer prognosis than cervical squamous cell carcinoma or adenocarcinoma, and its recurrence rates are higher than those for either (6). Here, the median survival time of patients with cervical small-cell neuroendocrine carcinoma was only 19 months. In a 2019 multi-center neuroendocrine cancer study, Ishikawa et al. (7) investigated the prognostic factors and best treatments for early cervical small-cell neuroendocrine carcinoma. Their multivariate analysis revealed that T3/T4, paraaortic lymph node metastasis, distant metastasis, and the number of chemotherapy cycles were independent prognostic factors for survival (8). In a meta-analysis of 1,901 patients, radiotherapy was also associated with poor survival, while chemotherapy was associated with prolonged survival, similar to the findings observed for patients with small-cell lung cancer (9). These findings suggest that the first-choice treatment for early-stage cervical small-cell neuroendocrine carcinoma should be surgery with adjuvant chemotherapy either before or after surgery, and that clinicians should remain cautious when considering radiotherapy. Moreover, it should be noted that patient age and clinical stage were risk factors in our study, thus indicating that advanced age, T3/T4, and adjuvant chemotherapy can significantly increase death risk.

Etoposide plus cisplatin and irinotecan plus cisplatin are currently the best chemotherapy regimens for cervical small-cell neuroendocrine carcinoma (10, 11). However, recent studies have identified potential targeted therapies, including PD-1, PI3K, and MEK inhibitors (12–15). Whether these and other molecular targeting strategies can benefit patients with cervical small-cell neuroendocrine carcinoma requires further research.

The largest case series included 42 cases of endometrial neuroendocrine carcinoma (15). This Japanese study reported that patients with stage III and IV simple small-cell neuroendocrine carcinomas exhibited significantly poorer prognosis than those with less advanced disease. Multivariate analysis indicated that the histological subtype and surgery were important prognostic factors. Thus, if radical surgery is possible, it should be the primary treatment for endometrial small-cell neuroendocrine carcinoma. Our findings indicated that the

TABLE 3 | Multivariable Cox regression for analyzing the prognosis factors for small-cell neuroendocrine carcinoma of the gynecologic tract (SCNCGT).

Subject characteristics	SCNCC		SCNCO		SCNCE	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Age at diagnosis (years)		**0.001**		0.557		
<45	Reference		Reference			
45–64	1.523(1.034–2.242)	0.033	0.825(0.302–2.250)	0.707		
65–84	2.581(1.607–4.146)	<0.001	0.526(0.172–1.606)	0.260		
≥85	2.343(0.673–8.162)	0.181	0.808(0.288–2.269)	0.686		
Stage		**<0.001**		**0.005**		
I	Reference		Reference			–
II	0.731(0.272–1.962)	0.534	1.816(0.590–5.586)	0.298	Reference	0.981
III	1.993(1.033–3.847)	0.040	3.512(1.617–7.629)	0.002	1.372(0.258–7.289)	0.710
IV	3.020(1.602–5.693)	**<0.001**	3.836(1.744–8.437)	0.001	5.120(0.954–27.472)	0.057
Unknown	NA	NA	NA	NA	NA	NA
Lymph nodes status		0.223		0.157		0.813
Negative	Reference		Reference		Reference	
Positive	3.513(0.665–18.571)	0.139	0.424(0.114–1.578)	0.201	1.044(0.255–4.277)	0.953
No examined	1.621(0.82–6.870)	0.512	0.355(0.123–1.025)	0.056	0.711(0.151–3.343)	0.666
Unknown	NA	NA	NA	NA	NA	NA
LN metastasis numbers		0.468		0.509		0.737
No	Reference		Reference		Reference	
1–3	1.138(0.477–2.715)	0.771	0.537(0.165–1.750)	0.302	1.679(0.416–6.776)	0.466
≥4	2.521(0.573–11.096)	0.221	0.780(0.329–1.848)	0.572	1.064(5.000–3.875)	0.924
Unknown	NA	NA	NA	NA	NA	NA
Surgery performed		0.550		**0.024**		**0.007**
Surgery	Reference		Reference		Reference	
No surgery	1.189(0.674–2.097)		2.127(1.103–4.101)		4.842(1.552–15.108)	
Unknown	NA	NA	NA	NA	NA	NA
Chemotherapy		**<0.001**		**0.014**		**0.042**
Yes	Reference		Reference		Reference	
No	2.784(1.902–4.075)		2.023(1.152–3.551)		2.102(0.964–4.584)	
Radiotherapy		0.664		**0.019**		0.108
Yes	Reference		Reference		Reference	
No	0.882(0.500–1.555)		5.988(1.350–26.560)		5.588(0.685–45.615)	

SCNCC, small-cell neuroendocrine carcinoma of the cervix; SCNCO, small-cell neuroendocrine carcinoma of the ovary; SCNCE, small-cell neuroendocrine carcinoma of the endometrium all factors with Unknown data were removed in logistic regression model. Bold value means $p < 0.05$.

median survival time of patients with endometrial small-cell neuroendocrine carcinoma was 12 months, with a 5-year survival rate of 25.9%. Factors associated with prognosis include not only surgery but also adjuvant chemotherapy and radiotherapy. Sawada et al. (16) reported the rare case of a patient with late endometrial small-cell carcinoma with liver and brain metastases who survived for 12 years. The patient underwent pelvic tumor reduction surgery and metastasis resection, postoperative treatment with irinotecan hydrochloride combined with cisplatin chemotherapy, and adjuvant radiotherapy. Viau et al. (17) presented the case of a patient diagnosed with stage IV uterine intimal small-cell carcinoma who underwent surgery, chemotherapy (cisplatin/etoposide), and radiotherapy. Five years after completing the treatment, the patient remained disease-free. These reports suggest that treatments based on surgery, adjuvant radiotherapy, and chemotherapy can improve patient survival.

Ovarian small-cell neuroendocrine carcinoma had the lowest median survival time among all gynecologic small-cell neuroendocrine carcinomas at only 11 months. The currently recommended chemotherapy regimen is a multi-drug combination of platinum and etoposide for postoperative chemotherapy (18, 19). In a study of 469 women, Nasioudis et al. (18) observed 5-year overall survival rates of 48.6, 30.7, 18, and 12.3% in patients with stages I–IV, respectively. Their multivariate analysis revealed that an earlier stage of the disease and chemotherapy use were associated with lower mortality, despite no association with lymph node dissection. This provides an important basis for performing lymph node dissection during ovarian small-cell neuroendocrine carcinoma. In our study, there were only 217 cases of ovarian small-cell neuroendocrine carcinoma, which had a 5-year overall survival rate of 22.0%. Based on these findings, adding surgery and radiotherapy to chemotherapy treatment may increase patient survival.

Although the SEER database does not mention the diagnosis and treatment of recurrent gynecologic small-cell neuroendocrine carcinoma, even early cases are associated with a 30% chance of recurrence (20). While there are international guidelines for diagnosing and treating cervical cancers, no such guidelines exist for diagnosing and treating recurrent cervical small-cell neuroendocrine carcinoma (21). In fact, the National

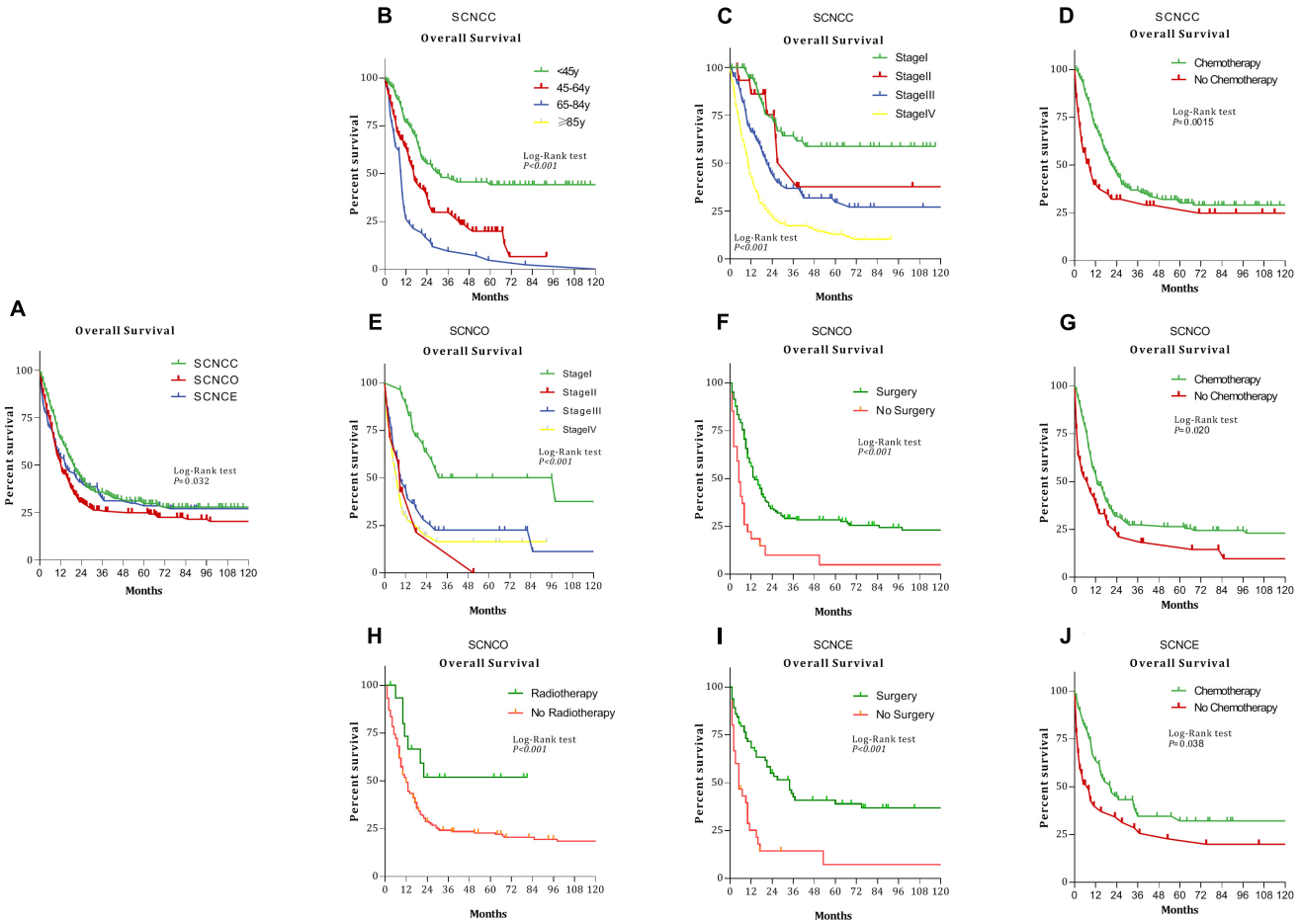

FIGURE 1 | Kaplan–Meier analysis of overall survival among patients with small-cell neuroendocrine carcinoma of the gynecologic tract (SCNCGT) ($P = 0.032$) **(A)**. Small-cell neuroendocrine carcinoma of the cervix (SCNCC) and age ($P < 0.001$) **(B)**. SCNCC and stage ($P < 0.001$) **(C)**. SCNCC and chemotherapy ($P = 0.0015$) **(D)**. Small-cell neuroendocrine carcinoma of the ovary (SCNCO) and stage ($P < 0.001$) **(E)**. SCNCO and surgery ($P = 0.0015$) **(F)**. SCNCO and chemotherapy ($P = 0.020$) **(G)**. SCNCO and radiotherapy ($P < 0.001$) **(H)**. Small-cell neuroendocrine carcinoma of the endometrium (SCNCE) and surgery ($P = 0.0015$) **(I)**. SCNCE and chemotherapy ($P = 0.038$) **(J)**.

Comprehensive Cancer Network Guidelines for the Treatment of Cervical Cancer clearly exclude advanced neuroendocrine cancers (22). Many scholars currently advocate combined chemotherapy using topotecan, paclitaxel, and bevacizumab. However, this approach is not particularly effective, with a median survival time of only 10 months (23). Currently, bevacizumab is the preferred chemotherapy drug and has been used in phase II clinical trials (24).

Strengths and Weaknesses

This study investigated the prevalence, risk factors, and survival outcomes of gynecologic small-cell neuroendocrine carcinoma using the largest publicly available cancer data set. However, there were certain limitations. The SEER database only provides information on whether and when (i.e., before or after surgery) radiotherapy and chemotherapy were performed, while the specific plan of treatment is not provided. Therefore, the clinical data were not detailed enough to determine whether specific regimens were associated with prognosis/survival. We also noticed that the degree of differentiation of the disease was very low in stages I–II and more concentrated in stages III–IV. Despite the grade not being a significant predictor in univariate and multivariate Cox risk regression analyses, there may be a certain correlation between the low survival rate of the disease and low degree of pathological differentiation. Lastly, given the rarity of gynecologic small-cell neuroendocrine carcinoma, the literature consists of only case reports and small case series.

Implications for Practice and Future Research

There is currently no conventional guideline, unified treatment plan, or method for prognostic evaluation for gynecologic small-cell neuroendocrine carcinoma. Large-scale multi-center studies are required to elucidate the biological behavior of the disease and explore the most suitable treatment methods for improving patient prognosis. However, future studies should focus on

exploring gene-targeted therapy, improving the preoperative diagnosis rate, and developing appropriate treatment guidelines.

CONCLUSION

The survival times of endometrial and ovarian small-cell neuroendocrine carcinoma are relatively short, and long-term survival is rarely reported. Based on our findings, we believe that comprehensive and individualized treatment for gynecologic small-cell neuroendocrine carcinoma may prolong patient survival.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

ETHICS STATEMENT

Ethical review and approval was not required for the study of human participants in accordance with the local legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

LP collected clinical data and wrote the manuscript. SZW helped design and revise the manuscript. Both authors contributed to the article and approved the submitted version.

REFERENCES

1. Patibandla JR, Fehniger JE, Levine DA, Jelinic P. Small cell cancers of the female genital tract: molecular and clinical aspects. *Gynecol Oncol.* (2018) 149:420–7.
2. McCusker ME, Cote TR, Clegg LX, Tavassoli FJ. Endocrine tumors of the uterine cervix: incidence, demographics, and survival with comparison to squamous cell carcinoma. *Gynecol Oncol.* (2003) 88:333–9. doi: 10.1016/s0090-8258(02)00150-6
3. Chen J, Macdonald OK, Gaffney DK. Incidence, mortality, and prognostic factors of small cell carcinoma of the cervix. *Obstet Gynecol.* (2008) 111:1394–402. doi: 10.1097/AOG.0b013e318173570b
4. Lee SW, Nam JH, Kim DY, Kim KR, Kim YM, Kim YT. Unfavorable prognosis of small cell neuroendocrine carcinoma of the uterine cervix: a retrospective matched case–control study. *Int J Gynecol Cancer.* (2010) 20:411–6. doi: 10.1111/IGC.0b013e3181ce427b
5. Viswanathan AN, Deavers MT, Jhingran A, Ramirez PT, Levenback C, Eifel PJ. Small cell neuroendocrine carcinoma of the cervix: outcome and patterns of recurrence. *Gynecol Oncol.* (2004) 93:27–33. doi: 10.1016/j.ygyno.2003.12.027
6. Bermudez A, Vighi S, Garcia A, Sardi J. Neuroendocrine cervical carcinoma: a diagnostic and therapeutic challenge. *Gynecol Oncol.* (2001) 82:32–9. doi: 10.1006/gyno.2001.6201
7. Ishikawa M, Kasamatsu T, Tsuda H, Fukunaga M, Sakamoto A, Kaku T, et al. Prognostic factors and optimal therapy for stages I-II neuroendocrine carcinomas of the uterine cervix: a multi-center retrospective study. *Gynecol Oncol.* (2018) 148:139–46. doi: 10.1016/j.ygyno.2017.10.027
8. Ishikawa M, Kasamatsu T, Tsuda H, Fukunaga M, Sakamoto A, Kaku T, et al. A multi-center retrospective study of neuroendocrine tumors of the uterine cervix: prognosis according to the new 2018 staging system, comparing outcomes for different chemotherapeutic regimens and histopathological subtypes. *Gynecol Oncol.* (2019) 155:444–51. doi: 10.1016/j.ygyno.2019.09.018
9. Xu F, Ma J, Yi H, Hu H, Fan L, Wu P, et al. Clinicopathological aspects of small cell neuroendocrine carcinoma of the uterine cervix: a multicenter retrospective study and meta-analysis. *Cell Physiol Biochem.* (2018) 50:1113–22. doi: 10.1159/000494538
10. Zivanovic O, Leitao MM Jr, Park KJ, Diaz JP, Konner J, Alektiar K, et al. Small cell neuroendocrine carcinoma of the cervix: analysis of outcome, recurrence pattern and the impact of platinum-based combination chemotherapy. *Gynecol Oncol.* (2009) 112:590–3. doi: 10.1016/j.ygyno.2008.11.010
11. Tokunaga H, Nagase S, Yoshinaga K, Tanaka S, Nagai T, Kurosawa H, et al. Small cell carcinoma of the uterine cervix: clinical outcome of concurrent chemoradiotherapy with a multidrug regimen. *Tohoku J Exp Med.* (2013) 229:75–81. doi: 10.1620/tjem.229.75
12. Lai ZY, Yeo HY, Chen YT, Chang KM, Chen TC, Chuang YJ, et al. PI3K inhibitor enhances the cytotoxic response to etoposide and cisplatin in a newly established neuroendocrine cervical carcinoma cell line. *Oncotarget.* (2017) 8:45323–34. doi: 10.18632/oncotarget.17335
13. Paraghamian SE, Longoria RC, Eskander RN. Metastatic small cell neuroendocrine carcinoma of the cervix treated with the PD-1 inhibitor, nivolumab: a case report. *Gynecol Oncol Res Pract.* (2017) 4:3. doi: 10.1186/s40661-017-0038-9
14. Pocrnich CE, Ramalingam P, Euscher ED, Malpica A. Neuroendocrine carcinoma of the endometrium: a clinicopathologic study of 25 cases. *Am J Surg Pathol.* (2016) 40:577–86. doi: 10.1097/PAS.0000000000000633
15. Matsumoto H, Shimokawa M, Nasu K, Shikama A, Shiozaki T, Futagami M, et al. Clinicopathologic features, treatment, prognosis and prognostic factors of neuroendocrine carcinoma of the endometrium: a retrospective analysis of 42 cases from the Kansai clinical oncology group/intergroup study in Japan. *Gynecol Oncol.* (2019) 30:e103. doi: 10.3802/jgo.2019.30.e103
16. Sawada M, Matsuzaki S, Yoshino K, Ueda Y, Yoshida S, Kimura T, et al. Long-term survival in small-cell carcinoma of the endometrium with liver and brain metastases. *Anticancer Drugs.* (2016) 27:138–43. doi: 10.1097/CAD.0000000000000289
17. Viau M, Baragar I, Altman AD. Long-term survival in a stage IV small cell carcinoma of the endometrium. *Gynecol Oncol Rep.* (2020) 32:100580. doi: 10.1016/j.gore.2020.100580
18. Nasioudis D, Chapman-Davis E, Frey MK, Caputo T, Witkin SS, Holcomb K, et al. Small cell carcinoma of the ovary: a rare tumor with a poor prognosis. *Int J Gynecol Cancer.* (2018) 28:932–8. doi: 10.1097/IGC.0000000000001243
19. Reed NS, Pautier P, Åvall-Lundqvist E, Choi CH, du Bois A, Friedlander M, et al. Gynecologic cancer intergroup (GCIG) consensus review for ovarian small cell cancers. *Int J Gynecol Cancer.* (2014) 24:S30–4. doi: 10.1097/IGC.0000000000000293
20. Cohen JG, Kapp DS, Shin JY, Urban R, Sherman AE, Chen LM, et al. Small cell carcinoma of the cervix: treatment and survival outcomes of 188 patients. *Am J Obstet Gynecol.* (2010) 203:1–6. doi: 10.1016/j.ajog.2010.04.019
21. Satoh T, Takei Y, Treilleux I, Devouassoux-Shisheboran M, Ledermann J, Viswanathan AS, et al. Gynecologic cancer intergroup (GCIG) consensus review for small cell carcinoma of the cervix. *Int J Gynecol Cancer.* (2014) 24:S102–8. doi: 10.1097/IGC.0000000000000262
22. Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, et al. Cervical cancer, version 3.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Cancer Netw.* (2019) 17:64–84. doi: 10.6004/jnccn.2019.0001

23. Frumovitz M, Munsell MF, Burzawa JK, Byers LA, Ramalingam P, Brown J, et al. Combination therapy with Topotecan, paclitaxel, and bevacizumab improves progression-free survival in recurrent small cell neuroendocrine carcinoma of the cervix. *Gynecol Oncol.* (2017) 144:46–50. doi: 10.1016/j.ygyno.2016.10.040
24. Frumovitz M, Westin SN, Salvo G, Zarifa A, Xu M, Yap TA, et al. Phase II study of pembrolizumab efficacy and safety in women with recurrent small cell neuroendocrine carcinoma of the lower genital tract. *Gynecol Oncol.* (2020) 158:570–5. doi: 10.1016/j.ygyno.2020.05.682

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Return of Sexual Activity Within Six Weeks of Childbirth Among Married Women Attending Postpartum Clinic of a Teaching Hospital in Ethiopia

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Introduction: Postpartum sexual health gets very little attention compared to pregnancy and childbirth, even though most maternal deaths and disabilities occur during this time. Therefore, the study aimed to assess return of sexual activity within 6 weeks of childbirth among married women attending postpartum clinic of a teaching hospital in Ethiopia, 2021.

Methods: The hospital-based cross-sectional study design was implemented from September to October 2021. Eligible postpartum women were sampled by systematic random sampling technique. The data was entered into EPI-info and exported to SPSS version 24 for further analysis. All variables with a p-value < 0.05 in multivariable analyses were taken as associated factors with the return to sexual activity before 6 weeks of childbirth.

Results: A total of 421 postpartum women participated in the study. The prevalence of women who return to sexual activity 6 weeks after childbirth was 31.6%. The study revealed that monogamy (Adjusted Odds Ratio (AOR) = 4.4, 95% Confidence Interval (CI) (2.1, 9.4)), parity (AOR= 0.11, 95% CI (0.02–0.81)) and (AOR = 0.1, 95% CI (0.015–0.72)), postnatal care (AOR= 1.8, 95% CI (1.01–3)) and infants feeding status (AOR=2.3, 95% CI (1.3–4)) were significantly associated with return of sexual activity before 6 weeks of childbirth.

Conclusion: The findings of this study suggested that, nearly one-third of postpartum women engaged to sexual activity within 6 weeks of childbirth. Return of sexual activity within 6 weeks of childbirth associated with monogamy type of marriage, parity, postnatal care, and child feeding status. Strengthening postpartum counseling regarding the appropriate time to resume sexual activity is crucial. Regular postpartum visits following deliveries should also be encouraged by health care providers.

Keywords: postpartum sexual activity, Ethiopia 2022, sexual resumption, early sexual activity, return to sex, sexual activity, six weeks of childbirth, Ethiopia

INTRODUCTION

The postpartum period has received less attention than pregnancy and childbirth, despite the fact that it is the time when most maternal deaths and disabilities occur (1). As sexual health undergoes fundamental changes during pregnancy, childbirth, and the postpartum period, postpartum sexual health is one of the emerging international issues. The World Health Organization (WHO) recommends that one of the most important issues to be addressed during the postpartum period is postpartum sexual health (2). Arousal, libido, orgasm and sexual pleasure are all signs of good sexual health after childbirth (3).

In fact there is a positive relationship between sexual and marital satisfaction which develops true relationships and benefits both partners in strengthening the family (4). However, pregnancy and the time after childbirth have a negative impact on women's and their partner's sexuality (5). The interest in sexual activity decreases during pregnancy but returns to normal soon after an average of 6 weeks after childbirth (6). It has lately been suggested that it is safe to resume postpartum sexual activity at least 6 weeks after childbirth (7).

The postpartum sexual resumption after childbirth may reduce the likelihood of compromising family's relationships and reduce the family's' health at risk due to sexually transmitted infections such as HIV/AIDS through being polygamous (8). However, according to the World Health WHO and other studies, more than half (50%), of women resume sexual activity within 6 weeks of childbirth (9–11). For instance, in Turkey 79.1% and China 68.7% of postpartum women engage sexual activity within the first 6 weeks of childbirth (12, 13).

Early sexual resumption is also common in African countries with varying and/or unpredictable durations such as Nigeria 38.7% and Uganda 21.6% (14–17). Studies in Ethiopia revealed that many women resumed sexual activity within 6 weeks of childbirth: Nekemte (20.2%) (18), Gondar town (26.9%) (15, 19), Jimma and Addis Ababa city, more than half (>50%) of women started sexual intercourse earlier after childbirth (3, 11).

It is generally recognized that after giving birth, women experience a variety of sexual health problems with variety of negative consequences such as wound infection, painful intercourse, vaginal dryness, inability to reach orgasm, vaginal laxity and decreased libido (3, 20, 21). While a temporary decrease in libido following childbirth is to be expected, women should not feel pain during sexual activity. If these symptoms are not addressed, there will be a fear of having sexual relations, and the problem will increase, resulting in physical and psychological illness (22).

In addition, early postpartum sexual resumption without using contraception can result in an unexpected pregnancy. This may result in poor maternal and infant health, as well as a high risk of death for infants under the age of 1 year (23). Previous studies showed that income, type of marriage, sexual intercourse during pregnancy, mode of delivery, contraceptive method utilization, parity, educational status, desire for additional baby, demand of the partner for intercourse and residence are factors associated with the early return to postpartum sexual activity (3, 7, 11, 13, 18).

In Ethiopia; sexual health after childbirth like when it is safe to resume sexual intercourse is not properly addressed in which health care practitioners rarely talk to postpartum women about sexual issues (3, 18). The majority of Ethiopian studies focused on the use of contraception to avoid rapid repeat pregnancies in order to resolve women's health problems following childbirth. This indicates the gaps of information on the factors associated with early postpartum sexual resumption after childbirth (18). Therefore, this study aimed to assess return of sexual activity within 6 weeks of childbirth among married women attending postpartum clinic of Salale University Comprehensive Specialized Teaching Hospital in Ethiopia, 2021.

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; COR, crude odds ratio; IRB, institutional review board; PNC, postnatal care; SVD, spontaneous vaginal delivery; SD, standard deviation; WHO, world health organization; SPSS, statistical package for the social sciences.

MATERIALS AND METHODS

Study Design, Period and Area

The hospital based cross-sectional study design was employed from September to October 2021. The study was conducted at Salale University Comprehensive Specialized Teaching Hospital. The hospital is located in Fiche Town, North Shewa District, and 112 kilometers away from Addis Ababa. It is one of the first-line hospitals in the North Shewa district, serving more than 1.5 million people each year and providing more than 3,978 postnatal services (PNC) per year.

Population

The source population of this study was postpartum women who went to Salale University Comprehensive Specialized Teaching Hospital for postpartum and child immunization services. The study population was postpartum women attending postpartum and child immunization services at Salale University Comprehensive Specialized Teaching Hospital during study period. All married postpartum women who visited postpartum or child immunization clinic during data collection period were included in the study. Women who were critically ill during the study period were excluded from the study.

Sample Size Determination and Sampling Procedure

The single population proportion formula used to calculate the sample size, with a 95% confidence level and 5% margin of error, the proportion (p) of early postpartum sexual intercourse 53.9% taken from a similar study conducted in Jimma district / Ethiopia (3). Finally, 421 eligible postpartum women were sampled by systematic random sampling technique. Individual clients who visited a postnatal clinic were approached using a sampling interval of K = 10 [N/n, where N is the average number of clients who visited a postnatal clinic and n is the computed final sample size]. The first participant was chosen using a lottery method based on the obtained interval.

Data Collection Instruments and Techniques

A semi-structured questionnaire was developed after a thorough review of the literature. The questionnaire was initially written in English, and then translated into Afan Oromo and again retranslated back to English to check for any inconsistencies or distortions in the meaning of terms and concepts. Socio-demographic characteristics, reproductive and maternal health service use-related characteristics, post-natal care-related factors, and sexual health during pregnancy and after birth-related characteristics were all included in the questionnaire. Data were collected using a semi-structured questionnaire in the Afan Oromo language version after pre-testing on 5% of the same-origin population outside the sample population. The pre-testing process was carried out in Muke Turi primary hospital, which accounted for 5% of the total sample size. The tool reliability test was checked by Cronbach's alpha, which indicated that 0.87. Two midwives collected the data after being briefed on the research and data collection protocols.

Data Processing and Analysis

The data entered into EPI-info and then exported to SPSS version 24 for further analysis. Descriptive analysis (such as frequencies, percentages, means, and standard deviation) and inferential analysis was performed. Bivariate and multivariable logistic regressions used to check the significance of the outcome variable and each of the independent variable using odds ratio with 95% confidence interval. All variables with p-value < 0.25 at bivariate was considered as a candidate for multivariable analysis and those variables with a p-value < 0.05 in multivariable analyses were taken as statistical significant associated factors with return to sexual activity before 6 weeks of childbirth. Multivariable logistic regression analyses were performed to control for possible confounding effects of the selected variables. The main assumption of the binary logistic regression model was tested. The assumption result showed that there is no existence of a significant effect modification. The multicollinearity among the independent variables was also evaluated using a multiple linear regression model. The evaluation result does not indicate evidence of multicollinearity. Model goodness-of-fit was tested by the Hosmer-Lemeshow model and the forward stepwise (likelihood ratio) method used. The p-value for the model fitness test was 0.935.

Variables

Dependent variable: return to sexual intercourse before 6 weeks of childbirth**.**

Independent variables: socio demographic characteristics (polygamy, educational status, occupation, age), reproductive and maternal health service use-related characteristics (gravidity, index of current pregnancy status, mode of delivery, place birth), post natal care related factors (postnatal care visit, current infant feeding status, resumption of menstruation), sexual health during pregnancy and after birth related characteristics (Practice of sexual intercourse during pregnancy, Last sex trimester, Reason to resume sexual intercourse).

Operational Definitions

The Time of Return to Sexual Activity

In this study the category given for return to sexual activity before 6 weeks of childbirth as code 1 and return to sexual activity after 6 weeks of childbirth as code 0.

Index of Current Pregnancy Status

Intention to have the child before conception.

Resumption of Menses After Delivery

Is the first menstrual cycle after childbirth.

Ethics Approval and Informed Consent

The research was carried out in agreement with the Helsinki Declaration. Salale University Ethical Review Committee authorized the ethical clearance of written consent for those over the age of 18 and an agreement form for those under the age of 18 from their partners with Ref. No. SLUERC/122/2021. Official authorization was received from the selected hospital, as well as a support letter from the North Showa Zone health office. After describing the study's goal to participants, written agreement was obtained. The privacy and anonymity of study subjects were preserved by omitting their names from the questionnaire and storing their data in a secure location.

The following figure illustrates the major methods and materials section (**Figure 1**).

RESULTS

Socio-Demographic Characteristics Among Married Post-partum Women at Salale University Comprehensive Specialized Teaching Hospital, From September to October 2021 ($n = 421$)

A total of 421 postpartum women participated in the study. The mean age of participants was 28.54 years (SD $\pm$ 5.08), and a majority of participants, 318 (75.5%), were of Oromo ethnicity. About 292 (69.4%) of the participants were monogamous, and nearly half, 213 (50.6%) of the participants had been living with their husbands for only 1 to 2 years. The majority, 297 (70.5%) of study participants lived in cities, accounting for more than two-third of women participated in the study, and 40.4% of postpartum women had a college education or higher (*See* **Table 1**).

Reproductive and Maternal Health Service Related Characteristics Among Married Post-partum Women at Salale University Comprehensive Specialized and Teaching Hospital, From September to October 2021 ($n = 421$)

According to the result of this study, more than three-quarters of the participants, 366 (86.9%), gave birth to their first child during the current delivery. Almost all, 399 (94.8%) of the study participants' index of the pregnancy status was planned and about 405(96.2%) had prenatal care during their last pregnancy. The

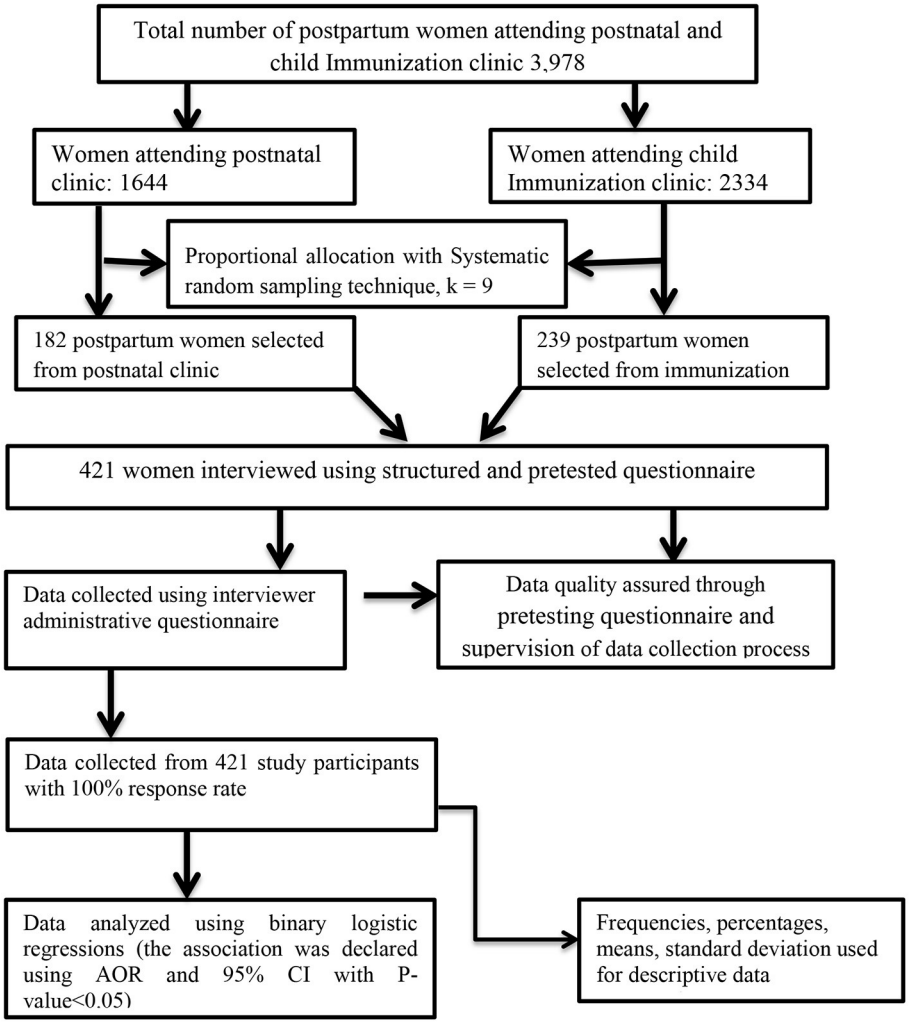

FIGURE 1 | Flow chart of materials and methods.

majority, 292 (69.4%) of women gave birth their last baby in a hospital. Regarding women's mode of delivery in this finding, about three-quarters, 318(75.5%) give birth by spontaneous vaginal delivery (SVD) without an episiotomy during their last delivery and 264(62.9%) of them were multiparous (*See* **Table 2**).

Post Natal Care Related Characteristics Among Married Post-partum Women at Salale University Comprehensive Specialized and Teaching Hospital, From September to October 2021 ($n = 421$)

The majority of women who participated in the study, 257 (61%) had postpartum care at their last delivery, and most of them, 279 (66.3%) had exclusively breastfed their infants. More than half, 233 (55.3%) of the study participants' menstruation cycle returned after a recent delivery, and 378 (89.8%) had a good understanding of any modern contraceptive method (*See* **Table 3**).

Sexual Health Characteristics of Early Return to Postpartum Sexual Intercourse Among Married Post-partum Women at Salale University Specialized and Teaching Hospital, From September to October 2021 ($n = 421$)

The majority, 353 (83.8%) of the women practiced sexual intercourse during their last pregnancy and from those who practiced sexual intercourse during pregnancy most of them, 220 (62%) end up the sexual activity during the third trimester pregnancy.

Most of the women, 221 (52.5%) discussed about return to postpartum sexual activity with their husbands to initiate

TABLE 1 | Socio-demographic characteristics of post-partum women at Salale University comprehensive specialized teaching hospital, September to October 2021 (n = 421).

Variables		Return to sexual intercourse after childbirth		Total
		<6 weeks	>6 weeks	
Maternal age (in years)	15–19	6 (1.4%)	0	6 (1.4%)
	20–24	29 (6.9)	59 (14%)	88 (20.9%)
	25–29	41 (9.7%)	111 (26.4%)	152 (36.1%)
	30–34	33 (7.8%)	78 (18.5%)	111 (26.4%)
	35–49	24 (5.7%)	40 (9.5%)	64 (15.2%)
Ethnicity	Oromo	95 (22.6%)	223 (53%)	318 (75.5%)
	Amhara	34 (8.1%)	60 (14.3%)	94 (22.3%)
	Tigre	2 (0.5%)	0	2 (0.5%)
	Other *	2 (0.5%)	5 (1.2%)	7 (1.7%)
Religion	Muslim	12 (2.9%)	28 (6.6%)	40 (9.5%)
	Orthodox	103 (31.9%)	220 (52.3%)	323 (76.7%)
	Protestant	15 (3.6%)	38 (9%)	53 (12.6%)
	Catholic	3 (0.7%)	2 (0.5%)	5 (1.2%)
Polygamy	Yes	20 (4.7%)	109 (25.9%)	129 (30.6%)
	No	113 (26.9%)	179 (42.5%)	292 (69.4%)
Maternal educational status	No formal education	22 (5.2%)	36 (8.6%)	58 (13.8%)
	Primary	34 (8.1%)	70 (16.6%)	104 (24.7%)
	Secondary	23 (5.5%)	66 (15.7%)	89 (21.1%)
	College and above	54 (12.8%)	116 (27.6%)	170 (40.4%)
Maternal occupation	Government employee	41 (9.7%)	89 (21.1%)	130 (30.9%)
	Self-employee	30 (7.1%)	59 (14%)	89 (21.1%)
	Housewife	52 (12.4%)	126 (29.9%)	178 (42.3%)
	Others **	10 (2.4%)	14 (3.3%)	24 (5.7%)
Residence	Urban	94 (22.3%)	203 (48.2%)	297 (70.5%)
	Rural	39 (9.3%)	85 (20.2%)	124 (29.5%)
Duration of living together with husband	1–2 years	74 (17.6%)	139 (33.0%)	213 (50.6%)
	3–5 years	35 (8.3%)	77 (18.3%)	112 (26.6%)
	>5 years	24 (5.7%)	72 (17.1%)	96 (22.8%)

*Others * = wolaita, Gurage ** = student, Non-governmental organization (NGO) employee and daily laborer.*

the sexual intercourse after recent childbirth, and 195 (46.3%) women resumed their sexual practices under the influence of their husbands.

According to the finding of this study, most of the women, 337 (80%) were not getting health education from health care providers regarding the time when to resume sexual intercourse after childbirth. Prevalence of women who return to sexual activity before 6 weeks after childbirth (non-recommended time) was 133 (31.6%) (*See* **Table 4**).

Factors Associated With Return to Sexual Intercourse Before 6 Weeks of Childbirth Among Married Post-partum Women at Salale University Specialized Teaching Hospital, From September to October 2021 (n = 421)

In the bivariate logistic regression those variables with p-value of ≤0.25 considered as the candidate for multivariable logistic regression analysis, such as parity, index of current pregnancy status, mode of delivery, postnatal care visit for the last births, infant feeding status, last trimester sexual activity during pregnancy, getting help and health education from healthcare providers after giving birth.

In multivariable logistic regression monogamy, parity (multi-parous, grand- multi parous), postnatal care visit for the recent birth and infant feeding status were found to be significantly associated with return to sexual activity before 6 weeks after childbirth at p-value <0.05 with 95% confidence interval.

This study revealed that participants with monogamy type of marriage were 4.4 times more likely to return to sexual activity before 6 weeks after childbirth than mothers whose type of marriage was polygamy [AOR = 4.4, 95% CI (2.1, 9.4)].

The study also showed that multiparous and grand-multi parous women were 89% and 90% less likely to have early postpartum intercourse [AOR= 0.11, 95% CI = (0.02, 0.81) and AOR = 0.10, 95% CI = (0.015, 0.72)].

TABLE 2 | Reproductive and maternal health service related characteristics among married post-partum women at Salale University Comprehensive Specialized and teaching hospital, from September to October 2021 ($n = 421$).

Variables		Return to sexual intercourse after childbirth		Total
		<6 weeks	>6 weeks	
Number of pregnancies	Primi-gravid	120 (28.5%)	246 (58.4%)	366 (86.9%)
	Multi gravid	13 (3.1%)	42 (10.0%)	55 (13.1%)
History of abortion	Yes	17 (4.0%)	35 (8.3%)	52 (12.4%)
	No	116 (27.6%)	253 (60.1%)	369 (87.6%)
Index of current pregnancy status	Planned	129 (30.6%)	270 (64.1%)	399 (94.8%)
	Un planned	4 (1.0%)	18 (4.3%)	22 (5.2%)
ANC visit during your last pregnancy	Yes	128 (30.4%)	277 (65.8%)	405 (96.2%)
	No	5 (1.2%)	11 (2.6%)	16 (3.8%)
Obstetric related complication	Yes	8 (1.9%)	24 (5.7%)	32 (7.6%)
	No	125 (29.7%)	264 (62.7%)	389 (92.4%)
Place birth for the last delivery	Health center	41 (9.7%)	67 (15.9%)	108 (25.7%)
	Hospital	87 (20.7%)	205 (48.7%)	292 (69.4%)
	Private clinic	0 (0.0%)	6 (1.4%)	6 (1.4%)
	Home	5 (1.2%)	10 (2.4%)	15 (3.6%)
Mode of delivery	SVD without episiotomy	107 (25.4%)	211 (50.1%)	318 (75.5%)
	SVD with episiotomy	16 (3.8%)	45 (10.7%)	61 (14.5%)
	Caesarian Section	10 (2.4%)	32 (7.6%)	42 (10.0%)
Parity	Primi-Para	46 (11%)	102 (24.3%)	148 (35.2%)
	Multi-Para	82 (19.5%)	182 (43.3%)	264 (62.9%)
	Grand- Multi-Para	5 (1.2%)	3 (0.7%)	8 (1.9%)

TABLE 3 | Post natal care related characteristics among married post-partum women at Salale University Comprehensive Specialized and Teaching hospital, from September to October 2021 ($n = 421$).

Variables		Return to sexual intercourse before 6 weeks of childbirth		Total	Chi-square
		<6 weeks	>6 weeks		
Postnatal care visit for the last births	Yes	93 (22.1%)	164 (39.0%)	257 (61.0%)	0.011*
	No	40 (9.5%)	124 (29.5%)	164 (39.0%)	
Current infant feeding status	Exclusive breast feeding	98 (23.3%)	181 (43.0%)	279 (66.3%)	0.029*
	Formula Feeding	35 (8.3%)	107 (25.4%)	142 (33.7%)	
Resumption of menstruation after recent birth	Yes	77 (18.3%)	156 (37.1%)	233 (55.3%)	0.474
	No	56(13.3%)	132(31.4%)	188(44.7%)	
Knowledge about modern contraceptive methods	Yes	121 (28.7%)	257 (61.0%)	378 (89.8%)	0.583
	No	12 (2.9%)	31 (7.4%)	43 (10.2%)	

* = *Statistically significant at $p < 0.05$.*

Correspondingly, women who had postnatal care visit for the last births were about 2 times more likely to resume sexual intercourse within 6 weeks of childbirth than mothers those who had no postnatal care visit for the last births (AOR = 1.8, 95% CI (1.01–3) and postpartum women using formula feeding as infant feeding were 2.3 times more likely to resume sexual intercourse within 6 weeks of childbirth than mothers with exclusive breastfeeding (AOR = 2.3, 95% CI (1.3–4). (*See* **Table 5**).

DISCUSSION

In this study, the prevalence of return of sexual activity within 6 weeks of childbirth was 31.6%. The study found that polygamy, number of deliveries (parity), postnatal care visits, and current infant feeding patterns were significantly associated with return of postpartum sexual activity within 6 weeks of childbirth. The prevalence of this study was comparable with the study done in Gondar (26.9%), Nekemte (20.2%), Uganda (21.5%), and Nigeria (21.9%) (16–19).

TABLE 4 | Sexual health characteristics of study participants who attending Salale University specialized and teaching hospital, from September to October 2021 (n = 421).

Variables		Return to sexual intercourse before 6 weeks of childbirth		Total	Chi-square
		<6 weeks	>6 weeks		
Practice of sexual intercourse during pregnancy	Yes	117 (27.8%)	238 (56.8%)	355 (84.3%)	0.202
	No	16 (3.8%)	50 (11.9%)	66 (15.7%)	
Last sex trimester	First trimester	11 (3.1%)	10 (2.8%)	21 (5.9%)	0.77
	Second trimester	41 (11.5%)	73 (20.6%)	114 (32.1%)	
	Third trimester	65 (18.3%)	155 (43.7%)	220 (62.0%)	
Reason to return to sexual activity	Husband demand for sex	64 (15.4%)	131 (31.1%)	195 (46.3%)	0.456
	Jointly discussion	67 (15.9%)	154 (36.6%)	221 (52.5%)	
	Others*	2 (0.5%)	3 (0.7%)	5 (1.2%)	
Help from health care provider	Yes	38 (9.0%)	67 (15.9%)	105 (24.9%)	0.242
	No	95 (22.6%)	221 (52.5%)	316 (75.1%)	
health education from health care provider after delivery	Get	33 (7.8%)	51 (12.1%)	84 (20.0%)	0.090
	Not get	100 (23.8%)	237 (56.7%)	337 (80.0%)	

Others = women's wish to have another child within a short period of time.*

The finding of this study was much lower than the findings of study conducted in Jimma town (53.9%), Uganda (66.4%), and Turkey (79.1%) (3, 12, 13). A possible reason for the difference may be due to differences in sociocultural differences. Another reason for the discrepancy could be where the study was conducted [specialized hospital versus (vs.) district hospital] and the differences in study design between the Turkish and the current study (cross-sectional vs. cohort study design).

The result of this study showed that women with monogamous type of marriage were 4.4 times more likely to resume sexual activity within 6 weeks of childbirth compared to women who were in polygamous type of marriage [AOR = 4.4, 95% CI = (2.1, 9.4)]. This is in line with research conducted in Ethiopia's Jimma district, which showed that women in monogamous form of marriage were more likely to resume sexual activity earlier than women in polygamous marriage (3). This might be justified that partners with a polygamous type of marriage have the option to have sexual intercourse with one of the wives, while postpartum mothers can abstain.

The study also showed that multiparous and grand-multi parous women were 89% and 90% less likely to have early postpartum intercourse [AOR = 0.11, 95% CI = (0.02, 0.81) and AOR =0.10, 95% CI = (0.015, 0.72)] compared with primiparous women, respectively. This is comparable to studies conducted at Aminu Kano Teaching Hospital (AKTH) in Nigeria, National Referral and Teaching Hospital in Murago Uganda, Nekemte town in western Ethiopia and Gondar city in northwestern Ethiopia (7, 16, 18, 19). These studies show that women with only one child return to sexual activity earlier than women with many children. The likely justification for this might be that women's wish to have another child within a short period of time.

Similarly, the current study also showed that women who had the postnatal care visit for the last births were about 2 times more likely to resume sexual intercourse earlier than women who had no postnatal care visit [AOR =1.8, 95% CI: (1.01, 3)]. This response is supported by the study done in Gondar city, Northwest Ethiopia (19) which indicated that women who obtained postnatal care had higher odds to initiate early sexual intercourse than who did not. This may be because postpartum visits allow women to receive more information and counseling about exclusive breastfeeding and postpartum contraceptives, thereby preventing unwanted pregnancies. As a result, they can start sexual activity earlier without worrying about an unwanted pregnancy.

Those who were currently formula-fed as an infant feeding were 2.3 times more likely to resume sexual activity than women who exclusively breastfed [AOR = 2.3, 95% CI: (1.3, 4)]. This is consistent with an analysis of study from 17 Asian and African countries (24), which showed that postpartum infant feeding status was significantly associated with early onset of postpartum intercourse. The reason for our study could be that postpartum women who are not breastfeeding are more likely to engage sexual activity because they are not subjected to the negative effects of breastfeeding, which include physical, hormonal, and psychological changes in the body. They are also devoid of the side effects of low estrogen caused by high prolactin hormone from nursing, which cause decreased vaginal lubrication and vaginal epithelial atrophy, making physical arousal difficult and intercourse unpleasant. Dyspareunia is a prevalent sexual dysfunction among breastfeeding mothers (5, 25). The additional reason may be the poor relationship of the women with their male partners (26).

TABLE 5 | Factors associated with return to sexual activity within 6 weeks of childbirth among married post-partum women attending Salale University specialized and teaching hospital, from September to October 2021 ($n = 421$).

Variables		Return to sexual activity after childbirth		COR 95%CI	AOR 95%CI
		<6 weeks	>6 weeks		
Type of Marriage	polygamy	20 (4.8%)	109 (25.9%)	1	1
	Monogamy	113 (26.8%)	179 (42.5%)	0.3 (0.17, 0.5)	4.4 (2.1, 9.4) *
Duration of living together with husband	1–2 years	74 (17.6%)	139 (33.0%)	1	1
	3–5 years	35 (8.3%)	77 (18.3%)	0.63 (0.36, 1.1)	1.3 (0.64, 2.5)
	>5 years	24 (5.7%)	72 (17.1%)	0.73 (0.4, 1.4)	1.5 (0.7, 3.2)
Occupation	Government employee	41 (9.7%)	89 (21.1%)	1	1
	Self-employee	30 (7.1%)	59 (14%)	0.8 (.47, 1.4)	0.28 (0.9, 1.9)
	Housewife	52 (12.4%)	126 (29.9%)	0.9 (0.55, 1.5)	0.4 (0.12, 1.3)
	Others**	10 (2.4%)	14 (3.3%)	0.5 (0.2, 1.3)	0.3 (0.01, 1.1)
Number of pregnancies	Primi-gravid	120 (28.5%)	246 (58.4%)	1	1
	Multi gravid	13 (3.1%)	42 (10.0%)	0.64 (0.33, 1.23)	0.56 (0.2, 1.5)
Parity	Primi-Para	46 (11%)	102 (24.3%)		1
	Multi-Para	82 (19.5%)	182 (43.3%)	3.7 (0.85, 16)	0.11 (0.02, 0.81) *
	Grand- Multi-Para	5 (1.2%)	3 (0.7%)	3.7 (0.86, 15.85)	0.1 (0.015, 0.72) *
Index of pregnancy status	Planned	129 (30.6%)	270 (64.1%)	1	1
	Un planned	4 (1.0%)	18 (4.3%)	0.5 (0.15, 1.4)	3.8 (0.97, 14.9)
Mode of delivery	SVD without episiotomy	107 (25.4%)	211 (50.1%)		1
	SVD with episiotomy	16 (3.8%)	45 (10.7%)	0.6 (0.3, 1.3)	1.6 (0.6, 4)
	Cesarean Section	10 (2.4%)	32 (7.6%)	0.9 (0.35, 2.2)	0.9 (0.28, 2.7)
Postnatal care visit for the last births	Yes	93 (22.1%)	164 (39.0%)	1	1
	No	40 (9.5%)	124 (29.5%)	0.6 (0.4, 0.9)	1.8 (1.01, 3) *
Currently infant feeding practice	Exclusive breast feeding	98 (23.3%)	181 (43.0%)	1	1
	Formula Feeding	35 (8.3%)	107 (25.4%)	0.6 (0.4, 0.95)	2.3 (1.3, 4) *
Last sex trimester of pregnancy	First trimester	11 (3.1%)	10 (2.8%)	1	1
	Second trimester	41 (11.5%)	73 (20.6%)	0.38 (0.15, 094)	2.5 (0.9, 7)
	Third trimester	65 (18.3%)	155 (43.7%)	0.75 (0.46, 1.2)	1.1 (0.6, 1.8)
Help from health care providers	Yes	38 (9.0%)	67 (15.9%)	1	1
	No	95 (22.6%)	221 (52.5%)	0.76 (0.5, 1.2)	0.6 (0.27, 1.5)
Postpartum health education care provider	Get	33 (7.8%)	51 (12.1%)	1	1
	Not get	100 (23.8%)	237 (56.7%)	0.65 (0.4, 1.1)	2 (0.8, 5.1)

** = Statistically significant at p <0.05; 1 = Reference; Others** = student, Non-governmental organization (NGO) employee and daily laborer; COR, Crude Odds Ratio; AOR, Adjusted Odds Ratio and 95% CI, 95% Confidence Interval.*

CONCLUSION

In the current study, about one-third of postpartum women returned to sexual activity within 6 weeks of childbirth. Monogamous marriage, parity, postpartum visits at last delivery, and current infant feeding status were found to be significantly associated with return of sexual activity within 6 weeks of childbirth. Strengthening postpartum counseling regarding the appropriate time to resume sexual activity is crucial. Regular postpartum visits following deliveries should also be encouraged by health care providers.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Salale University Ethical Review Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

DE, TE, and BD: conceptualization and investigation. DE, MA, and TE: data curation, formal analysis, and methodology. DE: funding acquisition, project administration, resources, and writing—original draft. BD and MA: software. TE: validation. DE and TE: visualization. DE and BD: writing—review and editing. All of the authors contributed to the proposal development, questionnaire development, data collecting process, and analysis.

The final version of the manuscript was read by all authors, who gave their approval for it to be considered for publication.

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REFERENCES

1. Odar E, Wandabwa J, Kiondo P. Sexual practices of women within six months of childbirth in Mulago hospital. *African Health Sci.* (2003) 3:117–23.
2. Rezaei N, Azadi A, Sayehmiri K, Valizadeh R. Postpartum sexual functioning and its predicting factors among Iranian women. *Malays J Med Sci.* (2017) 24:94–103. doi: 10.21315/mjms2017.24.1.10
3. Gadisa TB, G/Michael MW, Reda MM, Aboma BD. Early resumption of postpartum sexual intercourse and its associated risk factors among married postpartum women who visited public hospitals of Jimma zone, Southwest Ethiopia: a cross-sectional study. *PLoS ONE.* (2021) 16:e0247769. doi: 10.1371/journal.pone.0247769
4. Mbekenga CK, Pembe AB, Darj E, Christensson K, Olsson P. Prolonged sexual abstinence after childbirth: gendered norms and perceived family health risks, focus group discussions in a Tanzanian suburb. *BMC Int Health Hum Rights.* (2013) 13:4. doi: 10.1186/1472-698X-13-4
5. Malakoti J, Zamanzadeh J, Maleki A, Farshbaf Khalili A. Sexual function in breastfeeding women in family Health Centers of Tabriz, Iran, 2012. *J Caring Sci.* (2013) 2:141–6. doi: 10.5681/jcs.2013.017
6. Anzaku AS, Mikah S. Postpartum resumption of sexual activity, sexual morbidity and use of modern contraceptives among Nigerian women in Jos. *Ann MedHealth Sci Res.* (2014) 4:210–6. doi: 10.4103/2141-9248.129044
7. Iliyasu1 Z, Galadanci HS, Danlami KM, Salihu HM, Aliyu MH. Correlates of postpartum sexual activity and contraceptive use in Kano, Northern Nigeria African. *J Reprod Health.* (2018) 22:103–12. doi: 10.29063/ajrh2018/v22i1.10
8. Doke PP, Vaidya VM, Narula AP, Patil AV, Panchanadikar TM, Wagh GN. Risk of non-resumption of vaginal sex and dyspareunia among cesarean-delivered women. *J Family Med Prim Care.* (2021) 10:2600–7. doi: 10.4103/jfmpc.jfmpc_2482_20
9. Delgado-Pérez E, Rodríguez-Costa I, Vergara-Pérez F, Blanco-Morales M, Torres-Lacomba M. Recovering sexuality after childbirth. What strategies do women adopt? A qualitative study. *Int J Environ Res Public Health.* (2022) 19:950. doi: 10.3390/ijerph19020950
10. Shabangu Z, MadibaInt S. The role of culture in maintaining post-partum sexual abstinence of Swazi women. *J Environ Res Public Health.* (2019) 16:2590. doi: 10.3390/ijerph16142590
11. Tesfay F, Mesfin E, Gedefaw EMA. Resumption of postpartum sexual intercourse and use of modern contraceptive among in-union women in Addis Ababa: cross sectional study. *Ethiopian J Reprod Health*. (2018) 10:23–35. Available online at: https://ejrh.org/index.php/ejrh/article/view/21
12. Nkwabong E, Ilue EE, Njamen TN. Factors associated with the resumption of sexual intercourse before the scheduled six-week postpartum visit. *Trop Doct*. (2019) 49:260–64. doi: 10.1177/0049475519855294
13. Zhuang C, Li T, Li L. Resumption of sexual intercourse postpartum and the utilisation of contraceptive methods in China: a cross-sectional study. *BMJ Open.* (2019) 9:e026132. doi: 10.1136/bmjopen-2018-026132
14. Ndugwa RP, Cleland J, Madise NJ, Fotso JC, Zulu EM. Menstrual pattern, sexual behaviors, and contraceptive use among postpartum women in Nairobi Urban slums. *J Urban Health*. (2010) 88:241–354. doi: 10.1007/s11524-010-9452-6
15. Wamala R, Kabagenyi A, Kasasa S. Predictors of Time to Contraceptive Use From Resumption of Sexual Intercourse After Birth Among Women in Uganda. *DHS Working Papers No. 118*. Rockville, MD: ICF International (2015).
16. Alum AC, Kizza IB, Osingada CP, Katende G, Kaye DK. Factors associated with early resumption of sexual intercourse among postnatal women in Uganda. *Reprod Health*. (2015) 12:107. doi: 10.1186/s12978-015-0089-5
17. Adedokun B, Abdus-Salam RA, Babawarun T, Morhason-Bello I, Ojengbede O. Resumption of sexual intercourse and family planning use among postpartum women attending infant welfare clinics in Ibadan, southwest Nigeria – a cross-sectional study. *Niger J Clin Pract.* (2020) 23:1648–55. doi: 10.4103/njcp.njcp_76_20
18. Jambola ET, Gelagay AA, Belew AK, Abajobir AA. Early resumption of sexual intercourse and its associated factors among postpartum women in western Ethiopia: a cross-sectional study. *Int J Women's Health*. (2020) 12:381–91. doi: 10.2147/IJWH.S231859
19. Mekonnen BD. Factors associated with early resumption of sexual intercourse among women during extended postpartum period in Northwest Ethiopia: a cross sectional study. *Contracept Reprod Med*. (2020) 5:19. doi: 10.1186/s40834-020-00124-7
20. O'Malley D, Higgins A, Smith V. Exploring the complexities of postpartum sexual health. *Curr Sex Health Rep*. (2021) 13:128–35. doi: 10.1007/s11930-021-00315-6
21. Jeong YJ, Nho JH, Kim HY, Kim JY. Factors influencing quality of life in early postpartum women. *Int J Environ Res Public Health.* (2021) 18:2988. doi: 10.3390/ijerph18062988
22. Kettle C, Ismail K, O'Mahony F. Dyspareunia following childbirth. *Royal Coll Obstetr Gynecol.* (2005) 7:245–9. doi: 10.1576/toag.7.4.245.27119
23. Abate ZG, Obsie GW. Early postpartum modern family planning utilization and associated factors in Dilla town, southern Ethiopia;2019. *J Womens Health Gyn*. (2021) 8:1–9. doi: 10.17303/jwhg.2021.8.102
24. O'Malley D, Higgins A, Smith V. Return to sexual activity and family planning use in the extended postpartum period. *African J Reprod Health*. (2010) 14:75–80.
25. Rowland M, Foxcroft L, Wilma MH, Patel R. Breastfeeding and sexuality immediately postpartum. *Can Fam Phys.* (2005) 51:1366–7.
26. Chew PY, Choy CL, Sidi HB, Abdullah N, Che Roos NA, Salleh Sahimi HM, et al. The association between female sexual dysfunction and sexual dysfunction in the male partner: a systematic review and meta-analysis. *J Sex Med*. (2021) 18:99–112. doi: 10.1016/j.jsxm.2020.10.001

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CASE REPORT
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A Giant Ovarian Cystadenoma in A 20-Year-Old Nulliparous Woman: A Case Report

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Giant ovarian cyst itself is defined as a cyst >10 cm in diameter from radiological- examination or the size of the cyst exceeds the umbilicus. Extra-large benign and malignant cysts of the ovary are uncommon and involve diagnostic and management challenges. We present the case of a 20-year-old nulliparous woman who was referred to our center with complaints of abdominal pain and heavy breathing. She benefited from a salphingo-oophorectomy laparotomy procedure. Benign and malignant gynecologic and non-gynecologic etiologies are included in the differential diagnosis of an abdominal mass. Because of the infrequent occurrence or absence of distinctive clinical presentation of the giant ovarian cyst, accurate preoperative diagnosis is challenging.

Keywords: giant ovarian tumor, salphingo-oophorectomy, laparotomy, ovarian cyst, gynecological benign tumor

INTRODUCTION

A fluid-filled sac in the ovarian tissue is known as an ovarian cyst. A cyst is defined as a fluid-filled sac that is bigger than 5 cm in diameter (1, 2). Giant ovarian cyst itself is defined as a cyst >10 cm in diameter from radiological examination or the size of the cyst exceeds the umbilicus (3). Despite this, the many of ovarian cysts develop during the hormonally active stages of childhood and adolescence. Most are functional in nature and resolve without treatment. Ovarian cysts, on the other hand, can signal an underlying malignant process or, more likely, divert the clinician's attention away from a more dangerous illness, such as appendicitis, ovarian torsion, or ectopic pregnancy. On the other hand, there may be an inverse relationship between breast cancer and ovarian cysts. When ovarian cysts become large, painful, or persistent, or when radiographic or exam findings are alarming, surgery may be required, and the ovary may be removed (1, 3). Ovarian cysts can develop at any age, however they are more common during the reproductive years and are more common in menarchal females due to endogenous hormone production (4, 5).

In general, in the younger population, the goal of management is conservative, with observation and resolution of symptoms, prevention of complications, and, when necessary, proper treatment of malignant tumors while maintaining ovarian structure and function (6).

CASE REPORT

A 20-year-old woman, G0P0A0, came to Hospital's with complaints of tightness and difficulty in breathing because her abdomen is increasingly enlarged and hardened. Complaints were already present for three years ago, but she never sought medical attention until now because she started feeling short of breath. The patient also complained of generalized abdominal pain with a VAS score of 8. On physical examination, the patient appeared toxic but fully concious (GCS E4M5V6). Measurement of vital signs are as follow: blood pressure 130/80 mmHg; heart rate 89, regular; respiratory rate 22 breaths per minute, regular; axillar temperature 36C; and oxygen saturation 99%. The patient weighs 67 kg with 156 cm height (nutritional status is classified as obese, BMI 27.5 kg/m^2.

Inspection of the abdomen revealed significant distension (38 cm × 60 cm) (**Figure 1**). Bowel sound was absent on auscultation. Abdomen was dull on percussion, tenderness on palpation. Liver and spleen were unpalpable. Other systems appeared normal. Complete blood count examination revealed an increase in creatinine (0.9 mg/dL [normal range: 0.5–0.8 mg/dL]) and calcium (1.28 mmol/L [normal range 1.00–1.15 mmol/L]), other parameters were normal.

CT scan examination of the abdomen revealed a giant septal and lobulated cyst (30.7 cm × 30.72 cm × 31.67 cm), oval-shaped, located in abdominal and pelvis and abdominal cavity (**Figure 2**). The patient was then diagnosed with giant ovarian cyst and left salpingo- oophorectomy was done. Ovarian tumor was successfully removed (**Figure 3**) without any complications during and after surgery. No complications were observed in the 30 days after surgery. Histopathological examination results confirmed mucinous cystadenoma. The patient's perspective on the health services we provide is quite satisfactory

DISCUSSION

We hereby report a case of a 20-year-old woman suffering from giant ovarian cyst. Ovarian cysts are seen in girls and women of all ages. Extra-large benign and malignant cysts of the ovary are uncommon and involve diagnostic and management challenges. Many problems are linked with surgical care of these giant ovarian cyst tumors, including severe hypotension, heart failure, respiratory failure, intestinal distention, and hypovolemic shock (3).

The many of mucinous tumors were benign mucinous cystadenomas (85%). These tumors can grow to a very large size. They usually occur as large multicystic masses containing mucus and fluid, usually appearing in women in their 20 to 40 s. Its large size itself can be a sign of mucinous histology (7). Our patient's presentation was pathognomic: enlarged abdominal distension filled the entire abdominal cavity, accompanied by symptoms due to compression of adjacent organs including constipation, difficulty defecating, urinary disturbances, early satiety, and edema of the lower extremities due to venous pressure and lymphatic vessels. Patients come to a secondary hospital after being referred from a primary health facility (Community Health centers). In fact, the patient has felt that his stomach is getting bigger in the past year which is getting bigger and bigger. Because he did not experience severe complaints, this patient did not go to the

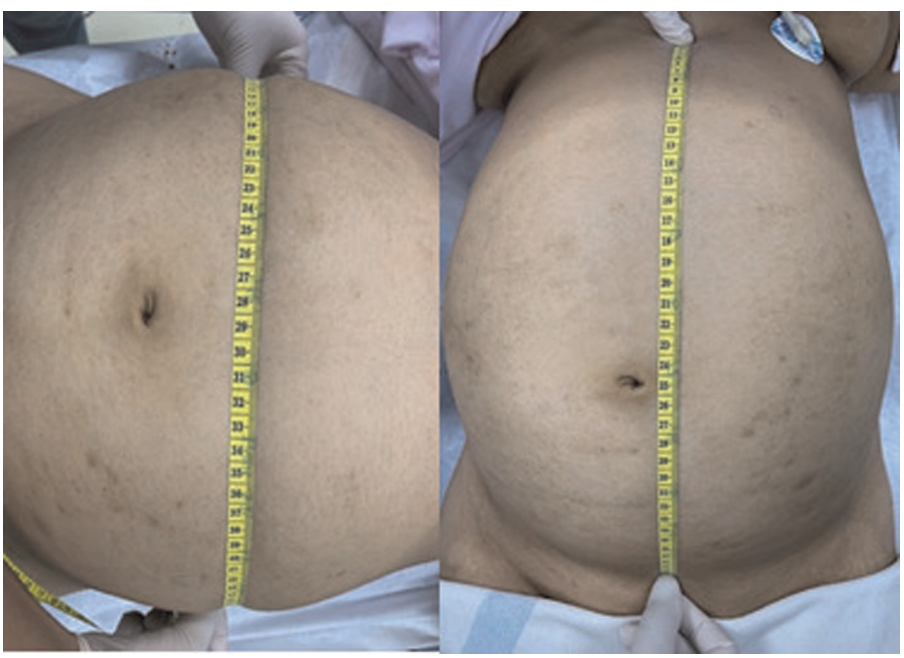

FIGURE 1 | Measurement of the abdominal mass during physical examination.

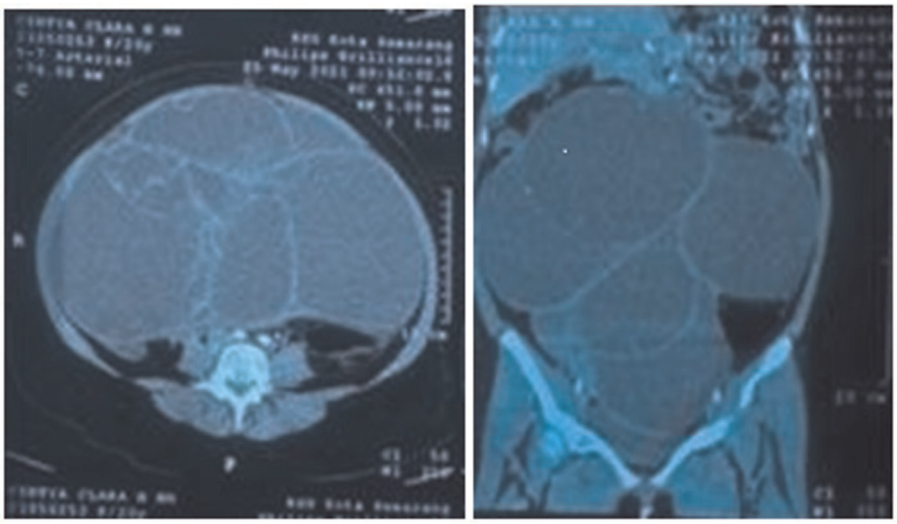

FIGURE 2 | Abdominal CT-scan revelaed a giant lobulated cyst in the abdominal and pelvic cavity.

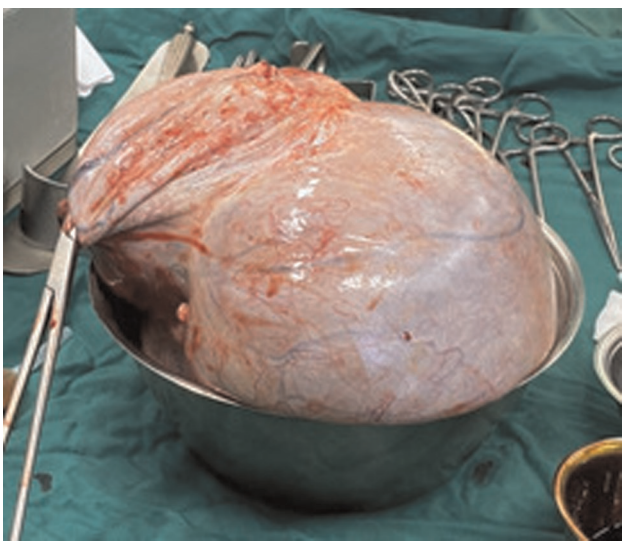

FIGURE 3 | Completely removed the giant ovarian tumor.

hospital. So far, she only goes to an independent practice doctor if there are complaints of pain or shortness of breath. Because the complaint of shortness of breath was getting worse and was not cured by taking medication, the patient came to the hospital. Social, economic, and educational factors affect patients late for treatment at the hospital.

Ovarian cyst frequency increased with age as adolescence progressed, ranging from 3.8%–31.3%. With a rate of 31.3 percent, the peak age for ovarian cysts was 15 years (8). Many simple ovarian cysts are asymptomatic and only discovered on ultrasound by chance. Ovarian cysts that are larger might produce discomfort and pressure feelings. A cyst that has been torn usually causes considerable pain and manifests as an acute abdomen. An ovarian torsion can occur in prepubescent girls without any adnexal disease (1).

Adolescents with a symptomatic ovarian mass include abdominal pain, menstrual disturbances, and an enlarged abdomen. Other complications can be accompanied by signs and symptoms that lead to compression, such as nausea, vomiting, weight loss or increased frequency of urination, urinary retention due to cysts pressing on the ureteral tract which can cause hydronephrosis, compression of the rectum so that the patient is constipated and dyspnea, torsion, intestinal infection or obstruction, and constitute a surgical emergency (9, 10).

The patient in this case didn't seek medical attention for years until these symptoms occur, which manifested as shortness of breath and abdominal pain. Transabdominal/transvaginal ultrasonography is the first radiologic examination used to diagnose an ovarian cyst (2). To support the diagnosis, preoperative investigations can be carried out by examination of tumor markers (CA-125), ultrasound scan, abdominal X-ray, computed tomography (CT) or magnetic resonance imaging scan (MRI) (11).

The main imaging modality for evaluating ovarian and adnexal masses is ultrasonography (US), which allows accurate identification in approximately 90% of cases. It has the advantage of being available, inexpensive, easy to perform (especially when in the hands of an experienced operator), and has no ionizing radiation (12).

This patient had an ultrasound examination, which indicated an adnexal mass on the right ovary, and a CT-scan was performed to further analyze this mass. A cyst may be classified as benign if at least one ultrasound feature of a benign mass (B-feature: unilocular cyst, presence of solid components where the largest component <7 mm, presence of acoustic shadowing Smooth multilocular tumour with largest diameter <100 mm, no blood flow) is present, and none of the

TABLE 1 | Short literature summary.

No.	First Author	Publication year	Age years	Imaging results, size, weight	Primary surgical procedure	Pathology
1.	Sanjay K Bhasin (16)	2014	85	Ultrasound was unable to identify ovarian cysts, showing characteristic ascites. Swelling mass measuring 32 cm in a cranio-caudal direction originating from the pelvis and extending to the diaphragm reveals fluid density.	Laparatomy, total excision of the cyst. That measured 975 gms by weigh	Mucinous cystadenoma
2.	Eugene Vernyuy Yeika (14)	2017	65	An abdominal ultrasonography suggested a large fluid-filled multilocular space of right ovarian origin with a thin coating and intestinal loop migration to the diaphragm. The cyst is excised with the membrane intact, dimensions 55 × 52 × 24 cm, weight 10.8 g.	Laparotomy, a right ovarian cystectomy	Mucinous cystadenoma
3.	Sibraogo Kiemtoré (15)	2019	25	CT scan of the abdomen and pelvis revealed a unilateral cystic mass (>10 cm). Cyst size 42 cm and weight 19.7 kg	Laparotomy, left total oophorectomy	Serous ovarian cystadenoma.
4.	Chipo Gwanzura (7)	2019	48	Computed tomography (CT) which showed a large, mostly cystic lesion occupying most of the abdomen and pelvis.	Laparotomy, a total abdominal hysterectomy	Mucinous cystadenoma
5.	Cipta Pramana (17)	2020	71	Ultrasound performed suggested a large, cystic lesion approximately 25 × 20 × 20 cm originating from the pelvis.	Laparotomy, left salphyngo-oophorectomy	Mucinous cystadenoma
6.	Banwari Lal Bairwa1 (18)	2020	16	Abdominal computed tomography (CECT) revealed a large, multilocal cystic mass measuring 24.3 × 21.5 × 20.2 cm.	Laparotomy, a right adnexectomy	An ovarian mucinous cystadenoma
7.	Cipta Pramana (19)	2021	40	Contrast abdominal CT scan showing a well-defined multilocular cystic mass with regular margins (16 cm × 11.94 cm × 19.48 cm) in the dominant left abdominal cavity,	Laparotomy, a left salpingo-oophorectomy	Mucinous borderline ovarian tumor
8.	Miyu Tanaka (20)	2021	54	CECT showed that the tumor occupied the entire abdominal cavity (38 cm × 40 cm × 48 cm).	Laparotomy, remove the right adnexa	Ovarian fibroma

Table 1 | Summarizes several case reports on giant ovarian cysts from various authors. The table includes the patient's age, year of publication of the journal, imaging results, tumor size and weight, surgical procedures performed and histopathological results. All cases underwent laparotomy surgery procedure, none were laparoscopic. Most cases underwent salpingo-oophorectomy or adenexectomy (four cases), the others underwent cystectomy, oophorectomy and hysterectomy in one case each (7, 14–20).

ultrasound features of malignancy (10). CT scan of the abdomen revealed a giant septal and lobulated cyst (30.7 cm × 30.72 cm × 31.67 cm), oval-shaped, located in abdominal and pelvis and abdominal cavity. In complex, multiloculated cysts, the risk of malignancy increases up to 36% (4). Blood tests should be done to measure CA-125, LDH, alpha fetoprotein, and hCG; to evaluate the risk of malignancy (13).

To estimate the risk of malignancy, ultrasound features without CA-125 levels have been shown to have high sensitivity, specificity, and likelihood ratios. Malignant ovarian cysts account for over 10% of all gigantic ovarian cysts, and their signs and symptoms, especially in the early stages of the disease, are ambiguous and non-specific, necessitating the exclusion of this possibility in all cases of ovarian cysts (11, 14).

The surgical management of giant ovarian cystadenoma must pay attention to various factors, especially in the case of adolescents, where the operative strategy is to cure, and also maintain fertility in the patient. And during surgery, do not take the part where there is no cyst, and only do a cystectomy (9). The management approach is determined on the size of the cyst, the equipment available, and the surgeon's level of skill. Many experts advise against aspirating the contents of the cyst because of problems such as infection, hemorrhage, cyst rupture, and a higher risk of peritoneal adhesion. An immediate complication to be feared when removing a giant ovarian cyst is the vacuum shock requiring a good preventive vascular filling (14, 15).

Laparoscopy can be used as an option for diagnostic purposes. It can be useful in the differential diagnosis between ovarian tumors and other intra-abdominal cystic masses when imaging evaluation cannot determine the organ of origin. In addition, the tumor can be inspected and, when there are signs of malignancy (abnormalities, adhesions to adjacent structures, etc.), the surgeon may change the procedure to an open laparotomy. Laparoscopically in giant ovarian cysts, especially those that reach the umbilicus, there is a risk of perforation when the trocar is inserted (10). In this case report, open salpingo-oophorectomy was done, without any perioperative complications.

CONCLUSION

I have reported a case of ovarian cystadenoma in a 20-year-old woman who underwent a left salpingo-oophorectomy, while the right adnexa (tubal and ovary) are still maintained, and the organ condition is good. So that the reproductive function is still possible to get pregnant.

Extra-large benign and malignant cysts of the ovary are uncommon and involve diagnostic and management challenges. The most ovarian cysts occur during the hormonally active stages of growth of childhood and adolescence. Abdominal pain, distension, bloating, constipation, and vomiting are common symptoms caused by the compressive action of a giant ovarian cyst. The management approach is determined on the size of the cyst, the equipment available, and the surgeon's level of skill. In this case report, open salpingo-oophorectomy was done, without any perioperative complications.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Clearance Committee of K.R.M.T. Wongsonegoro Hospital Semarang Indonesai. Written informed consent was obtained from the patient for publication of potentially identifiable images or data included in this manuscript.

AUTHOR CONTRIBUTIONS

All of the listed authors have made substantial, direct and intellectual contributions to the work and approved it for publication.

REFERENCES

1. Ritchie J, O'Mahony F, Garden A. Guideline for the management of ovarian cysts in children and adolescents. *Br Soc Paediatr Adolesc Gynaecol*. (2021):1–11. Available from: https://britspag.org/wp-content/uploads/2019/02/Ovarian-cyst-management-in-PAG-guideline-Dec-2018-1.pdf
2. How JA, Marino JL, Grover SR, Heloury Y, Sullivan M, Mellor A, et al. Surgically managed ovarian masses at the royal children's hospital, Melbourne –19 year experience. *J Pediatr Surg*. (2019) 54(9):1913–20. doi: 10.1016/j.jpedsurg.2019.05.005
3. Pramana C. Giant ovarian cyst: a case report from a post-menopausal woman. *Int J Psychosoc Rehabil*. (2020) 24(1):1652–6. doi: 10.37200/IJPR/V24I1/PR200265
4. Al Zahidy ZA. Causes and management of ovarian cysts. *Egypt J Hosp Med*. (2018) 70(10):1818–22. doi: 10.12816/0044759
5. Batt RE. Adnexal masses in Korean children and adolescents. *J Minim Invasive Gynecol*. (2010) 17(5):76–92. doi: 10.1016/j.jmig.2010.04.003
6. Kirkham YA, Lacy JA, Kives S, Allen L. Characteristics and management of adnexal masses in a Canadian pediatric and adolescent population. *J Obstet Gynaecol Canada*. (2011) 33(9):935–43. doi: 10.1016/S1701-2163(16)35019-8
7. Gwanzura C, Muyotcha AF, Magwali T, Chirenje ZM, Madziyire MG. Giant mucinous cystadenoma: A case report. *J Med Case Rep*. (2019) 13(1):1–6. doi: 10.1186/s13256-019-2102-z
8. Emeksiz HC, Derinöz O, Akkoyun EB, Pınarlı FG, Bideci A. Age-specific frequencies and characteristics of ovarian cysts in children and adolescents. *J Clin Res Pediatr Endocrinol*. (2017) 9(1):58–62. doi: 10.4274/jcrpe.3781
9. Persano G, Severi E, Cantone N, Incerti F, Ciardini E, Noccioli B. Surgical approach to giant ovarian masses in adolescents: Technical considerations. *Pediatr Rep*. (2018) 10(3):43–5. doi: 10.4081/pr.2018.7752
10. Grigore M, Murarasu M, Himiniuc LM, Toma BF, Duma O, Popovici R. Large ovarian tumors in adolescents, a systematic review of reported cases, diagnostic findings and surgical management. *Taiwan J Obstet Gynecol*. (2021) 60(4):602–8. doi: 10.1016/j.tjog.2021.05.005
11. Hernon M, McKenna J, Busby G, Sanders C, Garden A. The histology and management of ovarian cysts found in children and adolescents presenting to a children's hospital from 1991 to 2007: A call for more paediatric gynaecologists. *BJOG An Int J Obstet Gynaecol*. (2010) 117(2):181–4. doi: 10.1111/j.1471-0528.2009.02433.x
12. Khati NJ, Kim T, Riess J. Imaging of benign adnexal disease. *Radiol Clin North Am*. (2020) 58(2):257–73. doi: 10.1016/j.rcl.2019.10.009
13. Farahani L, Datta S. Benign ovarian cysts. *Obstet Gynaecol Reprod Med*. (2016) 26(9):271–5. doi: 10.1016/j.ogrm.2016.06.003
14. Yeika EV, Efie DT, Tolefac PN, Fomengia JN. Giant ovarian cyst masquerading as a massive ascites: A case report. *BMC Res Notes*. (2017) 10(1):8–11. doi: 10.1186/s13104-017-3093-8
15. Kiemtoré S, Zamané H, Sawadogo YA, Sib RS, Komboigo E, Ouédraogo A, et al. Diagnosis and management of a giant ovarian cyst in the gravid-puerperium period: A case report. *BMC Pregnancy Childbirth*. (2019) 19(1):1–7. doi: 10.1186/s12884-019-2678-8
16. Bhasin SK, El-agwany A, Bhasin SK, Kumar V, Kumar R. Giant Ovarian Cyst-A Case Report & Review of Literature. *JK Sci*. (2014) 16(3):131–3.
17. Pramana C. Giant ovarian cyst: a case report from a post-menopausal woman. *Int J Psychosoc Rehabil*. (2020) 24(1):1652–6. doi: 10.37200/IJPR/V24I1/PR200265
18. Lal Bairwa B. Giant ovarian mucinous cystadenoma in an adolescent girl: a case report. *Asian Res J Gynaecol Obstet*. (2020) 4(4):23–6.
19. Pramana C, Respati G, Wahyudi F. Successful management of giant mucinous borderline ovarian tumors in a 40-year-old woman: A case report. *Ann Rom Soc Cell Biol*. (2021) 25(1):2013–8.
20. Tanaka M, Yamanoi K, Kitamura S, Horikawa N, Chigusa Y, Horie A, et al. A 36 kg giant ovarian fibroma with meigs syndrome: a case report and literature review of extremely giant ovarian tumor. *Case Rep Obstet Gynecol*. (2021) 2021:1–8.

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Experience in the Management of Vaginal Cuff Dehiscence and Evisceration: A Retrospective 37-Year Single-Center Study

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Purpose: Vaginal cuff dehiscence (and evisceration) (VCD(E)) is an extremely rare and late-onset complication of total hysterectomy (TH). Limited evidence is available to guide clinicians in managing VCD(E). This study aimed to summarize the clinical characteristics of patients with VCD(E) treated in our center and share our experience in managing VCD(E).

Patients and methods: From 1983 to 2020, a total of 14 cases of VCD(E), including 10 cases in our hospital and 4 cases in other hospitals, were included. Medical records were reviewed to summarize the clinical features and management of VCD(E).

Results: The incidence of VCD(E) in our hospital was 10/46,993 (0.02%), and all 10 patients underwent laparoscopic hysterectomy. The median TH-to-VCD(E) interval was 3.13 months (8 days–27.43 months), and 11/14 (78.57%) patients experienced VCD (E) after coitus. The 3 major symptoms included abdominal pain in 11 patients, irregular vaginal bleeding in 8, and sensation of bulging or prolapsed organs in 4. Except for 2, most patients presented to our hospital within 72 h since the onset of the discomfort. All 14 cases were diagnosed through speculum examination: 3 had simple VCD, and 11 had VCDE. The protruding bowels of 4 patients were immediately manually repositioned in the emergency department without anesthesia. Regarding the surgical approach, 11 patients underwent simple transvaginal, 2 patients underwent laparoscopic-vaginal combined (transvaginal cuff closures), and 1 patient underwent laparoscopic. All but 1 patient did not undergo resection of the eviscerated organs. The median follow-up period was 39.33 (7.9–159.33) months. No patients showed any evidence of recurrence to date.

Conclusions: Laparoscopic hysterectomy is a risk factor for VCD(E), and early initiation of sexual intercourse is the most common trigger of VCD(E). Clinicians should educate patients

Abbreviations: BMI, body mass index; LH, laparoscopic hysterectomy; PUMCH, Peking Union Medical College Hospital; TH, total hysterectomy; VCC, transvaginal cuff closure; VCD(E), Vaginal cuff dehiscence (and evisceration).

to postpone sexual intercourse for at least 3–6 months after TH. Immediate medical attention and patient-specific surgical management are crucial to avoid serious complications.

Keywords: hysterectomy, laparoscopic hysterectomy, vaginal cuff dehiscence and evisceration, manual reduction, transvaginal cuff closure

INTRODUCTION

Total hysterectomy (TH) is one of the most common gynecological procedures (1) and is widely applied in various benign and malignant diseases. Genitourinary and gastrointestinal tract injury, bleeding, infection, and vaginal cuff dehiscence (VCD) are the most common complications of TH (2). In contrast to other complications of TH, VCD is an extremely rare and late-onset complication. VCD refers to the partial or full-thickness separation of the vaginal cuff (3). It is termed vaginal cuff dehiscence and evisceration (VCDE) when the intraperitoneal contents protrude from the cuff defect (4). The small bowel is the most frequently eviscerated organ, but evisceration of other organs, such as the sigmoid colon, greater omentum, appendix, and adnexa uteri (5), have also been reported. VCD is a rare and life-threatening condition that may lead to evisceration. The most common clinical presentations of VCD(E) are sudden lower abdominal pain and irregular vaginal bleeding. Patients with evisceration may also feel a bulging sensation or find the prolapsed organs.

Due to its low incidence, most reported cases are sporadic. Numerous studies have focused on the risk factors for VCD (E) and strategies to decrease its morbidity. Limited evidence is available to guide clinicians in managing VCD(E). Herein, we describe the clinical characteristics and management of 14 cases of VCD(E) treated in our hospital and share our original experience in the treatment of VCD(E).

MATERIALS AND METHODS

We searched and retrieved the medical records of patients who underwent TH and who were diagnosed with "VCD(E)" from 1983 to 2020 in the database of Peking Union Medical College Hospital (PUMCH). Data extracted from the medical records mainly included demographic and clinical characteristics of patients, details of hysterectomy and VCD(E), and management of VCD(E). Follow-up information was collected from the clinical database of PUMCH or through telephone interviews with patients. This study was approved by the Ethics Committee of PUMCH. Categorical variables are expressed as numbers and proportions, while continuous variables are described as medians and ranges. Statistical analysis was performed using SPSS version 25.0 (IBM SPSS Statistics).

RESULTS

Patient Characteristics

From 1983 to 2020, 46,993 patients underwent TH at PUMCH, and 10 (0.02%) experienced VCD(E) after laparoscopic hysterectomy (LH). In addition, 4 patients who had TH in other hospitals also experienced VCD(E) and were treated at PUMCH during this period. Therefore, 14 patients with VCD (E) were identified from the PUMCH database, and their medical records were reviewed. Demographic data of patients are detailed in **Table 1**. The patients' median age was 46 years (31–55 years). The median body mass index (BMI) was 23.53 kg/m^2 (18.29–25.71 kg/m^2); 6 (42.86%) patients were overweight but not obese according to Chinese standards, and 2 of them had diabetes mellitus.

Details of Total Hysterectomy

Three (21.43%) patients were menopausal before TH, and 6 (42.86%) underwent bilateral or unilateral oophorectomy during TH. Moreover, 5 patients received TH for benign diseases, 3 for precancerous lesions, 5 for malignancies, and 1 for prophylaxis and myoma. Among the 14 patients, 5 had a history of adjuvant therapy (3 of them for gynecological malignancy, and 2 of them for breast cancer). Regarding the surgical approach, only 1 patient (7.14%) underwent laparotomy with transabdominal cuff closure, 13 cases (92.86%) underwent laparoscopy, including transvaginal cuff closure (VCC) in 1 and laparoscopic cuff closure in 9; the other 3 were unknown (**Figure 1** and **Table 2**). All the 10

TABLE 1 | Demographic data of patients.

Case No.	Age (yr)	Parity	Delivery	BMI (kg/m^2)	Comordity
1	48	1	CS	20.14	Breast cancer(had adjuvant therapy)
2	52	2	VD	24.09	DM
3[a]	54	1	VD	18.90	No
4	52	1	CS	18.29	No
5[a]	44	1	VD	21.01	No
6[a]	31	1	CS	21.57	No
7	50	1	VD	24.09	No
8	42	1	VD	23.23	No
9	53	1	VD	24.22	No
10	55	1	VD	25.22	DM, HTN, Hyperlipidemia
11[a]	44	1	VD	24.22	No
12	39	0	/	20.96	No
13	44	1	CS	25.71	Breast cancer(had adjuvant therapy)
14	40	2	CS	23.83	No

VD, vaginal delivery; CS, cesarean section; BMI, body mass index; DM, diabetes mellitus;HTN hypertension.
[a]*Patients who underwent TH in other hospitals.*

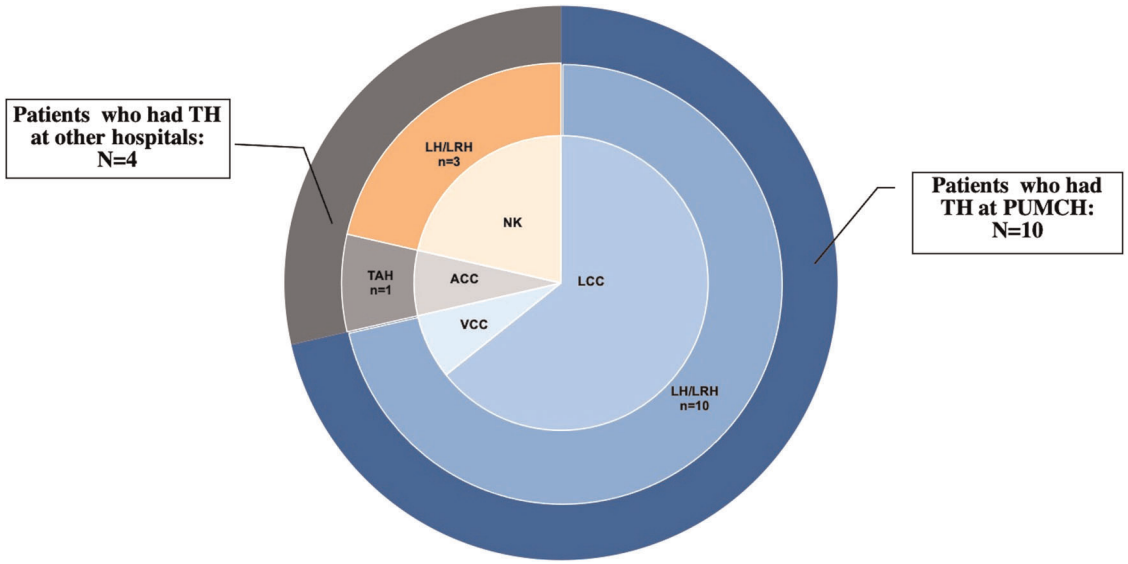

FIGURE 1 | The distribution of different types of TH and cuff closure.

patients who had LH at PUMCH underwent cuff closure with absorbable and continuous sutures. Information about TH in our study is presented in **Table 2**.

Clinical Features and Management of VCD(E)

As shown in **Table 3**, the median TH-to-VCD(E) interval was 3.13 months (8 days–27.43 months). Eleven (78.57%) patients noted VCD(E) to be triggered by intercourse, 1 patient (7.14%) noted VCD(E) during brachytherapy and was asymptomatic, and the other 2 (14.28%) noted VCD(E) to be caused by strenuous activity. In our series, the 3 major symptoms, presenting separately or concurrently, included lower abdominal pain in 11, irregular vaginal bleeding in 8, and sensation of bulge or prolapsed organs in 4. All 14 cases were diagnosed through speculum examination: 3 cases had simple VCD, while 11 cases had VCDE. The prolapsed organs in 11 cases of VCD(E) included the bowel in 9 (81.82%) and omentum in 2 (18.18%). Since the onset of discomfort, most patients presented to PUMCH in a timely manner, with 9 patients presenting within ≤24 h (7 patients ≤6 h), 3 in >24 but ≤72 h, and 2 patients after >72 h. One patient experienced abdominal pain after intercourse, which spontaneously resolved approximately 3 h later. On the 11th day after the intercourse, she noticed a prolapsed bowel and was referred to the hospital. The other patient visited PUMCH on the 8th day after she experienced acute abdominal pain and found prolapsed tissue after coitus.

Protruding bowels in 4 patients were manually repositioned without anesthesia in the emergency department. Then, they underwent cuff closure under anesthesia in the operating room. In our institution, 11 patients underwent a simple transvaginal approach, 2 underwent a combined laparoscopic-vaginal approach, and 1 underwent a laparoscopic approach. Of the 11 patients with VCDE, only one patient underwent partial resection of the eviscerated omentum because of necrosis. Different surgeons chose different sutures and suturing methods, in which absorbable antibacterial Vicryl sutures (VCP358H and VCP518H) and continuous sutures (simple running or interlock) were predominantly used. Oral or intravenous prophylactic antibiotics were administered perioperatively to each patient to avoid infection. More details are provided in **Table 3**.

Follow-up

Two patients were lost to follow-up. The median follow-up period was 39.33 months (7.9–159.33 months). Eleven patients had an unremarkable postoperative course. One patient complained of vaginal spotting on postoperative day 11. She was identified as having partial knot slippage on the right side of the vaginal stump. Fortunately, the patient healed well after hemostasis and activity restriction. To date, there is no evidence of recurrence.

DISCUSSION

Risk Factors

Surgical wound dehiscence is a potential complication post-surgery. A conceptual framework underlying surgical wound dehiscence has been developed (6), comprising physiological factors (comorbidities and lifestyle) and mechanical (intraoperative and postoperative) factors. Given the unique functional and anatomical characteristics of the vagina, VCD (E) is a special type of surgical wound dehiscence. We categorized the risk factors for VCD(E) into three groups: external force on the vaginal cuff, patient factors (physiological or pathological), and TH-related factors.

TABLE 2 | Information about TH.

Case No.	Indication	Menopause	Mode of hysterectomy	Additional procedure	Duration of operation (min)	EBL (mL)	Route of cuff closure	Type of suture	Suturing method	Intraoperative complication	Postoperative complication		Adjuvant therapy
											Anemia	Fever	
1	Atypical endometrial hyperplasia	Spontaneous menopause	LH	BSO	40	20	LCC	VCP358H	Simple running	No	Mild	No	None
2	Adenomyosis + Myoma	No	LH	BS	60	30	LCC	VCP518H	Simple running	No	Mild	No	None
3[a]	Ovarian Cyst	No	TAH	BSO	NK	NK	ACC	NK	NK	NK	NK	NK	None
4	Myoma + Ovarian Cyst	No	LH	BS + UO	90	40	LCC	VCP358H	Simple running	No	Mild	No	None
5[a]	Adenomyosis	No	LH	BS	NK	NK	NK	NK	NK	NK	NK	NK	None
6[a]	Cervical cancer	No	LRH	BS + LND + BOS	NK	NK	NK	NK	NK	NK	NK	NK	Chemotherapy and brachytherapy
7	Complex endometrial hyperplasia + Ovarian Cyst	No	LH	BS + Removal of ovarian cyst	60	50	LCC	VCP358H	Simple running	No	Moderate	No	None
8	Myoma	No	LH	BS	55	50	LCC	VCP358H	Simple running	No	Mild	No	None
9	CIN + Myoma	Spontaneous menopause	LH	BSO	95	50	LCC	VCP518H	Simple running	No	NK	No	None
10	Endometrial cancer	Spontaneous menopause	LH	BSO	85	20	LCC	VCP518H	Simple running	No	No	No	Brachytherapy
11[a]	Cervical cancer	No	LRH	BS + LND + BOS	NK	NK	NK	NK	NK	NK	NK	NK	None
12	Cervical cancer	No	LH	None	100	NK	VCC	1-0 Dexon	Interlock	No	Mild	No	None
13	Myoma + Prophylactic	No	LH	BSO	70	10	LCC	VCP518H	Simple running	No	NA	No	None
14	Cervical cancer	No	LRH	BS + LND + BOS	210	400	LCC	VCP518H	Simple running	No	Moderate	Yes	Chemotherapy and brachytherapy

TH, total hysterectomy; CIN, cervical intraepithelial neoplasia; LH, laparoscopic hysterectomy; TAH, transabdominal hysterectomy; LRH, laparoscopic radical hysterectomy; NK, not known; BS bilateral salpingectomy; BSO, bilateral salpingo-oophorectomy; UO, unilateral oophorectomy; LND, lymph node dissection; BOS, bilateral ovarian suspension; EBL, estimated blood loss; LCC, laparoscopic cuff closure; ACC, transabdominal cuff closure; VCC, transvaginal cuff closure.

[a]*Patients who underwent TH in other hospitals.*

TABLE 3 | Clinical features and management of VCD(E).

Case No.	TH-to-VCD(E) interval (d)	Trigger events	Onset-to-consultation interval	Symptoms	Anemia	Evisceration	Reposition prolapsed organs	Surigical interventions	Type of suture	Suturing method	Additional procedures	Antibiotics	Follow-up(d)	Recurrence
1	84	Postcoitus	6 h	Lower abdominal pain + found the prolapsed bowel	No	Bowel	UA	LCC	VCP358H	Figure-of-eight	/	Yes	791	No
2	102	Postcoitus	11 d	Lower abdominal pain	No	Bowel	UA	VCC	VCP358H	Simple running	/	Yes	237	No
3[a]	324	Postcoitus	1.5 h	Irregular vaginal bleeding + Lower abdominal pain	No	Bowel	WoA	VCC	VCP358H	Interlock	/	Yes	0	Lost of follow-up
4	80	Postcoitus	10.5 h	Lower abdominal pain + sensation of bulge	No	Bowel	UA	VCC	VCP603H	Interlock	/	Yes	884	No
5[a]	63	Postcoitus	1 h	Irregular vaginal bleeding + Lower abdominal pain + nausea and vomiting	No	Bowel	WoA	VCC	VCP358H	Interlock	Take a swab for culture(–)	Yes	1,219	No
6[a]	823	Postcoitus	5.5 h	Irregular vaginal bleeding + Lower abdominal pain	No	Bowel	UA	VCC	VCP518H	Figure-of-eight + interrupted	MBT of the bladder to consume bladder integrity preoperatively	Yes	1,107	No
7	135	Strenuous activity	2 d	Irregular vaginal bleeding + Lower abdominal pain	No	No	/	VCC	VCP358H	Interrupted	/	Yes	464	No
8	79	Postcoitus	1 d	Irregular vaginal bleeding	No	Omentum	UA	VCC	VCP518H	Interrupted	Take a swab for culture(-)+place a vaginal drainage-tube	Yes	2,431	No

(*continued*)

TABLE 3 | Continued

Case No.	TH-to-VCD(E) interval (d)	Trigger events	Onset-to-consultation interval	Symptoms	Anemia	Evisceration	Reposition prolapsed organs	Surigical interventions	Type of suture	Suturing method	Additional procedures	Antibiotics	Follow-up(d)	Recurrence
9	144	Postcoitus	0.5 h	Irregular vaginal bleeding + Lower abdominal pain	No	Bowel	WoA	VCC	VCP518H	Interlock	/	Yes	2,441	No
10	50	During radiotherapy	1 d	Asymptomatic	No	No	/	VCC + exploratory laporoscopy	VCP358H	Interlock	MBT of the bladder to consume bladder integrity intraoperatively	Yes	814	No
11[a]	105	Postcoitus	2 h	Lower abdominal pain + found the prolapsed bowel	No	Bowel	WoA	VCC	1B-401	Simple running	Creatinine level of drainage	Yes	0	Lost of follow-up
12	8	Strenuous activity + straining on stool	12 h	Irregular vaginal bleeding + dizziness and cold sweat	Mild	No	/	VCC	1-0 Dexon	Simple running	Blood transfuison(10U + 1,200 mL)	Yes	4,763	No
13	86	Postcoitus	6 h	Irregular vaginal bleeding + Lower abdominal pain + vaginal discharge	No	Bowel	UA	VCC	VCP358H	Interlock	/	Yes	3,480	No
14	770	Postcoitus	8 d	Lower abdominal pain + found the prolapsed bowels + vaginal discharge	No	Omentum	UA	VCC + laparocopy (partial omentectomy + BO)	VCP603H	Interlock	Pathological examination	Yes	644	No

VCD(E), vaginal cuff dehiscence (and evisceration); TH, total hysterectomy; UA, Under anesthesia; WoA, without anesthesia; LCC, Laparoscopic cuff closure; VCC, transvaginal cuff closure; BO, bilateral oophorectomy; MBT, methylene blue test.

[a]*Patients who underwent TH in other hospitals.*

Vaginal trauma during coitus is the most common trigger of VCD(E) (1, 4). Transvaginal procedures can also lead to VCD(E), including transvaginal ultrasonography (7) and intracavitary brachytherapy (8). Patient factors include three aspects (9): (1) factors impairing stump healing such as infection, hematoma, low estrogen status, glucocorticoid use, and immunosuppressant use; (2) increased abdominal pressure, such as in coughing, constipation, and strenuous activity; and (3) other factors, including BMI, age, and smoking. TH-related factors are mainly the method of colpotomy, type of vaginal cuff closure, and adjuvant therapy after TH. Most factors that affect wound healing are universal, but some risk factors differ between VCD(E) and other surgical wounds. For instance, obesity, high BMI, and old age are risk factors for surgical wound dehiscence but are protective factors against VCD(E) (10). A reasonable explanation is that elderly women are more likely to have lower estrogen levels and less sexual activity (11). We speculated that obese women with a higher BMI have a better buffering force against vaginal trauma during coitus than thin women with a normal or lower BMI. In our series, 9 patients were ≤50 years of age, and none were obese. It is important to note that 11 patients developed VCD(E) post-coitally, and 2 patients developed VCD(E) after strenuous activity. Two patients had comorbid diabetes mellitus, and VCDE was found in one of these two during brachytherapy. Five patients received adjuvant therapy for malignancy. Each patient in our study had at least 1 risk factor for VCD(E). Multiple factors contribute to VCD(E) (12) and having more risk factors compounds a patient's risk of VCD(E).

Being one of the most common gynecological interventions, TH can be performed in various ways. According to the surgical route of the procedure, TH is divided into transabdominal hysterectomy, vaginal hysterectomy, laparoscopic-assisted vaginal hysterectomy, laparoscopic hysterectomy (LH), and robotic hysterectomy. VCD(E) is possible from any type of TH, but its prevalence varies widely depending on the TH route (13). The influence of the surgical route and type of cuff closure on the incidence of VCD(E) has been discussed with conflicting theories. Many studies (10, 14) have pointed out a possibly higher rate of VCD(E) after minimally invasive procedures than after transabdominal hysterectomy and vaginal hysterectomy. Electrosurgical thermal energy and techniques, magnifying effects, shallow tissue bites (15), poor knot integrity (16), low surgeon laparoscopic expertise (17), and prolonged inflammatory phase (18) are responsible for the increased risk of VCD(E) in minimally invasive surgeries. In our study, 10 of 14 VCD(E) cases underwent TH at PUMCH, and all of these 10 cases had undergone laparoscopy. In other words, out of 46,993 cases of TH in PUMCH, only 10 cases of LH experienced VCD(E) postoperatively, suggesting that LH was associated with a higher rate of VCD(E). To date, VCD(E) remains a rare event. Laparoscopic techniques have undergone rapid development over the last 30 years. Although some patient factors attributed to VCD(E), including age and low estrogen status, cannot be improved perioperatively, we still believe that optimal perioperative management and improvement of surgical skills are of greater value to the prevention of VCD(E).

Clinical Features

The clinical presentation of VCD(E) could be abdominal pain, vaginal bleeding, vaginal discharge, and a sensation of a bulge yet free from any discomfort (4). Notably, evisceration could be observed in approximately one-third to more than half of VCDs, and up to 30% of VCD(E)s eventually undergo bowel resection. The severity of VCD(E) depends on the eviscerated organs, condition and duration of evisceration, and whether it is accompanied by serious complications, such as ileus, bowel necrosis, peritonitis, shock (hemorrhagic or septic), pneumoperitoneum (19), and pneumomediastinum (20). Of the 14 cases, 11 (78.57%) were accompanied by evisceration. Necrosis of the omentum only progressed in one case, and it was due to a late medical consultation. To address omentum necrosis, doctors performed partial omentectomy by laparoscopy. Nine of the 11 patients with VCDE had bowel protrusion from the split cuff. With timely medical consultation and intervention, none of the 9 patients developed incarceration, ischemia, or necrosis, and they all recovered without the need to remove the prolapsed bowel.

Diagnosis and Treatment

Normal wound healing is a complicated process comprising hemostasis (begins immediately after injury), inflammation (starts shortly thereafter), proliferation (begins within days), and remodeling (lasts for several months to a year) (18, 21). The healing wound attains about 40% of its final strength in the first month, and the wound strength continues to increase for as long as a year after injury, but multiple factors affect and interfere with the healing process. Different types of sutures have different complete absorption time, meaning they support wound healing for different periods (22). The tensile strength of sutures, suturing approach, and surgeon's experience may also affect the reliability of the closure, meaning that complete vaginal cuff healing varies. Early resumption of intercourse may be associated with incomplete vaginal cuff healing, especially in young adults (23).

VCD(E) typically occurs within the first 3 months postoperatively, but sporadic cases of VCD(E) have been historically reported as early as 3 days (24) and as late as 30 years (25) after TH. Consistent with published literature, the median TH-to-VCD(E) interval was 3.13 months in our study; half of the patients experienced VCD(E) within 3 months. The recommended time to resume sexual activities after TH was approximately 8 (13, 26) to 12 weeks (26) in the literature. Based on our experience, we suggest that patients resume normal sexual activities at least 3–6 months after TH.

A gynecologist should inform patients about the risk of VCD (E) after TH. Once patients present with symptoms related to VCD(E), medical advice should be provided at once. On the other hand, if patients present with complaints after TH, doctors should promptly conduct a medical history and physical examination. VCD(E) is a clinical diagnosis (13, 27) that should be made based on a history of TH and vaginal

examination. Notably, people who underwent TH for obstetrical reasons could also experience VCD(E) (28). Early recognition of VCD(E) is imperative as it allows clinicians to implement effective treatments and is critical to preventing serious complications. In our study, most patients visited hospitals promptly as they experienced discomfort and were well managed immediately.

The therapeutic regimen should be tailored to each patient's condition and surgeon's judgment. On speculum and abdominal examination, if patients are diagnosed with VCD(E) and without evidence of secondary injury and peritonitis, efforts should be made to reduce the eviscerated organs as soon as possible. In our case series, after noting that the herniated bowel was ruddy and peristalsis was good, the protruding bowels of 4 of 11 VCDE patients were smoothly repositioned to the peritoneal cavity with a warm-wet gauze pad without anesthesia in the emergency department. Vaginal bowel reduction has been reported in several studies (5, 29, 30); however, our study may be the first to propose repositioning of prolapsed organs without anesthesia in the emergency department. Although manual bowel reduction without anesthesia may be slightly painful for patients, it still has numerous benefits. First, it can immediately free the patients from bulges. Second, it can provide a clear visualization for subsequent transvaginal procedures. Finally, it can reduce the likelihood of ischemia and necrosis of the eviscerated organs to some extent.

Conservative treatment can be an alternative option when a patient is medically stable with a partial VCD and without evisceration. It mainly involves hemostasis (hemostatic and local compression), activity restriction, and prophylactic antibiotics. Zoë Boersen et al. (1) reported two cases that were successfully managed conservatively. Notably, if the patient's condition worsens, surgical intervention should be considered. Emergency cuff closure is mandatory in most cases. To date, no consensus has been reached regarding the optimal approach to separate cuff closure. Historically, VCD(E) was an indication for emergency surgery and suggested laparotomy (4). Subsequently, various techniques have been introduced (13), such as the transvaginal, laparoscopic, and combined abdominal-vaginal or laparoscopic-vaginal approaches. In our institution, 11 patients underwent a transvaginal approach, 2 patients underwent a combined laparoscopic-vaginal approach, and 1 patient underwent a laparoscopic approach. In case No.1, the serosal surface of the sigmoid colon adhered to the vaginal stump and continued with the top of the anterior vaginal wall. To decompress adhesion and repair the vaginal stump with good visualization, gynecologists converted from a transvaginal approach to a laparoscopic approach. A combined laparoscopic-vaginal approach was adopted in the other two, both of which underwent VCC. In case No.10, laparoscopy was performed at the end of VCC to confirm the integrity of the bladder using the methylene blue test. In case No.14, gynecologists conducted laparoscopy to resect a part of the necrotic omentum and bilateral ovaries preserved in the previous surgery. Importantly, the treatment strategy should be patient-specific. In medically stable patients who are free of any complications, vaginal repair is appropriate (5); it is economically prudent and avoids an extra surgical incision. In the case of women with a very narrow vagina or massive obesity (31), transvaginal procedures are challenging because of the limited visual fields. Laparoscopy has more advantages for recurrent VCD. Gerard-Peter reported a technique for laparoscopic repair using an omental flap (32). This approach allows the inspection of the peritoneal cavity and improves poor tissue vascularity. Certainly, when there is a need to excise the necrotic bowel or when there is a suspicion of peritonitis or intraperitoneal hematoma, an abdominal approach is appropriate (32, 33).

Other Interventions

Prophylactic antibiotics should be administered to patients with VCD(E) to prevent infections (32). For hemodynamically unstable patients, timely and aggressive fluid resuscitation and blood transfusion play a vital role in prognosis. One patient in our cohort progressed to hemorrhagic shock and received a blood transfusion containing 10 units of red cell suspension and 1,200 mL fresh frozen plasma intraoperatively. Finally, the patient recovered well. Intraoperative placement of a vaginal drainage tube is essential when patients present with heavy vaginal discharge. If there is any possibility of bladder injury, creatinine level of the discharge or methylene blue test could be used to verify the integrity of the bladder. Notably, these two methods are simple and less invasive than cystoscopy. To restore well-vascularized tissue, debridement of the necrotic tissue of the vaginal cuff is necessary (34). Pathological examination was conducted in one patient in our cohort, revealing no particular lesions other than acute and chronic inflammation, similar to previous reports (10, 34). Jennifer K (18) compared the vaginal cuff specimens of VCD(E) with those of non-VCD(E) patients and found that VCD demonstrated dramatically higher levels of inflammatory cells. A prolonged inflammatory phase was reported to possibly delay the healing of the vaginal cuff because it slows normal progression to the reparative state and collagen remodeling (18). Considering these findings, pathological examination of the excised cuff tissue is valuable and will be essential for exploring the relationship between inflammation and VCD(E) in the future. Multidisciplinary cooperation also plays a key role in the management of VCD(E). It primarily involves the General Surgical Department, Blood Transfusion Department, Emergency Operating Room, and Anesthesiology Department.

The strength of the present study is that it shares our unique experience and suggests new, less invasive and individualized treatment approaches for VCD(E). Considering the extremely low incidence of VCD(E) and mature surgical techniques for TH, prompt management bears more importance than the prevention of VCD(E). The limitations of this study are consistent with those of previous studies. Our study was retrospective, and although the sample size was large, it is still limited. A large number of cases and a longer follow-up period in future studies are needed to validate the utility of our suggestions.

CONCLUSION

LH is a risk factor for VCD(E), and early resumption of sex after TH is the most common trigger of VCD(E). Clinicians should educate patients to postpone coitus for at least 3–6 months after TH. Timely medical attention and patient-specific surgical management are crucial to avoid serious complications. Manual reduction of eviscerated organs without anesthesia in the emergency department, along with VCC, is feasible and minimally invasive.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Peking Union Medical College Hospital Ethnics Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Y-XD conceived and designed the study. XM collected the data and wrote the original draft. Y-XD and D-YC participated in writing, reviewing, and editing the manuscript. All authors contributed to the article and approved the submitted version,

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REFERENCES

1. Boersen Z, Aalders CIM, Klinkert ER, Maas JWM, Nap AW. Vaginal cuff dehiscence after endometriosis surgery. *J Soc Laparoendosc Surg*. (2019) 23(3): e2019.00018. doi: 10.4293/JSLS.2019.00018
2. Clarke-Pearson DL, Geller EJ. Complications of hysterectomy. *Obstet Gynecol*. (2013) 121(3):654–73. doi: 10.1097/AOG.0b013e3182841594
3. Vardar B, Midkiff B. Vaginal cuff dehiscence: report of two cases. *Radiol Case Rep*. (2021) 16(8):2231–5. doi: 10.1016/j.radcr.2021.05.038
4. Hur HC, Lightfoot M, McMillin MG, Kho KA. Vaginal cuff dehiscence and evisceration: a review of the literature. *Curr Opin Obstet Gynecol*. (2016) 28(4):297–303. doi: 10.1097/GCO.0000000000000294
5. Zhou Y, Zhang Y, Liu W, Zhang W, Wang X, Yu X, et al. Spontaneous vaginal cuff dehiscence and evisceration of multiple organs: a case report. *Medicine (Baltimore)*. (2018) 97(50):e13670. doi: 10.1097/MD.0000000000013670
6. Sandy-Hodgetts K, Carville K, Leslie GD. Surgical wound dehiscence: a conceptual framework for patient assessment. *J Wound Care*. (2018) 27(3): 119–26. doi: 10.12968/jowc.2018.27.3.119
7. Lundvall L, Jensen F, Roed H, Ottosen C, Ewertsen C, Henriksen BM. Vaginal rupture caused by transvaginal ultrasonography in follow-up for ovarian cancer. *BMJ Case Rep*. (2009) 2009:bcr05.2009.1860. doi: 10.1136/bcr.05.2009.1860
8. Cattaneo 2nd R, Bellon M, Elshaikh MA. Vaginal cuff dehiscence after vaginal cuff brachytherapy for uterine cancer. A case report. *J Contemp Brachytherapy*. (2013) 5(3):164–6. doi: 10.5114/jcb.2013.37418
9. Nezhat C, Kennedy Burns M, Wood M, Nezhat C, Nezhat A, Nezhat F. Vaginal cuff dehiscence and evisceration: a review. *Obstet Gynecol*. (2018) 132(4):972–85. doi: 10.1097/AOG.0000000000002852
10. Escobar PA, Gressel GM, Goldberg GL, Kuo DY. Delayed presentation of vaginal cuff dehiscence after robotic hysterectomy for gynecologic cancer: a case series and review of the literature. *Case Rep Obstet Gynecol*. (2016) 2016:5296536. doi: 10.1155/2016/5296536
11. Gandhi J, Chen A, Dagur G, Suh Y, Smith N, Cali B, et al. Genitourinary syndrome of menopause: an overview of clinical manifestations, pathophysiology, etiology, evaluation, and management. *Am J Obstet Gynecol*. (2016) 215(6):704–11. doi: 10.1016/j.ajog.2016.07.045
12. O'Connor SK, Ryley DA, Obasiolu CW, Esselen KM, Skiadas CC, Kuohung W. Vaginal cuff dehiscence following transvaginal oocyte retrieval: a case report. *Fertil Res Pract*. (2020) 6:16. doi: 10.1186/s40738-020-00085-0
13. Agrawal A, Huang KG, Mendoza MCV. Emergency laparoscopic repair of coitus-induced vaginal cuff dehiscence: a case report. *J Med Case Rep*. (2020) 14(1):40. doi: 10.1186/s13256-020-02362-4
14. Karacan T, Ozyurek E, Usta T, Odacilar E, Hanli U, Kovalak E, et al. Comparison of barbed unidirectional suture with figure-of-eight standard sutures in vaginal cuff closure in total laparoscopic hysterectomy. *J Obstet Gynaecol*. (2018) 38(6):842–7. doi: 10.1080/01443615.2017.1416597
15. Cronin B, Sung VW, Matteson KA. Vaginal cuff dehiscence: risk factors and management. *Am J Obstet Gynecol*. (2012) 206(4):284–8. doi: 10.1016/j.ajog.2011.08.026
16. Uccella S, Ghezzi F, Mariani A, Cromi A, Bogani G, Serati M, et al. Vaginal cuff closure after minimally invasive hysterectomy: our experience and systematic review of the literature. *Am J Obstet Gynecol*. (2011) 205(2): 119.e1–12. doi: 10.1016/j.ajog.2011.03.024
17. Radosa JC, Radosa MP, Zimmermann JSM, Braun EM, Findeklee S, Wieczorek A, et al. Incidence of and risk factors for vaginal cuff dehiscence following total laparoscopic hysterectomy: a monocentric hospital analysis. *Arch Gynecol Obstet*. (2021) 304(2):447–54. doi: 10.1007/s00404-021-06064-0
18. Klauschie J, Wen Y, Chen B, Zhou L, Nunez-Nateras R, Ocal IT, et al. Histologic characteristics of vaginal cuff tissue from patients with vaginal cuff dehiscence. *J Minim Invasive Gynecol*. (2014) 21(3):442–6. doi: 10.1016/j.jmig.2013.11.013
19. Munger D, Iannamorelli M, Galvez C, Service C. Vaginal cuff dehiscence presenting with free air 60 days after robotic-assisted hysterectomy. *Case Rep Surg*. (2017) 2017:5052634. doi: 10.1155/2017/5052634
20. Mou T, Asfaw T. Pneumomediastinum from vaginal cuff dehiscence four months after laparoscopic-assisted vaginal hysterectomy: a case report. *Int J Surg Case Rep*. (2017) 41:431–3. doi: 10.1016/j.ijscr.2017.10.035
21. Hunt TK, Hopf H, Hussain Z. Physiology of wound healing. *Adv Skin Wound Care*. (2000) 13(2 Suppl):6–11. PMID: 11074996
22. Drudi L, Press JZ, Lau S, Gotlieb R, How J, Eniu I, et al. Vaginal vault cehiscence after robotic hysterectomy for gynecologic cancers: search for risk factors and literature review. *Int J Gynecol Cancer*. (2013) 23(5): 943–50. doi: 10.1097/IGC.0b013e31828f38e1

23. Percalli L, Pricolo R, Passalia L, Croce P, Ricco M, Berretta R, et al. Vaginal cuff dehiscence resulting in small-bowel evisceration. A case report. *Acta Biomed*. (2016) 87(2):212–4. PMID: 27649006
24. Cardosi R. Vaginal evisceration after hysterectomy in premenopausal women. *Obstet Gynecol*. (1999) 94(5):859. doi: 10.1016/s0029-7844(99)00530-x
25. Moen MD, Desai M, Sulkowski R. Vaginal evisceration managed by transvaginal bowel resection and vaginal repair. *Int Urogynecol J Pelvic Floor Dysfunct*. (2003) 14(3):218–20. doi: 10.1007/s00192-003-1056-1
26. Kahramanoglu I, Sal V, Bese T. Post-coital vaginal cuff dehiscence with small bowel evisceration after laparoscopic type II radical hysterectomy: a case report. *Int J Surg Case Rep*. (2016) 26:81–3. doi: 10.1016/j.ijscr.2016.07.024
27. Newell CF, Larson NP, Yoo MJ. Small bowel in vagina: a case for pelvic exams. *Cureus*. (2021) 13(8):e17412. doi: 10.7759/cureus.17412
28. Avcioglu SN, Altinkaya SO, Kucuk M, Yuksel H, Demircan-Sezer S. Vaginal repair of vaginal vault dehiscence after postpartum hysterectomy. *J Surg Case Rep*. (2014) 2014(2):rjt127. doi: 10.1093/jscr/rjt127
29. Suzuki Y, Imai Y, Ruiz-Yokota N, Miyagi E. Laparoscopic repair of the vaginal cuff dehiscence: dehiscence occurring after the first sexual intercourse after the laparoscopic modified radical hysterectomy. *Clin Case Rep*. (2018) 6(12):2495–7. doi: 10.1002/ccr3.1906
30. Bleull S, Smith H, Shapiro R. Transvaginal management of vaginal cuff dehiscence with bowel evisceration following delayed diagnosis. *Case Rep Obstet Gynecol*. (2017) 2017:4985382. doi: 10.1155/2017/4985382
31. O'Hanlan KA, Emeney PL, Peters A, Sten MS, McCutcheon SP, Struck DM, et al. Analysis of a standardized technique for laparoscopic cuff closure following 1924 total laparoscopic hysterectomies. *Minim Invasive Surg*. (2016) 2016:1372685. doi: 10.1155/2016/1372685
32. Frank GP, Rhemrev J, Westerterp M, English J. Recurrent vaginal cuff dehiscence after surgery for endometriosis: a technique for laparoscopic repair with an omental flap. *BMJ Case Rep*. (2021) 14(3):e239540. doi: 10.1136/bcr-2020-239540
33. Matsuhashi T, Nakanishi K, Hamano E, Kamoi S, Takeshita T. Laparoscopic repair of vaginal evisceration after abdominal hysterectomy for uterine corpus cancer: a case report and literature review. *J Nippon Med Sch*. (2017) 84(2):90–5. doi: 10.1272/jnms.84.90
34. Sendy F, Simone L, Albaut M, Lambert A, Nohuz E. Laparoscopic assessment and transvaginal reparation of post-coital vaginal cuff dehiscence with bowel evisceration: a case report. *Pan Afr Med J*. (2020) 35:118. doi: 10.11604/pamj.2020.35.118.2136

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The Influence of HbA1c and Gestational Weight Gain on Pregnancy Outcomes in Pregnant Women With Gestational Diabetes Mellitus

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Background: To investigate the influence of HbA1c level and GWG on pregnancy outcomes in pregnant women with GDM.

Methods: A total of 2,171 pregnant women with GDM were retrospectively included and categorized as follows: (1) normal (HbA1c <6%) and elevated (HbA1c ≥6%) HbA1c groups according to the HbA1c level in the second trimester, and (2) inadequate, appropriate, and excessive GWG groups according to the IOM guidelines.

Results: In pregnant women with GDM, advanced age and high pre-pregnancy BMI were high-risk factors for elevated HbA1c. Pregnant women with elevated HbA1c had higher OGTT levels than those with normal HbA1c, and the risks of adverse pregnancy outcomes were higher ($P < 0.05$). The risks of primary cesarean section, hypertensive disorders during pregnancy, and macrosomia in pregnant women with excessive GWG were significantly higher than those with inadequate and appropriate GWG ($P < 0.05$). When GWG was appropriate, the risk of hypertensive disorders during pregnancy in the elevated HbA1c group was higher than that in the normal HbA1c group. When GWG was excessive, the risks of postpartum hemorrhage, macrosomia, and neonatal asphyxia in the elevated HbA1c group were significantly higher than in the normal HbA1c group ($P < 0.05$).

Conclusion: Monitoring and controlling blood glucose levels have shown effectiveness in reducing the adverse pregnancy outcomes in women with GDM, particularly for those who had excessive GWG.

Keywords: gestational diabetes mellitus, glycated hemoglobin, gestational weight gain, pregnancy outcomes, HbA1c

INTRODUCTION

Gestational diabetes mellitus (GDM) refers to diabetes that appears or is diagnosed during pregnancy in women with normal glucose metabolism or potentially impaired glucose tolerance before pregnancy (1). With the improvement of living standards and the popularization of screening for gestational diabetes, the prevalence of GDM has been increasing over the years (2–4). It has become one of the main pregnancy complications that endanger the health of mothers and babies (5, 6). GDM not only increases the risk of adverse perinatal outcomes, such as macrosomia, intrauterine growth restriction, fetal malformation, neonatal respiratory distress syndrome, neonatal hypoglycemia, and so on, but also causes long-term complications in the offspring, including hypertension and type 2 diabetes (7–11).

Glycated hemoglobin (HbA1c) reflects average blood glucose levels during the preceding 8–12 weeks. As the gold standard for assessing long-term glycemic control, it has been widely used in blood glucose monitoring and management of people with diabetes. The increase in HbA1c levels is closely related to the adverse pregnancy outcome (12). In addition, the gestational weight gain (GWG) of pregnant women with GDM also has an important impact on the perinatal outcomes (13). In 2009, the American Institute of Medicine (IOM) formulated a reasonable range of GWG for pregnant women with different pre-pregnancy BMI values. It is indicated that the HbA1c level above 5% in the third trimester of pregnancy and excessive GWG are both risk factors for neonatal complications in women with gestational diabetes (14). However, in China, a few large-scale studies have focused on the effect of HbA1c on the outcomes in GDM, let alone prospective research about the effect of GWG on the pregnancy outcomes with different HbA1c levels.

This study retrospectively included 2,171 pregnant women with GDM, and aimed at exploring the effects of second-trimester HbA1c levels on pregnancy outcomes of GDM and analyzing the role of GWG on the pregnancy outcomes with different HbA1c levels, thus providing the basis for precise intervention and personalized, risk-stratified weight management for gestational diabetic women with different HbA1c levels.

MATERIALS AND METHODS

Study Design and Data Sources

A retrospective collection of pregnant women with GDM who had undergone regular antenatal checkups and gave birth at the Women's Hospital School of Medicine Zhejiang University from 1 July 2017 to 30 June 30 2018. Inclusion criteria were as follows: (1) diagnosis of GDM in the second trimester using the oral glucose tolerance test (OGTT); (2) singleton pregnancy; (3) gestational age at birth ≥28 weeks; and (4) complete medical records. Exclusion criteria were as follows: (1) coupled with pre-gestational diabetes; (2) coupled with chronic hypertension, or diseases of the liver, kidney, heart, lung, and other major organs, or coupled with tumors; (3) coupled with Sjogren's syndrome, anticardiolipin syndrome, or other autoimmune diseases. A total of 2,352 pregnant women met the inclusion criteria. After the application of the exclusion criteria, a total of 2,171 cases were eventually included in this study (**Figure 1**).

The relevant information regarding the pregnant women was retrieved through the electronic medical record system of the Women's Hospital School of Medicine, Zhejiang University, which included pregnant women's age, height, pre-pregnancy weight (within 1 month before pregnancy), gestational weight gain, pregnancy parity, OGTT value (fasting, 1 h, and 2 h after oral glucose load), second-trimester glycated hemoglobin level, mode of delivery, gestational age at birth, birth weight of newborn, and pregnancy complications, such as hypertensive disorders during pregnancy (including gestational hypertension, preeclampsia, and eclampsia), placental abruption, postpartum hemorrhage, intrahepatic cholestasis of pregnancy, neonatal asphyxia, etc.

The study was approved by the Human Ethics Committee at Women's Hospital, School of Medicine, Zhejiang University.

Measurements and Calculations

The normal glucose values of fasting, 1-h and 2-h 75-g OGTT, according to IADPSG criteria, were <5.1 mmol/ L, 10.0 mmol/L, and 8.5 mmol/L, respectively (15). Any abnormal blood glucose level should be diagnosed as GDM. Body mass index (BMI) is defined as weight divided by the square of height (kg/m²). GWG (kg) is the difference between the weight before delivery and the weight before pregnancy. According to the 2009 IOM guidelines in the United States, the suggested GWG is 12.7–18.1 kg, 11.3–15.8 kg, 6.8–11.3 kg, and 5.0–9.1 kg for pregnant women with pre-pregnancy BMI categorized as underweight (BMI < 18.5 kg/m²), normal weight (BMI: 18.5 kg/m²−24.9 kg/m²), overweight (BMI: 25.0 kg/m²−29.9 kg/m²), and obese (BMI ≥ 30.0 kg/m²), respectively. One is considered to have inadequate GWG or excessive GWG if the GWG is less than or exceeding the appropriate value, respectively.

Gestational hypertension is the first incidence of high blood pressure at ≥20 weeks of gestation, with a systolic blood pressure of 140 mmHg and/or diastolic blood pressure of 90 mmHg in the absence of proteinuria or new signs of end-organ dysfunction. Preeclampsia is defined as a combination of one or more of the following conditions based on the diagnosis of gestational hypertension: proteinuria or other target organ dysfunction or uteroplacental function obstacle. Meanwhile, eclampsia is a seizure that occurs as a result of preeclampsia and cannot be explained by other factors. Placental abruption occurs when the placenta in its usual location becomes partly or totally separated from the uterine wall before the fetus is born after 20 weeks of pregnancy or during labor. Postpartum hemorrhage is defined as bleeding more than 500 ml after vaginal birth or more than 1,000 ml after cesarean delivery within 24 h of the birth of the fetus. Intrahepatic cholestasis of pregnancy is a pregnancy problem that manifests clinically as skin pruritus and increased bile acids in the second and third trimesters. The primary cesarean section is defined as the section that is performed on women who never had a cesarean delivery before. The neonatal Apgar score is presently used to diagnose newborn asphyxia, which is based on five indicators measured at 1 min after birth: heart rate, breathing, muscular tone, laryngeal reflex, and skin color. The normal score is 8–10 points, moderate asphyxia is given 4–7 points, and severe asphyxia is given 0–3 points. Macrosomia is defined as newborns with a birth weight ≥4,000 g.

Statistical Analysis

The data of the normal distribution were expressed as $x \pm s$, and the difference between the means of the two groups was analyzed by the *t*-test. Count data were expressed in frequency and rate, and the difference between groups was compared using the chi-squared (χ^2) test. Multivariate logistic regression analysis was performed to evaluate the effect of glycated hemoglobin and GWG on pregnancy outcomes in pregnant women with GDM, while Fisher's exact test was used to examine the effect of GWG on the pregnancy outcomes of groups with different levels of HbA1c. A *p*-value of 0.05 or less was considered to be statistically significant. All statistical analyses were done using

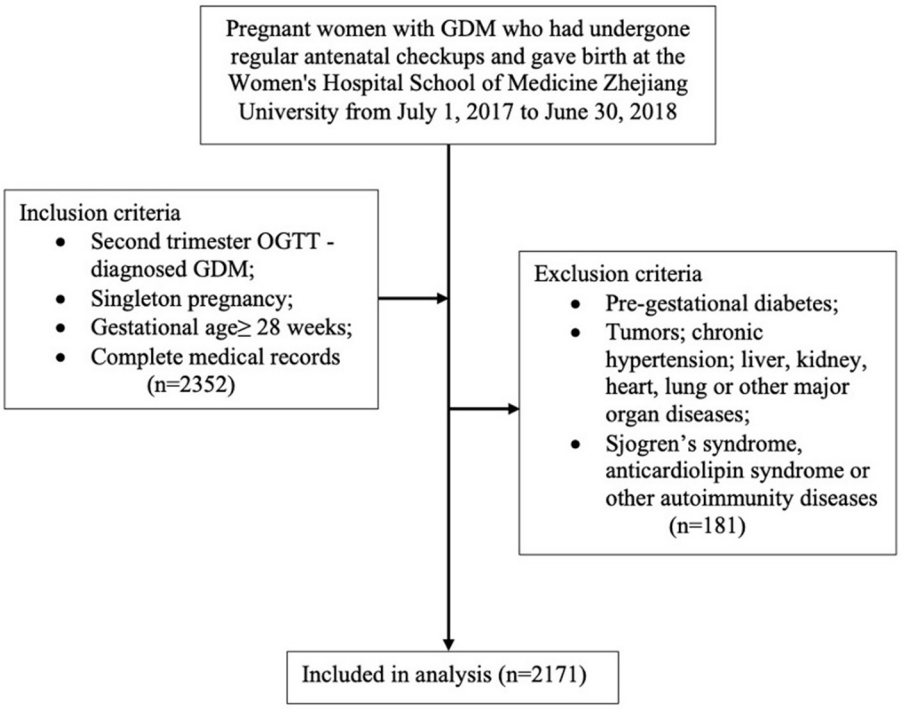

FIGURE 1 | Participant flowchart.

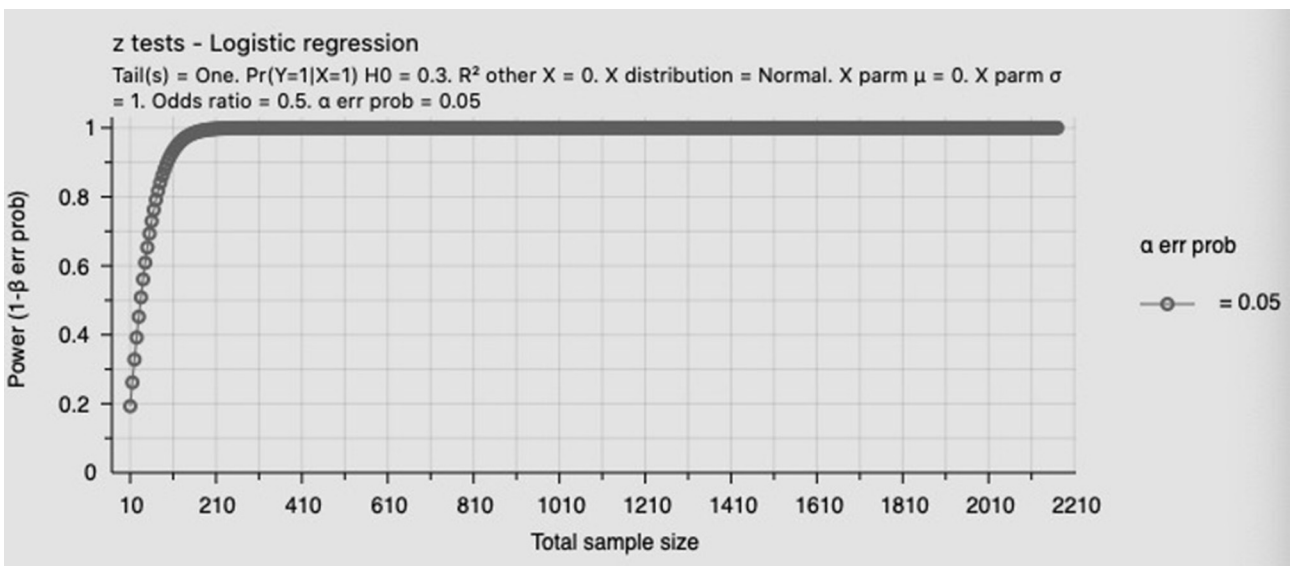

FIGURE 2 | Power analysis for total population.

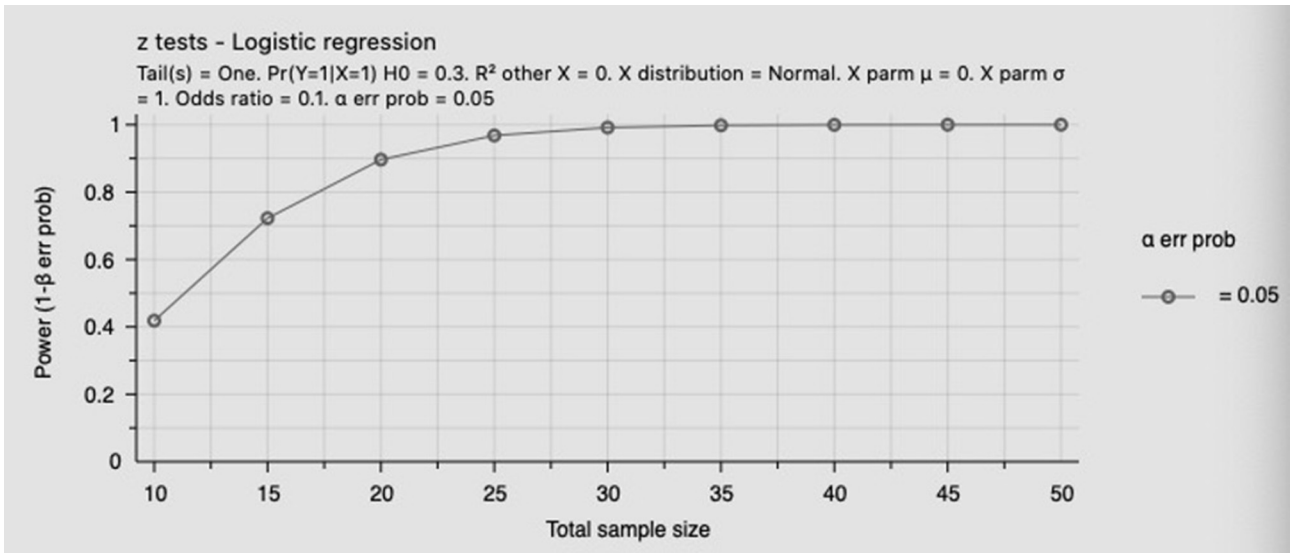

FIGURE 3 | Power analysis for high HbA1c group.

SPSS Statistics 25.0. Power analysis for total population and high HbA1c group was shown in **Figures 2**, **3**.

RESULTS

Comparison of General Clinical Characteristics and Pregnancy Outcomes in Two Groups With Different Glycated Hemoglobin Levels

We analyzed the risks factors of adverse pregnancy outcomes between groups with normal and elevated HbA1c levels. The results showed that the age, pre-pregnancy BMI, OGTT blood glucose level, primary cesarean section, and newborn's birth weight were significantly higher in the pregnant women of elevated HbA1c group when compared to those of the normal group, while the gestational age at birth was found to be decreased ($P = 0.031$, $P = 0.000$, $P = 0.000$, $P = 0.016$, $P = 0.004$, respectively). Meanwhile, the risk of hypertensive disorders during pregnancy, postpartum hemorrhage, placental abruption, neonatal asphyxia, and macrosomia was also significantly higher in the elevated HbA1c group ($P = 0.007$, $P = 0.018$, $P = 0.044$, $P = 0.000$, $P = 0.004$) (**Table 1**).

Comparison of Pregnancy Outcomes in Gestational Diabetic Women With Different Gestational Weight Gain During Pregnancy

By comparing the incidence of pregnancy outcomes among the three groups with different gestational weight gain, we found that the risks of hypertensive disorders during pregnancy, macrosomia, and primary cesarean section were significantly higher in the GDM women of the excessive GWG group when compared to those of inadequate and appropriate GWG groups ($P = 0.000$) (**Table 2**).

The Influence of HbA1c and GWG on Pregnancy Outcomes in GDM Women

Through multivariate logistic regression analysis, we found that high HbA1c levels increased the risk of primary cesarean section, hypertensive disorders during pregnancy, and macrosomia. GDM women with more GWG have been shown to be at increased risk of primary cesarean section, intrahepatic cholestasis of pregnancy, and macrosomia. The differences were found to be statistically significant ($P < 0.05$) (**Table 3**).

The Effect of Gestational Weight Gain on Pregnancy Outcomes in Different Groups of HbA1c

When pregnant women with GDM had inadequate GWG, there was no significant difference in the risk of hypertensive disorders during pregnancy, postpartum hemorrhage, placental abruption, macrosomia, and neonatal asphyxia between the normal and elevated HbA1c groups. However, the risk of hypertensive disorders during pregnancy in the elevated HbA1c subgroup was significantly higher in the appropriate GWG group ($P = 0.032$). In addition, in the excessive GWG group, the incidence of postpartum hemorrhage, neonatal asphyxia, and macrosomia was also significantly higher in the elevated HbA1c subgroup than in the normal HbA1c subgroup ($P = 0.009$, $P = 0.044$, $P = 0.027$, $P = 0.003$) (**Table 4**).

DISCUSSION

The second-trimester HbA1c value ≥6% and gestational weight gain exceeding the IOM recommendations were risk factors for

TABLE 1 | Comparison of general clinical characteristics and pregnancy outcomes between two groups with different glycated hemoglobin levels.

		Normal HbA1c *N* = 2122	Elevated HbA1c *N* = 49	*P*
Age (Years)		32.38 ± 4.44	33.78 ± 5.24	0.031 *
Gravidity		2.29 ± 1.28	2.43 ± 1.32	0.469
Parity		0.52 ± 0.53	0.55 ± 0.68	0.665
Pre-pregnancy BMI (kg/m²)		21.73 ± 3.12	24.67 ± 4.40	0.000*
Gestational weight gain (kg)		12.50 ± 4.12	12.64 ± 5.02	0.469
OGTT blood glucose level (mmol/L)	Fasting	4.66 ± 0.48	5.35 ± 0.68	0.000*
	1 h	9.97 ± 61.28	11.11 ± 1.42	0.000*
	2 h	8.67 ± 1.16	9.23 ± 1.08	0.001*
Gestational age at birth (weeks)		38.35 ± 1.60	37.69 ± 1.77	0.005*
Birth weight (g)		3292.04 ± 497.18	3500.00 ± 584.69	0.004*
Methods of delivery	Vaginal delivery	977 (46.0 %)	15 (30.6 %)	0.100
	Forceps delivery	70 (3.3 %)	2 (4.1 %)	
	Cesarean section	1,075 (50.7 %)	32 (65.3 %)	
Primary cesarean section		578 (27.2 %)	21 (42.9 %)	0.016*
Intrahepatic cholestasis of pregnancy		97 (4.6 %)	1 (2.0 %)	0.399
Hypertensive disorders during pregnancy		164 (7.7 %)	9 (18.4 %)	0.007*
Postpartum hemorrhage		78 (3.7 %)	5 (10.2 %)	0.018*
Placental abruption		22 (1.0 %)	2 (4.1 %)	0.044*
Neonatal asphyxia		19 (0.9 %)	4 (8.2 %)	0.000*
Macrosomia		129 (6.1 %)	8 (16.3 %)	0.004*

*$P < 0.05$.

TABLE 2 | Comparison of pregnancy outcomes in gestational diabetic women with different weight gains during pregnancy.

		Inadequate GWG *N* = 815	Appropriate GWG *N* = 897	Excessive GWG *N* = 459	*P*
Methods of delivery	Vaginal delivery	394 (48.3 %)	418 (46.6 %)	180 (39.2 %)	0.022
	Forceps delivery	29 (3.6 %)	29 (3.2 %)	14 (3.1 %)	
	Cesarean section	392 (48.1 %)	450 (50.2 %)	265 (57.7 %)	
Primary cesarean section		198 (24.3 %)	239 (26.6 %)	162 (35.3 %)	0.000*
Intrahepatic cholestasis of pregnancy		44 (5.4 %)	41 (4.6 %)	13 (2.8 %)	0.105
Hypertensive disorders during pregnancy		43 (5.3 %)	67 (7.5 %)	63 (13.7 %)	0.000*
Postpartum hemorrhage		24 (2.9 %)	36 (4.0 %)	23 (5.0 %)	0.169
Placental abruption		8 (1.0 %)	13 (1.4 %)	3 (0.7 %)	0.379
Neonatal asphyxia		6 (0.7 %)	10 (1.1 %)	7 (1.5 %)	0.409
Macrosomia		28 (3.4 %)	56 (6.2 %)	53 (11.5 %)	0.000*

*$P < 0.05$.

adverse pregnancy outcomes in pregnant women with gestational diabetes. In this study, we noted a significantly increased risk of adverse pregnancy outcomes among pregnant women with GDM in the elevated HbA1c group and excessive GWG group compared to those in the normal HbA1c group and appropriate and inadequate GWG groups, respectively. Moreover, GDM women with both high HbA1c levels and excessive GWG had a higher risk of postpartum hemorrhage, neonatal asphyxia, and macrosomia.

Gestational diabetes is one of the most common complications of pregnancy (5). In addition to the short-term risks during pregnancy and childbirth, the risk of long-term adverse outcomes in women with gestational diabetes and their offspring, such as diabetes, obesity, cardiovascular and metabolic diseases, disorders of blood glucose regulation in children and adolescents, and other metabolic syndromes, also increased significantly (10, 11, 16, 17). Therefore, targeted intervention strategies and measures to prevent the occurrence and development of GDM in high-risk groups, along with further management and control of hyperglycemia and weight during pregnancy, are vital to improving the glucose metabolism of women and their offspring, thus reducing the risk of cardiovascular and metabolic diseases.

Although OGTT is the gold standard for the effective diagnosis of gestational diabetes at present, it is susceptible to

short-term lifestyle changes, such as diet and activity before the test. HbA1c is a class of stable compounds in which glucose is covalently bonded to the N-terminal valine residues of the β-chain of hemoglobin (18). It can accurately reflect the long-term blood glucose levels over the past 2–3 months and is not easily affected by short-term fluctuations in the blood glucose concentration, and thus it is used as an indicator in the diagnosis and monitoring of diabetes (19). In addition, blood can be collected at any time to measure HbA1c levels. This is typically a non-fasting test and no special preparation is needed, and the diagnosis can be made on the day of treatment (20). Therefore, the role of HbA1c in the management of gestational diabetes has received increasing attention. It is not only a core indicator for the evaluation of hypoglycemic efficacy, but is also an indispensable indicator in the development of clinical trials related to gestational diabetes-related pregnancy outcomes (21). Studies have shown that elevated first- or second-trimester HbA1c levels are associated with adverse pregnancy outcomes (21, 22). The Classification of Diabetes Mellitus issued by the World Health Organization in 2019 recommends the use of HbA1c to diagnose diabetes in countries and regions where equipment is available, and the HbA1c cut-off point for the identification of diabetes is ≥6.5%. According to the ADA's 2016 Standards of Care, under ideal circumstances, the HbA1c value of <6% (42 mmol/mol) is optimal during pregnancy, if it can be achieved without significant hypoglycemia (23). Therefore, we set the cut-off value of 6% for HbA1c grouping in this study based on the above-mentioned criteria. Based on this cut-off value, our study found that pregnant women with GDM in the elevated HbA1c group in the second trimester of pregnancy had a significantly higher risk of gestational hypertension, postpartum hemorrhage, placental abruption, neonatal asphyxia, and macrosomia when compared to those of the normal HbA1c group.

In pace with the improvement of living standards and attaching importance to nutrition during pregnancy, recently, researchers have been paying more attention to the appropriate GWG in perinatal health care. For instance, the 2009 IOM revised guidelines for gestational weight gain provide clinicians with a practical basis. The guidelines recommend an optimal amount of GWG for pregnant women according to pre-pregnancy BMI (underweight, normal weight, overweight, and obese) (24).

TABLE 3 | Influence of glycated hemoglobin and gestational weight gain on pregnancy outcome of pregnant women with GDM.

	β value	OR	95%CI	*P*-value
Primary cesarean section				
HbA1c	0.440	1.552	(1.174, 2.052)	0.002[2*]
GWG	0.035	1.035	(1.012, 1.059)	0.002*
Intrahepatic cholestasis of pregnancy				
HbA1c	−0.022	0.942	(0.537, 1.782)	0.942
GWG	−0.059	0.943	(0.895, 0.993)	0.025*
Hypertensive disorders during pregnancy				
HbA1c	1.290	3.634	(2.357, 5.603)	0.000*
GWG	0.033	1.034	(0.997, 1.072)	0.070
Postpartum hemorrhage				
HbA1c	0.357	1.428	(0.756, 2.698)	0.272
GWG	0.048	1.050	(0.999, 1.103)	0.057
Placental abruption				
HbA1c	0.914	2.494	(0.842, 7.385)	0.099
GWG	−0.023	0.978	(0.886, 1.078)	0.651
Neonatal asphyxia				
HbA1c	0.602	1.825	(0.575, 5.792)	0.307
GWG	0.083	1.087	(0.996, 1.186)	0.062
Macrosomia				
HbA1c	1.241	3.460	(2.138, 5.598)	0.000*
GWG	0.089	1.093	(1.052, 1.136)	0.000*

*$P < 0.05$.
OR values were adjusted for maternal age, gravidity, parity, and pre-pregnancy BMI.

TABLE 4 | Effect of gestational weight gain on the pregnancy outcomes of different groups based on HbA1c levels.

	Hypertensive disorders during pregnancy	Post-partum hemorrhage	Placental abruption	Primary cesarean section	Neonatal asphyxia	Macrosomia
Inadequate GWG (*n* = 815)						
Normal HbA1c	41 (5.1 %)	23 (2.9 %)	7 (0.9 %)	191 (23.8%)	5 (0.6 %)	28 (3.5 %)
Elevated HbA1c	2 (14.3 %)	1 (7.1 %)	1 (7.1 %)	7 (50.0%)	1 (7.1 %)	0
P	0.166	0.344	0.130	0.051	0.099	/
Appropriate GWG (*n* = 897)						
Normal HbA1c	63 (7.2 %)	30 (4.1 %)	12 (1.4 %)	232 (26.4%)	9 (1.0 %)	54 (6.1 %)
Elevated HbA1c	4 (23.5 %)	0	1 (5.9 %)	7 (41.2%)	1 (5.93 %)	2 (11.8 %)
P	0.032	/	0.222	0.174	0.175	0.287
Excessive GWG (*n* = 459)						
Normal HbA1c	60 (13.6 %)	19 (4.3 %)	3 (0.7 %)	155 (35.1%)	5 (1.1 %)	47 (10.7 %)
Elevated HbA1c	3 (16.7 %)	4 (22.2 %)	0	7 (38.9%)	2 (11.1 %)	6 (33.3 %)
P	0.724	0.009*	/	0.803	0.027*	0.003*

*$P < 0.05$.

Although some domestic scholars have taken the differences between Chinese and western women in terms of body shape, dietary structure, cultural beliefs, and practices of pregnancy into account and thereby formulated the range of GWG according to the classification of Chinese adult BMI (25), Rebecca F Goldstein et al. (26) conducted a meta-analysis of more than one million pregnant women with gestational diabetes and found that the IOM guidelines were applicable to the pregnant women of the United States, Western Europe, and East Asia. Therefore, GWG was still categorized according to the IOM recommendations in this study. Several studies have previously shown that GWG is associated with gestational diabetes. Qi et al. (27) analyzed 8,356 pregnant women and found that excessive weight gain in the first and second trimester of pregnancy is a high-risk factor for gestational diabetes. Moreover, a large number of studies have shown that excessive GWG is a risk factor for various adverse maternal and infant outcomes in pregnant women with diabetes (28, 29). Research by Kim et al. (30) demonstrated that excessive weight gain during pregnancy is an independent predictor of the occurrence of fetal macrosomia, while appropriate GWG reduces the occurrence of fetal macrosomia in pregnant women with gestational diabetes by one-third. Xueqin Zhang et al. (31) pointed out that excessive weight gain in the second trimester of pregnancy is a high-risk factor for large-for-gestational-age (LGA) infants, whereas excessive weight gain in the third trimester of pregnancy is a high-risk factor for preeclampsia and cesarean section. A systematic review conducted by Rebecca F Goldstein et al. (29) reported that inadequate GWG is a high-risk factor for small-for-gestational-age (SGA) infants. Our study showed that excessive GWG is a high-risk factor for primary cesarean section, hypertensive disorders during pregnancy, and macrosomia, which is consistent with the previous research reports. In view of this, it is apparent that appropriate weight management during pregnancy is also crucial for improving perinatal outcomes.

In general, weight management during pregnancy plays an important role in reducing adverse pregnancy outcomes. However, a few studies were conducted at home and abroad to determine whether weight management during pregnancy can still work for gestational diabetic women with elevated HbA1c levels. Lise L. Kurtzhals et al. (32) revealed that the pregnant women with GDM who gained excessive weight had a significant increase in HbA1c in the third trimester and a significant increase in newborn birth weight, compared to patients with well-controlled weight gain. In pregnant women with strict weight control, HbA1c in the third trimester of pregnancy was significantly reduced without increasing the incidence of SGA infants. Combined with prior results, we speculated that GWG and HbA1c levels might have an interactive effect on the pregnancy outcomes in pregnant women with gestational diabetes. Therefore, we analyzed the influence of HbA1c on pregnancy outcomes in each group of pregnant women with stratification of GWG. The results showed that when the GWG was inadequate or appropriate, there was no significant difference in the risk of postpartum hemorrhage, placental abruption, neonatal asphyxia, and macrosomia between the two groups of pregnant women with GDM. However, among pregnant women with excessive GWG, the risk of postpartum hemorrhage, neonatal asphyxia, and macrosomia in the elevated HbA1c group was significantly increased. In addition, even if the GWG was appropriate, the risk of hypertensive disorders during pregnancy in the elevated HbA1c group was still higher than that observed in the normal HbA1c group. Therefore, it is confirmed that appropriate weight management during pregnancy is essential. Moreover, monitoring and controlling of the blood glucose levels may reduce the risk of adverse pregnancy outcomes among those GDM women who had excessive GWG. We recommend that HbA1c should also be considered as an important indicator of glycemic control for GDM women, particularly for those who gained excessive weight during pregnancy, to further reduce the occurrence of adverse pregnancy outcomes.

However, our study has some limitations. First, given that it is a retrospective study, selection and recall bias was inevitable. Second, the population included in this study was pregnant women attending the Women's Hospital School of Medicine, Zhejiang University, and the sample suggests a lack of representativeness. In addition, the sample size was inadequate, as there were only 49 pregnant women with GDM in the elevated HbA1c group. Moreover, the lack of data on HbA1c levels in the third trimester of pregnancy made it impossible to study the effect of gestational weight gain on this parameter. The above-mentioned deficiencies need to be addressed in further follow-up research.

In summary, the second-trimester HbA1c level is an important indicator for predicting adverse pregnancy outcomes in pregnant women with gestational diabetes, and therefore should be taken into account in the regular obstetric examination. Meanwhile, weight management during pregnancy significantly improves pregnancy outcomes, and reasonable weight gain suggestions should be given to the pregnant women in the first trimester of pregnancy based on pre-pregnancy BMI. For pregnant women with GDM who gained excessive weight during pregnancy, it is particularly necessary to conduct obstetric examination and follow-up education, monitor and control blood glucose levels, and strictly manage the weight during pregnancy, in order to further reduce the occurrence of adverse pregnancy outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Human Ethics Committee at Women's Hospital, School of Medicine, Zhejiang University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceptualization of the study is done by QZ and CL. Data curation is performed by QZ and LZ. Formal analysis and investigated the study are made by QZ, CL, LZ, and QW. QZ contributed to funding acquisition, project administration, and methodology. CL and QW contributed to resources. YC, DC, and LQ supervised the study. QZ, CL, LZ, YC, DC, and LQ validated the study and wrote the original draft. CL performed visualization. QZ, CL, and ZL contributed to writing, reviewing, and editing the manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Classification and diagnosis of diabetes: standards med care diabetes. *Diab Care*. (2020) 43:02. doi: 10.2337/dc20-S002
2. Ferrara. Increasing prevalence of gestational diabetes mellitus: a public health perspective. *Diab Care*. (2007) 30 (Supplement 2):206. doi: 10.2337/dc07-s206
3. Dabelea D, Snell-Bergeon JK, Hartsfield CL, Bischoff KJ, Hamman RF, McDuffie RS, et al. Increasing prevalence of gestational diabetes mellitus (GDM) over time and by birth cohort: kaiser permanente of Colorado GDM screening program. *Diabetes Care*. (2005) 28:579. doi: 10.2337/diacare.28.3.579
4. Saeedi M, Cao Y, Fadl H, Gustafson H, Simmons D. Increasing prevalence of gestational diabetes mellitus when implementing the IADPSG criteria: a systematic review and meta-analysis. *Diab Res Clin Pract*. 172:108642. doi: 10.1016/j.diabres.2020.108642
5. Buchanan TA, Xiang AH, Page KA. Gestational diabetes mellitus: risks and management during and after pregnancy. *Nat Rev Endocrinol*. (2012) 8:96. doi: 10.1038/nrendo.2012.96
6. Mitanchez D. Foetal and neonatal complications in gestational diabetes: perinatal mortality, congenital malformations, macrosomia, shoulder dystocia, birth injuries, neonatal complications. *Diab Metabol*. (2010) 36:13. doi: 10.1016/j.diabet.2010.11.013
7. Hyperglycemia and adverse pregnancy outcomes. *N Eng J Med*. (2008) 358:7943. doi: 10.1056/NEJMoa0707943
8. Doyle-Delgado K, Chamberlain JJ, Shubrook JH, Skolnik N, Trujillo J. Pharmacologic approaches to glycemic treatment of type 2 diabetes: synopsis of the 2020 american diabetes association's standards of medical care in diabetes clinical guideline. *Ann Int Med*. (2020) 173:2470. doi: 10.7326/M20-2470
9. Mitanchez D. What neonatal complications should the pediatrician be aware of in case of maternal gestational diabetes? *World Jf Diab*. (2015). 6:734. doi: 10.4239/wjd.v6.i5.734
10. Metzger BE. Long-term outcomes in mothers diagnosed with gestational diabetes mellitus and their offspring. *Clin Obst Gynecol*. (2007) 50:e31815. doi: 10.1097/GRF.0b013e31815a61d6
11. Garcia-Vargas L, Addison SS, Nistala R, Kurukulasuriya D, Sowers JR. Gestational diabetes and the offspring: implications in the development of the cardiorenal metabolic syndrome in offspring. *Cardio Med*. (2012) 2:7734. doi: 10.1159/000337734
12. Mañé L, Flores-Le Roux JA, Benaiges D, Rodríguez M, Marcelo I, Chillarón JJ, et al. Role of first trimester HbA1c as a predictor of adverse obstetric outcomes in a multi-ethnic cohort. *J Clin Endocrinol Metabol*. (2016) 2016:2581. doi: 10.1210/jc.2016-2581
13. Choi SK, Park IY, Shin JC. Effect of gestational weight gain on perinatal outcomes in low risk pregnancies with normal prepregnancy body mass index. *BioMed Res Int*. (2019). 2019:8601. doi: 10.1155/2019/3768601
14. Barquiel B, Herranz L, Hillman N, Burgos MA, Grande C, Tukia KM, et al. HbA1c and gestational weight gain are factors that influence neonatal outcome in mothers with gestational diabetes. *J Women's Health*. (2016) 25:5432. doi: 10.1089/jwh.2015.5432
15. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*. (2010) 33:676–82. doi: 10.2337/dc 09-1848
16. Retnakaran R, Qi Y, Connelly PW, Sermer M, Zinman B, Hanley AJ. Glucose intolerance in pregnancy and postpartum risk of metabolic syndrome in young women. *J Clin Endocrinol Metabol*. (2010) 9:1990. doi: 10.1210/jc.2009-1990
17. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet*. (2009) 373:60731. doi: 10.1016/S0140-6736(09)60731-5
18. Bao Y. Glycated hemoglobin: still predominant and irreplaceable. *Chinese J Diab Mell*. (2020) 12:7–20. doi: 10.3760/cma.j.issn.1674-5809.2020.01.003
19. Derr R, Garrett E, Stacy GA, Saudek CD. Is HbA1c affected by glycemic instability? *Diab Care*. (2003) 26:2728. doi: 10.2337/diacare.26.10.2728
20. Sherwani SI, Khan HA, Ekhzaimy A, Masood A, Sakharkar MK. Significance of HbA1c test in diagnosis and prognosis of diabetic patients. *Biomarker Insights*. (2016) 11:38440. doi: 10.4137/BMI.S38440
21. Sweeting AN, Ross GP, Hyett J, Molyneaux L, Tan K, Constantino M, et al.Baseline HbA1c to identify high risk gestational diabetes: utility in early vs. standard gestational diabetes. *J Clin Endocrinol Metabol*. (2016). doi: 10.1210/jc.2016-2951
22. Hughes RC, Moore MP, Gullam JE, Mohamed K, Rowan J. an early pregnancy HbA1c ≥5.9% (41 mmol/mol) is optimal for detecting diabetes and identifies women at increased risk of adverse pregnancy outcomes. *Diab Care*. (2014) 37:1312. doi: 10.2337/dc14-1312
23. Management of diabetes in pregnancy. *Diab Care*. (2016) 39 (Supplement_1):S94–8. doi: 10.2337/dc16-S015
24. American College of Obstetricians and Gynecologists. ACOG committee opinion no. 548: weight gain during pregnancy. *Obstet Gynecol*. (2013) 121:210–2. doi: 10.1097/01.aog.0000425668.87506.4c
25. Zhai G, Yang H. Appropriate weight gain during pregnancy in women complicated with gestational abnormal glucose metabolism. *Chinese J Peri Med*. (2009) 12:250–52. doi: 10.3760/cma.j.issn.1007-9408.2009.04.003
26. Goldstein RF, Abell SK, Ranasinha S, Misso ML, Boyle JA, Harrison CL, et al. Gestational weight gain across continents and ethnicity: systematic review and meta-analysis of maternal and infant outcomes in more than one million women. *BMC Med*. (2018) 16:1128. doi: 10.1186/s12916-018-1128-1
27. Qi Y, Sun X, Tan J, Zhang G, Chen M, Xiong Y, et al. Excessive gestational weight gain in the first and second trimester is a risk factor for gestational diabetes mellitus among women pregnant with singletons: a repeated measures analysis. *J Diab Invest*. (2020) 11:13280. doi: 10.1111/jdi.13280
28. Wong T, Barnes RA, Ross GP, Cheung NW, Flack JR. Are the Institute of Medicine weight gain targets applicable in women with gestational diabetes mellitus? *Diabetologia*. (2017) 60:4173. doi: 10.1007/s00125-016-4173-3
29. Goldstein RF, Abell SK, Ranasinha S, Misso M, Boyle JA, Black MH, et al. Association of gestational weight gain with maternal and infant outcomes. *JAMA*. (2017) 317:3635. doi: 10.1001/jama.2017.3635
30. Kim SY, Sharma AJ, Sappenfield W, Salihu HM. Preventing large birth size in women with preexisting diabetes mellitus: the benefit of appropriate gestational weight gain. *Prevent Med*. (2016) 91:26. doi: 10.1016/j.ypmed.2016.08.026
31. Zhang X, Xiao Y. The association between trimester-specific weight gain and severe preeclampsia/adverse perinatal outcome in gestational diabetes mellitus complicated by preeclampsia: a retrospective case study. *Diab Therapy*. (2019) 10:589. doi: 10.1007/s13300-019-0589-3
32. Kurtzhals LL, Nørgaard SK, Secher AL, Nichum VL, Ronneby H, Tabor A, et al. The impact of restricted gestational weight gain by dietary intervention

on fetal growth in women with gestational diabetes mellitus. *Diabetologia*. (2018) 61:4736. doi: 10.1007/s00125-018-4736-6

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REVIEW
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Potential Serum Biomarkers in Prenatal Diagnosis of Placenta Accreta Spectrum

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Placenta accreta spectrum (PAS) refers to the abnormal invasion of trophoblastic tissues. Because of its increasing morbidity and possibility of catastrophic outcomes, PAS requires an antenatal diagnosis and making full preparations in advance to realize safe delivery. Current clinical screening modalities for PAS are not always conclusive. Recently, it has been reported that bio-markers detected in maternal serum have the potential for predicting PAS during pregnancy. Some of these biomarkers, such as β-hcg, AFP, PAPP-A, and cffDNA, can be clinically detected. It is convenient for us to test and compare with standard threshold. However, how can we distinguishing PAS from other pregnancy complications through these biomarkers remains complicated. Some biomarkers are specific, such as microRNA and placenta-specific mRNA. They are stability and reliability. These biomarkers are currently research hotspots. This study aims to summarize the characteristics of the newly reported biomarkers and to point out their potential application and current limitations to provide a basis for future research. Finally, the combination of imageological examination and biomarkers will be an attractive future theme to study in diagnosing this challenging condition.

Keywords: biomarker, prenatal diagnosis, maternal blood, pregnancy, placenta accreta spectrum

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INTRODUCTION

Placenta accreta spectrum (PAS) refers to the penetration of trophoblastic tissues through the decidua basalis into the uterine myometrium, uterine serosa or beyond, extending to the parametrium or the adjacent pelvic organs. PAS is classified depending on the degree of invasion, as placenta adherenta or creta (PC), placenta increta (PI), or placenta percreta (PP) (1). The prevalence of PAS in studies published between 1982 and 2018 ranged from 1 in 100 to 1 in 10,000. The incidence of PAS has been increasing over the past several decades, and can be attributed to the history of cesarean section (CS), previous placenta accreta, placenta previa, maternal age, IVF pregnancies, and Maternal obesity (2, 3).

Women with placenta increta and percreta have a considerably high risk of surgical morbidity and mortality. The adverse pregnancy outcomes (APOs) caused by PAS including the following:(i) Hemorrhage is one of the major complications, and the surgical blood loss could be up to several liters, possibly leading to disseminated intravascular coagulation (DIC), shock, and even death. (ii) Hysterectomy and urinary tract injury are other common outcomes, which may have a profound influence on women's long-term life quality. All these terrible outcomes harm both the women's mental and physical health (4).

An antenatal diagnosis of PAS and identifying the type of PAS can provide time for preoperative management. Preoperative coordination with protocol-based interdisciplinary care could optimize intraoperative and postoperative outcomes. Being fully prepared with enough blood, hemostatic and oxytocic drugs, prophylactic positioning of balloon vascular catheters, placement of ureteric stents preoperatively, and autologous cell salvage equipment can also reduce APOs and minimize manual interventions (5, 6). In the UK, a cohort study demonstrated that antenatal diagnosis was associated with reduced levels of hemorrhage (median estimated blood loss 2,750 vs. 6,100 ml, $p = 0.008$) and a reduced need for blood transfusions (59 vs. 94%, $p = 0.014$) (7).

In recent years, it has been reported that a variety of biomarkers are associated with PAS. Because ultrasound and MRI do not provide a sufficient diagnosis for PAS, biomarkers of PAS might be clinically useful. This review aims to discuss some of the recent advances in these biomarkers.

BIOMARKERS

Alpha-Fetoprotein (AFP)

Maternal serum alpha-fetoprotein (MS-AFP) is a glycoprotein comprising an α-globulin of 591 amino acids and a partial carbohydrate. MS-AFP is synthesized by the yolk sac during early pregnancy, and later by the fetal gastrointestinal tract and liver, which is the main source throughout the rest of the pregnancy. AFP is transported to maternal serum through the placenta or by diffusion across fetal membranes. As a result, AFP is the principal serum binding protein in the fetus. As a second-trimester biochemical marker, MS-AFP has been widely applied for prenatal screening in practice. High or low MS-AFP suggests a high risk of fetal open neural tube defects (ONTDs) or chromosomal aneuploidy (8).

In recent years, new researchers found that elevated AFP levels associated with PAS. Because of early placental vascular damage, MS-AFP may be more absorbed into maternal blood flow. A retrospective case-control study in Israel confirmed this viewpoint. Berezowsky et al. observed that each individual PAS group had a higher median MS-AFP of median (MoM) than the controls ($p = 0.033$) in the second trimester. They also calculated that the receiver operating characteristics (ROC) area under the curve (AUC) of the AFP area was 0.573 (95% CI 0.515–0.630, $p < 0.0274$) and a cut-off value above 0.99 MoM demonstrated a sensitivity and specificity of 71 and 46%, respectively, for the prediction of PAS (9). Furthermore, increased second trimester MS-AFP levels can also independently predict PAS requiring hysterectomy among women with placenta previa totalis in a previous study. In a retrospective review of 316 pregnant women whom identified as cases of placenta previa totalis, Oztas et al. found that MS-AFP levels were significantly higher in second-trimester screenings of patients with PAS requiring hysterectomy ($p < 0.001$). The predictive AUC of ROC was 0.742 (95% CI: 0.505–0.979). The best MS-AFP cut-off value was 1.25 Mom, with 85.94% sensitivity and 71.43% specificity ($p = 0.036$). A multivariate logistic regression analysis was carried out to verify that MS-AFP was an independent predictor of PAS requiring hysterectomy [odds ratio (OR) = 25.329, 95% CI:1.487–43.143, $p = 0.025$] (10).

AFP is wildly applied in clinical treatments, including monitoring specific types of cancer and screening for fetal malformation. This implies that AFP testing methods are mature and its price is affordable, which makes screening for PAS convenience. However, even though MS-AFP has been shown to be a predictable factor of PAS in the second trimester and can also independently predict PAS requiring hysterectomy, the following restrictions remain: (i) Until now, few articles have demonstrated the relationship between MS-AFP and PAS, and this relationship's reliability and accuracy are insufficient. (ii) Whether MS-AFP can predict PAS in the first trimester or whether MS-AFP can predict other PAS-associated complications remains unknown. (iii) In addition, the cut-off value of MS-AFP to distinguish PAS varied across studies; thus, further prospective studies with larger populations are needed to find an exact cut-off value. (iv) Because MS-AFP is influenced by several factors, including fetal abnormalities and other types of placental abnormalities, these factors must be considered in future studies to reduce bias. Therefore, significant work remains to apply MS-AFP in practice to predict PAS.

Human Chorionic Gonadotropin (hCG)

A glycoprotein composed of 244 amino acids and with a molecular mass of 36.7 kDa. hCG is produced by the syncytiotrophoblast and maintains pregnancy by stimulating progesterone synthesis by the corpus luteum. Furthermore, HCG is a heterodimeric molecule composed of an alpha subunit that is identical to several hormones and a beta (β) subunit that is unique. In normal pregnancies, maternal circulating concentrations of ß-hCG show an increase from 9 to 11 weeks of gestation, followed by a decline thereafter. β-hCG is also synthesized by the fetal kidney and fetal liver. Free β-hCG promotes angiogenesis, and cytotrophoblast differentiation, and blocks the phagocytosis of invading trophoblastic cells, immunosuppression and blocks the phagocytosis of invading trophoblast cells (11).

Research has shown that β-hCG maternal serum levels are differential in cases of PAS during gestation. A team in Taiwan first reported this phenomenon in 1999, noting that abnormally elevated second-trimester free β-hCG levels were a risk factor for placenta accrete, and placenta previa (11). In 2015, in a prospective observational cohort study, Thompson et al. obtained maternal serum of 516 pregnancies, including 344 normal controls, 17 with abnormally invasive placentation (AIP) and 155 placenta previa cases in the first trimester. They demonstrated a median free β-hCG MoM of 1.04 in the control group, and 1.08 ($p = 0.859$) in the placenta previa group compared to 0.81 in the AIP group ($p = 0.06$), which suggested the relationship between PAS and β-hCG (12). Another study in Turkey arrived at the same conclusion. When Buke et al. found that patients with placenta accreta had higher statistically significant serum fβ-hCG MoM (1.42 vs. 0.93, respectively, $p = 0.042$) values than patients without accreta in the first trimester (13). In another study, which evaluated the association between second trimester biochemical markers

and pathological placentation for hCG, the AUC was 0.662 (95% CI 0.605–0.715, $p < 0.0001$), and the cut-off value of 1.25 MoM demonstrated a sensitivity and specificity of 53 and 68%, respectively (9). All of these studies confirmed the association between β-hCG and PAS. Currently, serum β-hCG levels are wildly used in clinical practice, including identifying the pregnancy, monitoring embryo changes, suggesting certain types of cancer etc. Thus, MS-AFP and β-hCG are all excellent options for prenatal diagnosis PAS in the future. There remain some difficulties that must be solved. For instance, β-hCG levels fluctuate wildly during the first trimester, reaching up to 100,000 U/ml. This variation trend in hCG must be further understood to choose the appropriate cut-off value to predict PAS. Furthermore, serum hCG levels are also associated with some other conditions, including miscarriage, ectopic pregnancy, and fetal abnormalities. It is difficult to distinguish the maternal serum hCG levels of PAS from those other conditions. Therefore, these difficulties must be overcome to make detecting biomarkers feasible in the future.

Pregnancy-Associated Plasma Protein A (PAPP-A)

PAPP-A, a zinc metalloproteinase produced by placental syncytiotrophoblasts, is secreted into the maternal circulation in increasing concentrations until delivery. Although its function is not well-understood, PAPP-A is commonly recognized as being responsible for proteolysis of insulin-like growth factor (IGF) from IGF-binding protein-4(IGFBP-4), implying a role in growth. In previous studies, scientists have demonstrated that low PAPP-A has been associated with poor placental invasion, resulting in placental insufficiency, intrauterine growth restriction, preeclampsia, stillbirth, abruption, and premature birth etc. Based on these findings, PAPP-A may play a significant role in regulating trophoblastic invasion (12, 14).

Owing to trophoblastic abnormal invasion, PAS's association with PAPP-A was first reported in 2014, when PAPP-A was found to be elevated during the first trimester in cases of PAS. The median PAPP-A MoM of 1.68 in accreta was significantly >0.98 in non-accreta ($p = 0.002$) (11). In a subsequent study, several researchers confirmed this conclusion. In 2015, Thompson et al. provided an overall PAPP-A median MoM of 1.40 ($p = 0.002$) in the first trimester by analyzing an AIP dataset from London and New York (12). In the same year, Lyell et al. also confirmed that elevated PAPP-A was associated with PAS among women with previa in the first trimester (14). However, while serum PAPP-A cannot be a diagnostic marker because there is significant overlap with the distribution of unaffected pregnancies, it can be used as a tool to modify the risk of placenta accreta. Furthermore, as a PAS biomarkers, serum PAPP-A can also predict the prognosis of PAS. Penzhoyan et al. found a significant correlation ($p < 0.15$) between the PAPP-A and the blood loss volume (PAPP-P M?M was 1.37 ± 1.20 in the not higher than 1,000 mL (LBL) subgroup and 1.91 ± 1.24 in the higher than 1,000 mL (HBL) subgroup MoM indicators, $p = 0.091$). This research revealed that the PAPP-A level in the first trimester may be helpful for the early prognosis of pathological blood loss at delivery for pregnant women with PAS and for forming a high-risk group for PAS (15). Hence, PAPP-A plays an important role in identifying high-risk population for PAS. Based on the levels of measurement technology, it is easy for researchers to test maternal-serum PAPP-A. Because PAPP-A isn't an independent risk factor for PAS, a model must be created to predict the risk of PAS. Previous research studies have presented prediction models. Research bottlenecks include finding proper influential factors and building an optimal model are research bottlenecks. To break these bottlenecks, bioinformatics specialists must participate in the research.

Angiogenic Factor

When abnormal placentation results in PAS, the process of excessive neovascularization occurs and upregulates angiogenic factors, such as vascular endothelial growth factor (VEGF) and angiopoietin 2 (Ang-2), and downregulates anti angiogenic factors, such as soluble Fms-like tyrosine kinase 1 (sFlt-1) and VEGFR-2 in syncytiotrophoblast. Accordingly, placental growth factor (PLGF), a high-affinity binder to VEGFR-2, is increased in serum levels. Researchers have quantified all these serum factors using enzyme-linked immunosorbent assays (ELISAs). Thus, when PAS happens, maternal serum angiogenesis factors could change. In the third trimester, women with PAS have significantly lower maternal serum VEGF levels because oxidative stress might lead to a down regulation of VEGF, and PLGF and sFlt-1 were significantly higher in PAS. Thus, these indicators can help predict PAS. Furthermore, in a multicenter case-control study design in Germany, Schwikert et al. collected gestational age-matched serum samples from pregnant women with AIP ($n = 44$) and uncomplicated pregnancies ($n = 55$) before delivery (GA median: 35 weeks). They concluded that maternal serum VEGF levels exhibited a significantly negative correlation with the FIGO AIP degree of invasion (Spearman'srho $= -0.37$; $p < 0.001$). Serum VEGF was able to predict the need for peripartum hysterectomy by plotting RUC curves (AUC = 0.698, 95% CI 0.564–0.832, LR+2.4, LR−0.3, $p = 0.004$). This phenomenon provides a clear advantage for clinical application (16–18). However, due to the study's sample sizes and limited relevant reports, these remain controversial conclusions. In researching angiogentic factors, a 2016 case–control study in Turkey demonstrated that there was no statistical difference in the maternal serum values of sFlt1, PlGF, sFlt1/PlGF ratio, and VEGF in groups with placental abnormalities compared to controls (19). However, these findings were not confirmed in subsequent studies.

In summary, the reviewed research studies indicate that PLGF, VEGF, and sFlt-1 have great application prospects in the future, although research on them is limited. Future research must focus on influential factors, such as diabetes, hypertension, pulmonary and cardiovascular disorders, FGR, inflammatory or connective tissue disorders, liver or renal failure, and placenta separation. How to rule out the effects of these factors and choose an appropriate cut-off value for them must still be resolved. Furthermore, the reviewed studies were all performed in the third trimesters. Whether such results could be acquired from samples taken during other trimesters remains unknown.

Cell-Free Fetal DNA (cffDNA)

In 1997, Y M Dennis Lo etc. first reported that cffDNA was present in maternal plasma and serum, and it is believed to originate from the apoptosis of cytotrophoblast and syncytiotrophoblast cells (20). It is generally recognized that these cells are destroyed by the maternal immune system during the implantation process. In a previous study, cffDNA occurred during pregnancy and rapidly cleared no more than 2 h after delivery. Gradually, the finding's applicating became widespread in clinical practice, aiming to find chromosomal aneuploidies. The level of cffDNA has also been shown to be associated with some pregnancy pathologies, including preterm birth, fetal growth restriction, and preeclampsia.

In 2002, a study verified that the concentration of fetal DNA within maternal plasma was significantly increased in the third trimester of two cases of invasive placentas (20). Since then, scientists have realized that cffDNA is related to PAS. In 2003, Jimbo et al. applied plasma cffDNA in PI's postpartum monitoring. After a gestation of 37 weeks and 3 days, a pregnant woman delivered and was diagnosed with PI through her clinical symptoms and magnetic resonance imaging findings. A small part of the placenta (7 cm in diameter) could not be removed from her uterus. The doctors monitored serum cffDNA regularly. The patient had intermittent vaginal bleeding until fetal DNA (DYS14 DNA) could no longer be detected in her plasma around 10 weeks post-delivery. The remaining portion of the placenta was spontaneously delivered 10 weeks postpartum. This case indicated that cffDNA in the plasma of pregnant women might serve as a molecular marker for the detection of AIP. In 2020, another case reported that a patient with AIP had a highly elevated level of cffDNA fraction (35.3%) at the end of the first trimester, whereas the median level of cffDNA fraction in normal pregnancies at this gestational age was only around 10.4%. The cffDNA fraction then decreased to 26.1% at 26 + 6 weeks of gestation (the median level at this gestational age was around 18%, according to a previous report) (21). Therefore, this supports the assumption that the cffDNA fraction may be a better biomarker for PAS. However, there are still some contradictory results to these findings. In 2013, a pilot study was carried out with 20 women [seven cases of placenta accreta, six cases of placenta previa and seven cases of normal placentation with prior cesarean deliveries (CD)]. After qualifying maternal serum cffDNA levels in the third trimester, the mean fraction of cffDNA prior to delivery did not differ significantly by group (accreta = 19.1%, previa = 27.2%, prior CD = 28.9%, $p = 0.26$), nor did the median (accreta = 17.0%, previa = 30.1%, prior CD = 22.7%), after controlling for no significant difference in maternal weight, placental weight, number of prior cesarean deliveries, or years from prior cesarean delivery (20). However, it may also be possible that the PAS process occurs much earlier in gestation, and it has been suggested that a significant difference between groups could be seen during the first trimester. Thus, from above study, the definite relationship between cffDNA and PAS is unclear. Since cffDNA is stable and can be detected in the early trimester, it can be an appropriate bio-marker. However, serum cffDNA samples are easily influenced by many factors, including their concentrations, the technique for isolation of DNA, gestation of the acquired sample, and length range of cffDNA. Further research must be performed in consideration of these factors. The number of samples in the current study is still too low. A larger clinical cohort trial of cffDNA is expected to be conducted in the future. In conclusion, the testing of maternal serum cffDNA for PAS is in its early stage. CffDNA as a possible marker of subsequent APS could help to improve the accuracy of the prenatal diagnoses of PAS.

Placenta-Specific mRNA

The placenta is a major contributor to Cell-free mRNA. Circulating cell-free placental mRNAs in maternal plasma can be stably isolated, quantified, and rapidly cleared after delivery. The mechanism of these actions is still unclear. The mRNA may transfer between the placenta and the maternal circulation due to a thin and dysfunctional decidua (26). Therefore, placenta mRNA could be investigated as a potential markers for placental function and placental-related disorders. Researchers mainly pay attention to two major placenta-specific mRNAs: β-human chorionic gonadotropin (β-hCG) and human placental lactogen (hPL) placental mRNAs.

Human Placental Lactogen (hPL) mRNA

During placental formation, trophoblast cells play an important role in placenta invasion into the uterus. Cell-free hPL mRNA is mainly produced in the mature syncytiotrophoblasts. In 2005, Masuzaki et al. demonstrated that a patient with placenta percreta had a residual placental mass at the internal os. They found that hPL mRNA could be used to monitor the efficacy of methotrexate therapy for PP, which suggested placental mRNA may be useful as a predictive marker for PAS (27). In 2014, by comparing the plasma of pregnant women at 28–32 weeks of gestation, Kawashima concluded that expression of hPL mRNA is increased in the plasma of women with invasive placenta ($p < 0.05$) (28). Subsequently, in a case-control study, Jing et al. collected peripheral blood from each woman at 28–30 weeks of gestation and measured maternal plasma hPL mRNA concentrations by real-time reverse-transcription polymerase chain reaction (PCR) in 2019. They came to the same conclusion that the multiple of the median (median, range) for hPL mRNA was significantly higher for the placenta accreta group (2.78, 1.09–4.56) than the control (1.00, 0.29–2.98) or placenta previa (1.12, 0.33–3.25) groups (Steel–Dwass test, $p < 0.001$ and $p = 0.005$, respectively). Furthermore, in 2008, a case-control study demonstrated that the cell-free hPL mRNA concentration in maternal plasma has the potential to predict a subgroup of placenta accreta resulting in hysterectomy; however, the results were not convincing due to the limited simple size (26).

β-Human Chorionic Gonadotropin (β-hCG) mRNA

Cell-free β-hCG mRNA is primarily produced by proliferating cytotrophoblasts. In 2005, it was reported that β-hCG mRNA could be used to monitor the efficacy of methotrexate therapy for placenta percreta. Therefore, it may be possible for β-hCG mRNA to predict PAS. Zhou et al. compared β-hCG mRNA concentrations of blood plasma from 68 pregnant

TABLE 1 | miRNAs in PAS.

miRNAs	Trend	Sample	Gestational weeks	Target signaling molecular	Function	Ref
hsa-miR-10524-5p hsa-miR-133a-3p hsa-miR-937-3p hsa-miR-34b-5p hsa-miR-3529-3p hsa-miR-488-3p hsa-miR-490-3p	↑/↓	Peripheral blood plasma	Before cesarean section	–	Angiogenesis and blood vessel morphogensis	(22)
hsa-miR-17-5p hsa-miR-21-5p hsa-miR-25-3p hsa-miR-92a-3p hsa-miR-320a-3p	↑	Peripheral blood plasma	30–34w	Clusterin	Regulate the epithelial-mesenchymal transition, decrease the expression level of clusterin	(23)
miR-196a-5p, miR-518a-3p, miR-139-3p miR-671-3p	↓	Venous blood	third trimester	NF-κB, ANXA1, MMP11, E-cadherin	Angiogenesis, embryonic development, cell migration and adhesion, and tumor-related pathways	(24)
Micro-7	↓	Peripheral blood plasma	–	TGF-β	Promotes trophoblast invasion	(25)

women between 28–30 weeks. They reported that cell-free-β-hCG mRNA concentrations (MoM, range) were significantly higher in women with placenta accreta (3.65, 2.78–7.19) than in women with placenta previa (0.94, 0.00–2.97) or normal placentation (1.00, 0.00–2.69; Steele-Dwass test, $p < 0.01$ and $p < 0.01$, respectively). Furthermore, they found that seven women who underwent hysterectomies in the placenta previa/accreta group had higher concentrations of cell-free β-hCG mRNA (4.41, 3.49–7.19) compared with women whose deliveries did not result in hysterectomy (3.20, 2.78–3.70; Manne-Whitney *U*-test, $p = 0.012$), which demonstrates β-hCG mRNA may be related to a prognosis of PAS (29). Currently, with the emergence of real-time polymerase chain reaction (RT-PCR) technology, doctors can easily to monitor placental-specific mRNA levels. Placental-specific mRNAs are not only potential biomarkers to predict PAS, but they also have the possibility to predict APOs. However, large prospective studies remain to be performed to confirm the role of hPL mRNA and cell-free-β-hCG mRNA in predicting AIP and the best time to harvest maternal blood. The technology's cost should be reduced to increase its applicability. The present study did not explore the association of placental-specific mRNA with the degree of PAS. Further studies with subdivisions are needed.

Because the range of mRNA is wider than that of protein, the use of plasma mRNA markers may increase the number of markers that can be used for prenatal monitoring and its greater specificity and sensitivity make the prenatal diagnosis of PAS more exact.

MicroRNA

MicroRNA, a non-coding RNA of ∼22 nucleotides, interferes with mRNA or DNA expression and occurs at the transcriptional and post-transcriptional levels. Circulating miRNAs can be detected in plasma and serum stably, because of their resistance to endogenous ribonuclease activity and can function as vesicles forming exosomes with lipoprotein membranous complexes or clusters. Micro-RNAs have been shown to modulate cell differentiation, embryonic development, adhesion, migration, apoptosis, and angiogenesis during placental development, and the altered expression of miRNA has been associated with various pregnancy complications. According to the mechanism, researchers can obtain a sample of maternal peripheral blood plasma, isolated the RNA from the sample, perform reverse transcription and qRT-PCR, and then conduct a quantitative analysis. Therefore, some studies have revealed that level of microRNA is in accordance with the PAS (**Table 1**). It is believed that miRNAs may predict PAS. Recently, scientists have also proven that some microRNAs, such as miR-17-5p, miR-21-5p, miR-25-3p, miR-92a-3p, and miR-320a-3, are associated with severity of PAS (23). Researchers also found that miRNA can predict PAS prognosis. In one study, Tian Yang et al. indicated that the expression of hsa-miR-490-3p and hsa-miR-133a-3p was positively correlated with operation-related blood volume loss. Furthermore, another study found that the amount of blood loss was negatively correlated with the expression of miR-139-3 p, and miR-196a-5p, with correlation coefficients of 0.215 and 0.172, respectively ($p < 0.01$ and $p < 0.05$, respectively) (24). For its specify and variety, MicroRNAs have bright prospects for prenatal diagnosis of PAS. At present, more than 20,000 miRNAs can be detected in the placenta; however, only a few miRNAs have been confirmed to be associated with PAS. More research must be conducted to find additional related miRNAs. Recently, miRNA research has become a hotspot. Nearly all of above miRNAs have been mentioned only once in existing research, which indicates very low reliability. More research is needed to find suitable miRNAs in PAS and to verify the finding in larger samples. Another difficulty is that detecting miRNA is a tedious process, which means it comes at a high price. Thus, simplifying process and decreasing price to make miRNA detection affordable will be other important tasks in the future.

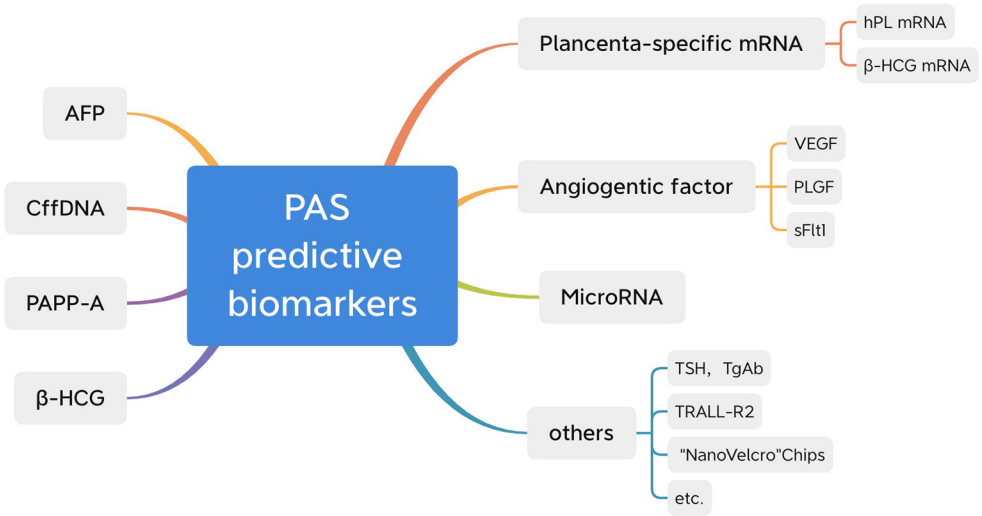

FIGURE 1 | Biomarkers related to PAS.

Others

Researchers have also found other biomarkers related to PAS. Shainker et al. used an aptamer-based proteomics platform to examine the maternal plasma samples from 16 patients with PAS for alterations in 1,305 unique proteins, finding 50 proteins with expression levels that were significantly different ($p < 0.01$). After analyses, the researchers found that the proteins were mostly inflammatory cytokines, factors that regulate vascular remodeling, and extracellular matrix proteins that regulate invasion. All of them may be potential biomarkers for diagnosing PAS and require further study (30). In reality, some proteins with specific functions are reportedly associated with PAS. A prospective case-control study reported that the maternal serum thyroid-stimulating hormone (TSH) and thyroid antibodies against thyroglobulin (TgAb) levels were significantly lower in a PAS group than placenta previa and control groups early in the third trimester. Decreased serum TSH and TgAb levels were also found to be independently associated with an increased rate of cesarean hysterectomy and massive blood transfusions in PAS cases (31). TRAIL-R2 is widely known as a death receptor (DR) and induces apoptotic signaling. Serum TRAIL-R2 levels have been shown to be significantly lower in a PA group (median 19.85 pg/mL) when compared with both non-adherent placenta previa (median 25.99 pg/mL) and control groups (median 25.87 pg/mL; $p < 0.05$). Thus, not only is TRALL-R2 associated with PAS, but it also plays a possible role in apoptosis in PAS (32). In addition to protein, some specific genes may also be related to PAS. However, only one case report found a possible association between placenta accreta and manifestations of the A3243G mutation in mtDNA (33). Other genomic research studies have been performed at the placental level. Hundreds of genes have significantly different detection levels in placental tissues. Whether these genes are the same in peripheral blood is not known. Today, NanoVelcro chips, which are nanostructure-embedded microchips, can efficiently enrich both single and clustered circulating trophoblasts (cTBs) from maternal blood. In a multicenter observational cohort study of 168 pregnant women, the combined cTB assays achieved an area under ROC curves of 0.942 (throughout gestation) and 0.924 (early gestation) for distinguishing PAS from non-PAS. For its simple operation procedure and high accuracy, the combination of cTBs and cTB clusters captured on the NanoVelcro chips for detecting PAS early in gestation will enable a promising quantitative assay to serve as a non-invasive test (34).

Potential Biomarkers

According to the current study, some biomarkers have been detected to be significantly different in placenta tissues, which may identify them as potential maternal biomarkers to predict PAS. For example, in 2019, to explore lncRNA differential expression, Huishan Zhang et al. screened five pairs of placenta tissues of patients with PAS. Using RNA microarray analysis, a total of 329 lncRNAs (101 upregulated; 228 downregulated) and 179 mRNAs (95 upregulated; 84 downregulated) were identified as having differential expressions in PAS. This makes it easier to select further biomarkers (35). Furthermore, by sequencing the placenta tissues of five women with PAS and five healthy pregnant women, Qiao et al. found that 23 hub genes were differentially expressed at both the mRNA and protein levels and that the expression trends were the same (36). Hub genes and bottleneck genes may have more specificity for detecting PAS. With the progression of omics studies in PAS and increasing sample sizes, the genetic features of PAS will be clearer, and the structural variations of hub genes will be more statistically significant, which will provide potential predictive and therapeutic targets for PAS.

TABLE 2 | Biomarkers of aneuploidy in PAS.

Marker	Study	Trimester	Gestational weeks	Total case	Cut-off value	Sensitivity	Specificity	*P*	Predict the prognosis
AFP	Oztas et al.	second	16–20w	316	1.25MoM	0.8594	0.7143	=0.036	Y
	Berezowsky et al.	second	16–19+6w	301	0.99MoM	0.71	0.46	<0.027	Y
β-hcg	Thompson et al.	first	11–13w	560	0.81MoM	–	–	=0.061	N
	Buke et al.	first	–	88	1.42MoM	–	–	=0.042	N
	Berezowsky et al.	second	16–19+6w	301	1.25MoM	0.53	0.68	<0.0001	Y
PAPP-A	Thompson et al.	first	11–13w	560 (33AIP)	1.40MoM	–	–	=0.002	N
	Lyell et al.	first	10w 0d−13w 6d	736 (37AIP)	2.63MoM	–	–	–	N
	Penzhoyan et al.	first	11w 0d−13w 6d	87 (25AIP)	1.30MoM	–	–	=0.640	Y

N, No; Y, Yes.

Current Situation and Prospective Future of PAS

PAS is one of the main causes of increasing maternal morbidity and mortality, with consequences ranging from excessive hemorrhage, the need for hysterectomy, DIC, massive transfusions, ureteral/bladder/bowel injury, and even death. Neonates also have a higher risk of suffering neonatal complications, such as NICU admission and transient tachypnea of newborns (TTN). Considering the risks and APOs among patients with PAS, the significance of the condition and the need for early diagnosis has become more apparent. Antenatal diagnosis could transfer pregnant women to highly experienced maternity centers in time. Furthermore, it allows obstetricians to organize a comprehensive multidisciplinary care team and make full preparations, including advanced surgical planning, abundant blood supplies, preoperative preparations, and appropriate time allotted for delivery. In 2018, the American College of Obstetricians and Gynecologists (ACOG) guidelines for PAS advised that delivery at 34 0/7–35 6/7 weeks of gestation is the preferred gestational age for scheduled cesarean delivery or hysterectomy, absent extenuating circumstances, in a stable patient. Earlier delivery may be required in cases of persistent bleeding, preeclampsia, labor, rupture of membranes, fetal compromise, or developing maternal comorbidities. The guidelines also recommend the use of antenatal corticosteroids for lung maturation in women with antenatally diagnosed PAS (37). All these recommendations attach great importance in prenatal diagnosis PAS.

This study reviewed the existing literature and summarized around 10 potential biomarkers to assist in the prenatal diagnosis of PAS (**Figure 1**). Some of them, such as β-hCG, AFP, cffDNA, and PAPP-A, have already been widely applied in clinical practice for other purposes. As PAS is a new domain and its morbidity is still low, scientists have yet to produce comprehensive research. Though we have already known that they are associated with PAS, more convincing published results will accelerate the application of such biomarkers. Little research exists on other newly reported biomarkers, such as microRNAs, placenta-specific mRNA and NanoVelcro chips; however, they are more specific and less influenced by other complications. The most significant hurdle is the cost of testing technology. With more thorough research, these biomarkers may have a bright future. According to previous studies, combining certain biomarkers with ultrasounds may improve the accuracy of a PAS diagnosis. In a study of cell-free placental mRNA, Behery et al. found that all six of the false-positive cases diagnosed by ultrasound and color Doppler in their study were from the group confirmed without placenta accreta, with an insignificant rise in cell-free placental mRNA levels (27). Furthermore, NanoVelcro chips can improve ultrasound accuracy. Thus, based on the current research, these two biomarkers can be further explored in the future. In addition, the current study about PAS complications is mostly related to hemorrhage and hysterectomy. Some other complications, including newborns' health conditions, premature labor, bladder invasion, and influence on the next pregnancy, were rarely counted and discussed. More focus should be placed on these areas in the future.

Currently, prenatal Down syndrome screening is widely performed on the basis of second-trimester or first-trimester maternal serum markers in clinical studies. By testing a combination of maternal serum levels of AFP, uE3, HCG, and PAPP-A, doctors can screen for antenatal aneuploidy diseases, including Down syndrome, trisomy 18 syndrome, and neural tube defects (NTD). The sensitivity of the test is 60–70%. Except for uE3, other biomarkers have been associated with PAS. In this way, co-analyzed serum markers may be beneficial for the antenatal screening of PAS and could assess the risk of PAS disorders. A retrospective case-control study in Israel co-analyzed maternal serum AFP and HCG in the second trimesters. The AUC was 0.668 (95% CI 0.611–0.721, $p < 0.0001$), and the sensitivity and specificity were 63 and 64%, respectively. Thus, they distinguished a percentile MoM cut-off approach between two groups: a high-risk group [patients with AFP, HCG, or both above the 75th percentile, with an odds ratio (OR) for pathological placentation of 2.27, 95% CI 1.42–3.63] and a low-risk group (patients with AFP, HCG, or both below the 25th percentile, with an OR for pathological placentation of 0.38, 95% CI 0.24–0.60) (9). Therefore, according to AFP and HCG values, researchers can focus on patients at higher risk of PAS, which is convenient for doctors making prenatal diagnoses of PAS. Biomarkers of aneuploidy in PAS are re-listed in **Table 2** in detail. Different studies have provided significantly

different cut-off values. Only a few studies have explored the relationship between biomarkers and the prognosis of PAS. Thus, the best appropriate cut-off value in Chinese should be found, and extensive research must be conducted that includes APOs to find a relationship between biomarkers and the prognosis of PAS. Few studies have researched co-analyzing biomarkers, and most of them only researched two biomarkers. Similar to an aneuploid prenatal diagnosis, researchers must explore whether a better combination of biomarkers exists for predicting the type of PAS and the prognosis of PAS. Once again, a more appropriate cut-off value must be found for the Chinese. Once we finish these series of research, they are easy to be wildly used in clinical. Their mature detection methods and affordable prices greatly reduce our obstruction and save our research time.

Today, many pregnant women have prenatal examinations in basic medical institutions without the necessary clinical requirements or experienced doctors. Therefore, some pregnant women with a potentially high risk of PAS may be misdiagnosed. This study suggests a new method for predicting PAS. First, all pregnant women should be divided into different risk groups for PAS. Second, follow-up ultrasounds and specific biomarker tests should be performed for not-low-risk pregnant women to guard against typical warning signs. Finally, a PAS scoring system should be created to predict PAS prognosis, which would provide exceptional convenience for clinical work.

CONCLUSION

Although this study was devoted to the antenatal diagnosis of PAS, up to 50% of pregnancies with PAS go undiagnosed before delivery in clinical practice, which results in increased morbidity. Today, ultrasound is still the first-line detection method for PAS. Summarizing the published literature revealed eight biomarkers in maternal serum that could be used to predict PAS in the future. However, how these biomarkers predict the severity of PAS and their relationships with PAS complications are still not fully understood. Some suggestions for increasing the accuracy of diagnosing PAS have been proposed and must be further explored. With the third-child policy carried out in China, the number of women becoming pregnant again after a cesarean section will increase significantly, which will subsequently increase the incidence of PAS. Therefore, it is important to identify PAS early and make accurate risk stratification. Applying this process in clinical settings will benefit countless families.

AUTHOR CONTRIBUTIONS

SW generated the idea. TZ wrote the article. Both authors contributed to the article, revised the manuscript, and approved the submitted version.

REFERENCES

1. Jauniaux E, Ayres-de-Campos D, Diagnosis FPA, Management Expert Consensus P. Figo consensus guidelines on placenta accreta spectrum disorders: introduction. *Int J Gynaecol Obstet.* (2018) 140:261–4. doi: 10.1002/ijgo.12406
2. Ali H, Chandraharan E. Etiopathogenesis and risk factors for placental accreta spectrum disorders. *Best Pract Res Clin Obstet Gynaecol.* (2021) 72:4–12. doi: 10.1016/j.bpobgyn.2020.07.006
3. Jauniaux E, Bunce C, Gronbeck L, Langhoff-Roos J. Prevalence and main outcomes of placenta accreta spectrum: a systematic review and meta-analysis. *Am J Obstet Gynecol.* (2019) 221:208–18. doi: 10.1016/j.ajog.2019.01.233
4. Matsuzaki S, Mandelbaum RS, Sangara RN, McCarthy LE, Vestal NL, Klar M, et al. Trends, characteristics, and outcomes of placenta accreta spectrum: a national study in the United States. *Am J Obstet Gynecol.* (2021) 225:534.e1–38. doi: 10.1097/01.ogx.0000831500.24034.6f
5. Allen L, Jauniaux E, Hobson S, Papillon-Smith J, Belfort MA, Diagnosis FPA, et al. Figo consensus guidelines on placenta accreta spectrum disorders: nonconservative surgical management. *Int J Gynaecol Obstet.* (2018) 140:281–90. doi: 10.1002/ijgo.12409
6. Gulino FA, Guardo FD, Zambrotta E, Di Gregorio LM, Miranda A, Capriglione S, et al. Placenta accreta and balloon catheterization: the experience of a single center and an update of latest evidence of literature. *Arch Gynecol Obstet.* (2018) 298:83–8. doi: 10.1007/s00404-018-4780-y
7. Fitzpatrick KE, Sellers S, Spark P, Kurinczuk JJ, Brocklehurst P, Knight M. The management and outcomes of placenta accreta, increta, and percreta in the UK: a population-based descriptive study. *BJOG.* (2014) 121:62–70. doi: 10.1111/1471-0528.12405
8. Hu J, Zhang J, He G, Zhu S, Tang X, Su J, et al. First-trimester maternal serum alpha-fetoprotein is not a good predictor for adverse pregnancy outcomes: a retrospective study of 3,325 cases. *BMC Pregnancy Childbirth.* (2020) 20:104. doi: 10.1186/s12884-020-2789-2
9. Berezowsky A, Pardo J, Ben-Zion M, Wiznitzer A, Aviram A. Second trimester biochemical markers as possible predictors of pathological placentation: a retrospective case-control study. *Fetal Diagn Ther.* (2019) 46:187–92. doi: 10.1159/000492829
10. Oztas E, Ozler S, Caglar AT, Yucel A. Analysis of first and second trimester maternal serum analytes for the prediction of morbidly adherent placenta requiring hysterectomy. *Kaohsiung J Med Sci.* (2016) 32:579–85. doi: 10.1016/j.kjms.2016.08.011
11. Bartels HC, Postle JD, Downey P, Brennan DJ. Placenta accreta spectrum: a review of pathology, molecular biology, and biomarkers. *Dis Markers.* (2018) 2018:1507674. doi: 10.1155/2018/1507674
12. Thompson O, Otigbah C, Nnochiri A, Sumithran E, Spencer K. First trimester maternal serum biochemical markers of aneuploidy in pregnancies with abnormally invasive placentation. *BJOG.* (2015) 122:1370–6. doi: 10.1111/1471-0528.13298
13. Buke B, Akkaya H, Demir S, Sagol S, Simsek D, Basol G, et al. Relationship between first trimester aneuploidy screening test serum analytes and placenta accreta. *J Matern Fetal Neonatal Med.* (2018) 31:59–62. doi: 10.1080/14767058.2016.1275546
14. Lyell DJ, Faucett AM, Baer RJ, Blumenfeld YJ, Druzin ML, El-Sayed YY, et al. Maternal serum markers, characteristics and morbidly adherent placenta in women with previa. *J Perinatol.* (2015) 35:570–4. doi: 10.1038/jp.2015.40
15. Penzhoyan GA, Makukhina TB. Significance of the routine first-trimester antenatal screening program for aneuploidy in the assessment of the risk of placenta accreta spectrum disorders. *J Perinat Med.* (2019) 48:21–6. doi: 10.1515/jpm-2019-0261
16. Faraji A, Akbarzadeh-Jahromi M, Bahrami S, Gharamani S, Raeisi Shahraki H, Kasraeian M, et al. Predictive value of vascular endothelial growth factor and placenta growth factor for placenta accreta spectrum. *J Obstet Gynaecol.* (2021). doi: 10.1080/01443615.2021.1955337. [Epub ahead of print].
17. Schwickert A, Chantraine F, Ehrlich L, Henrich W, Muallem MZ, Nonnenmacher A, et al. Maternal serum vegf predicts abnormally invasive placenta better than nt-probnp: a multicenter case-control study. *Reprod Sci.* (2021) 28:361–70. doi: 10.1007/s43032-020-00319-y
18. Wang N, Shi D, Li N, Qi H. Clinical value of serum vegf and sflt-1 in pernicious placenta previa. *Ann Med.* (2021) 53:2041–9. doi: 10.1080/07853890.2021.1999492

19. Biberoglu E, Kirbas A, Daglar K, Biberoglu K, Timur H, Demirtas C, et al. Serum angiogenic profile in abnormal placentation. *J Matern Fetal Neonatal Med.* (2016) 29:3193–7. doi: 10.3109/14767058.2015.1118044
20. Samuel A, Bonanno C, Oliphant A, Batey A, Wright JD. Fraction of cell-free fetal dna in the maternal serum as a predictor of abnormal placental invasion-a pilot study. *Prenat Diagn.* (2013) 33:1050–3. doi: 10.1002/pd.4195
21. Wertaschnigg D, Lucovnik M, Klieser E, Huber-Katamay J, Moertl MG. Increased cell-free fetal dna fraction in the first trimester: a sign of abnormally invasive placenta? *Ultraschall Med.* (2020) 41:560–1. doi: 10.1055/a-0770-5209
22. Yang T, Li N, Hou R, Qiao C, Liu C. Development and validation of a four-microrna signature for placenta accreta spectrum: an integrated competing endogenous RNA network analysis. *Ann Transl Med.* (2020) 8:919. doi: 10.21037/atm-20-1150
23. Timofeeva AV, Fedorov IS, Pirogova MM, Vasilchenko ON, Chagovets VV, Ezhova LS, et al. Clusterin and its potential regulatory micrornas as a part of secretome for the diagnosis of abnormally invasive placenta: accreta, increta, and percreta cases. *Life.* (2021) 11:270. doi: 10.3390/life11040270
24. Chen S, Pang D, Li Y, Zhou J, Liu Y, Yang S, et al. Serum mirna biomarker discovery for placenta accreta spectrum. *Placenta.* (2020) 101:215–20. doi: 10.1016/j.placenta.2020.09.068
25. Shih JC, Lin HH, Hsiao AC, Su YT, Tsai S, Chien CL, et al. Unveiling the role of microrna-7 in linking tgf-beta-smad-mediated epithelial-mesenchymal transition with negative regulation of trophoblast invasion. *FASEB J.* (2019) 33:6281–95. doi: 10.1096/fj.201801898RR
26. Li J, Zhang N, Zhang Y, Hu X, Gao G, Ye Y, et al. Human placental lactogen mrna in maternal plasma play a role in prenatal diagnosis of abnormally invasive placenta: yes or no? *Gynecol Endocrinol.* (2019) 35:631–4. doi: 10.1080/09513590.2019.1576607
27. El Behery MM, Rasha LE, El Alfy Y. Cell-free placental mrna in maternal plasma to predict placental invasion in patients with placenta accreta. *Int J Gynaecol Obstet.* (2010) 109:30–3. doi: 10.1016/j.ijgo.2009.11.013
28. Kawashima A, Sekizawa A, Ventura W, Koide K, Hori K, Okai T, et al. Increased levels of cell-free human placental lactogen mrna at 28–32 gestational weeks in plasma of pregnant women with placenta previa and invasive placenta. *Reprod Sci.* (2014) 21:215–20. doi: 10.1177/1933719113492209
29. Zhou J, Li J, Yan P, Ye YH, Peng W, Wang S, et al. Maternal plasma levels of cell-free beta-hcg mrna as a prenatal diagnostic indicator of placenta accrete. *Placenta.* (2014) 35:691–5. doi: 10.1016/j.placenta.2014.07.007
30. Shainker SA, Silver RM, Modest AM, Hacker MR, Hecht JL, Salahuddin S, et al. Placenta accreta spectrum: biomarker discovery using plasma proteomics. *Am J Obstet Gynecol.* (2020) 223:433 e1–14. doi: 10.1016/j.ajog.2020.03.019
31. Ozler S, Oztas E, Kebapcilar A, Caglar AT. The role of thyroid-stimulating hormone and thyroglobulin antibody in abnormally invasive placenta. *J Matern Fetal Neonatal Med.* (2021). doi: 10.1080/14767058.2021.1875430. [Epub ahead of print].
32. Oztas E, Ozler S, Ersoy AO, Ersoy E, Caglar AT, Uygur D, et al. Decreased placental and maternal serum trail-r2 levels are associated with placenta accreta. *Placenta.* (2016) 39:1–6. doi: 10.1016/j.placenta.2016.01.004
33. Aggarwal P, Gill-Randall R, Wheatley T, Buchalter MB, Metcalfe J, Alcolado JC. Identification of mtdna mutation in a pedigree with gestational diabetes, deafness, wolff-parkinson-white syndrome and placenta accreta. *Hum Hered.* (2001) 51:114–6. doi: 10.1159/000022950
34. Afshar Y, Dong J, Zhao P, Li L, Wang S, Zhang RY, et al. Circulating trophoblast cell clusters for early detection of placenta accreta spectrum disorders. *Nat Commun.* (2021) 12:4408. doi: 10.1038/s41467-021-24627-2
35. Wu S, Zhang H, Liu Y, Wang R, Ye S, Zeng M, et al. Long non-coding RNAs show different expression profiles and display competing endogenous RNA potential in placenta accreta spectrum disorders. *J South Med Univ.* (2019) 39:1253–9. doi: 10.12122/j.issn.1673-4254.2019.10.19
36. Chen B, Wang D, Bian Y, Li J, Yang T, Li N, et al. Systematic identification of hub genes in placenta accreta spectrum based on integrated transcriptomic and proteomic analysis. *Front Genet.* (2020) 11:551495. doi: 10.3389/fgene.2020.551495
37. Society of Gynecologic O, American College of O, Gynecologists, the Society for Maternal-Fetal M, Cahill AG, Beigi R, et al. Placenta accreta spectrum. *Am J Obstet Gynecol.* (2018) 219:B2–16. doi: 10.1016/j.ajog.2018.09.042

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CASE REPORT
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Case Report: Anesthesia for Cesarean Section in Parturients With Chronic Renal Failure Requiring Hemodialysis: Case Reports and Literature Review

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Pregnancies are rare in women with chronic renal failure requiring hemodialysis. Although a chance of successful pregnancy and delivery in hemodialysis women has increased over the years, it is still very low, and with high maternal and fetal mortality and morbidity rate compared to normal population. And cesarean section is usually used for delivery. The first case was a 32-year-old Chinese woman with chronic kidney disease stage V undergoing maintenance hemodialysis for six years. The second case was also a 32-year-old patient with a 6-year history of hemodialysis for chronic glomerulonephritis. And due to a history of atrial septal defect and hypertension she received intensive hemodialysis during pregnancy. Both cases were scheduled for cesarean delivery under epidural anesthesia. To help develop reasonable anesthetic methods and management objectives for such patients, we described our anesthetic management and performed a literature search on published cases of cesarean section with chronic renal failure undergoing hemodialysis.

Keywords: Chronic renal failure, cesarean section, anesthesia, hemodialysis, uremia

INTRODUCTION

Patients with chronic kidney disease (CKD) are less able to make the renal adaptations needed for a healthy pregnancy. In the past, any degree of renal impairment was considered incompatible with pregnancy and those patients were usually advised to terminal the pregnancy (1). In fact, since a study in 1971 reported the first case of a 35-year-old end-stage renal failure woman on hemodialysis (HD) who achieved a full-term pregnancy, the further cases followed (2). The effect of pregnancy on maternal kidney disease may manifest as a loss of renal function. CKD, even when mild, can lead to the high risk of adverse pregnancy outcomes, including preeclampsia, preterm delivery, and small-for-gestational age infants or neonatal intensive care unit (NICU) admission, and these risks increase with the severity of the underlying renal dysfunction, degree of proteinuria, as well as the frequent coexistence of hypertension (3). A study reported that compared to patients without kidney disease, those with kidney disease

had 52% increased odds of preterm delivery and 33% increased odds of delivery via cesarean section (4). Compared with babies born to parturients without kidney disease, babies born to parturients with kidney disease had 71% increased odds of admission to neonatal intensive care unit (NICU) or infant death and the chance of low birth weight has tripled (4).

Anesthesia for such patients entails many risks, such as changes increased gastric acid secretion, cardiovascular instability, in drug metabolism and platelet dysfunction (5). For such patients, anesthesia management is very important, but few literatures mentioned it at present. In this paper we obtained the written informed consent of the patients and shared our experience of epidural anesthesia in parturients with chronic renal failure (CRF) on HD.

CASE REPORT

Case 1

A 32-year-old woman with 3 gravida and one para (G3P1) was scheduled for cesarean delivery at 36 weeks and two days' gestation. She had delivered a live baby 12 years before due to umbilical cord around the neck. She weighed 63.5 kg and was 150 cm tall. She had a 17-year history of chronic glomerulonephritis and has been on HD three times per week after progressing to CKD stage V six years before. The family history of this patient was unremarkable. During pregnancy, the patient's renal function was stable without complications such as anemia, hypertension, and edema. She was admitted to the hospital for cesarean section due to obstetrical B-ultrasound indicating severe fetal growth restriction (FGR). She received heparin-free HD 13 h before operation. Her laboratory data during her admission is summarized in the **Table 1**.

Noninvasive blood pressure (NIBP:100/62 mmHg), electrocardiography (ECG), heart rate (HR:95/ min), and SpO_2 (98%) were monitored after entering the operating room and invasive arterial catheterization was performed from the right radial artery under local anesthesia (because an arteriovenous fistula was being used for HD on the left side). After checking the normal thrombelastography (TEG) and activated clotting time of whole blood (ACT), and their international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (APTT) and platelet count are normal, considering that there was no contraindication of epidural anesthesia, we decided to perform cesarean section under epidural anesthesia.

Epidural anesthesia with 5 mL test dose of 2% lidocaine was successfully performed at the L1-2 intervertebral space in the right-lateral position. After 5 min, there was no general spinal

TABLE 1 | Preoperative, postoperative and discharge laboratory values.

		Preoperative		Postoperative (the day after the operation)		Discharge	
		Case 1	Case 2	**Case 1**	Case 2	**Case 1**	Case 2
Blood	RBC ($\times10^{12}$/L)	3.33	3.59	2.95	3.46	3.07	3.47
	Hemoglobin (g/dL)	11.7	10.0	10.1	10.0	10.6	9.8
	Haematocrit (%)	36.1	33.5	31.4	32.4	32.4	31.5
	Platelet count ($\times10^{9}$/L)	161	339	146	352	174	324
Coagulation tests	INR	0.92	1.06	–	–	–	–
	PT (seconds)	10.5	12.2	–	–	–	–
	APTT (seconds)	27.4	28	–	–	–	–
	Fibrinogen (g/L)	6.94	5.22	–	–	–	–
	D-dimer (mg/L)	2.22	1.86	–	–	–	–
Renal function and electrolytes	Urea (mmol/L)	18.7	34.2	18.9	–	11.6	39.1
	Creatinine (μmol/L)	978	927	888	–	666	1011
	K (mmol/L)	4.7	4.7	4.1	5.6	4.1	5.3
	Na (mmol/L)	139	138	–	136	135	132
	Ca (mmol/L)	2.23	2.31	2.15	–	2.07	2.19
	Cl (mmol/L)	105	103	–	99	99	93
	Total protein (g/L)	62	70	–	–	51	–
	Albumin (g/L)	35	37	–	–	27	–
Arterial blood gases	PH	7.45	7.50	–	–	–	–
	$PaCO_2$ (mmHg)	34	33	–	–	–	–
	PaO_2 (mmHg)	106	90	–	–	–	–
	HCO_3^- (mmol/L)	24.2	25.7	–	–	–	–
	Glucose (mmol/L)	4.8	4.9	–	–	–	–
TEG	R (min)	7.3	5.4	–	–	–	–
	K (min)	1.4	0.8	–	–	–	–
	Angle (deg)	69.5	80.2	–	–	–	–
	MA (mm)	72.5	73.3	–	–	–	–

ACT, activated clotting time of whole blood; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; TEG, thrombelastography.

anesthesia and local anesthetic poisoning, and 2% lidocaine 7 mL was added. Epidural anesthesia level having reached the T8 to S dermatomes, the operation was started. A 1,770 g baby with an Apgar score of 10 in one minute and 10 in five minutes was delivered 12 min after the beginning of surgery. Invasive blood pressure and HR were stable during the surgery and **Figure 1** shows the values. No headache, nausea or vomiting were present during surgery. The operation lasted for 50 min, with 1,100 mL intraoperative crystalloid fluid, 200 mL bleeding, and no urine.

After the operation, the epidural catheter was removed after measuring the anesthesia level (T10-S). No bleeding was observed at the puncture point, and the patient was sent back to the ward after the patient controlled intravenous analgesia (PCIA) was placed.

Case 2

Another 32-year-old G4P1 woman had a 6-year history of dialysis for chronic glomerulonephritis. Her weight was 62 kg and her height was 158 cm. The parturient had a history of atrial septal defect and hypertension and received intensive HD (5 / week) during pregnancy. The patient regularly took nifedipine controlled-release tablets 30 mg QD for hypertension. During pregnancy, her blood pressure was poorly controlled, fluctuating between 150–190/70–100 mmHg, and it was deemed necessary to add labetalol. The patient has anemia and disorders of electrolytes like most patients with end-stage renal disease. She used erythropoietin (EPO) regularly for a long time and increased the dose during pregnancy. Preoperative investigations showed hemoglobin of 10 g/dL and normal serum potassium. During pregnancy, the woman did not have edema of both lower extremities. A decision to perform cesarean section was taken at 33 weeks and 5 days due to heart failure in the context of a viral infection. Her Brain Natriuretic Peptide (BNP) was over 35,000 ng/L. And the echocardiogram of this patient showed atrial septal defect, left atrium and left ventricle enlargement, pulmonary artery systolic pressure (PASP) 35 mmHg, and left ventricular ejection fraction (LVEF) 42%. Her last dialysis was performed 17 h before surgery using heparin-free HD.

In the operation room, monitoring included NIBP (176/99 mmHg), ECG, HR (106/min), and SpO_2 (99%), but urine output was not monitored. Invasive arterial catheterization was performed and the TEG was normal. Epidural anesthesia was successfully given at the L2-3 intervertebral space using 4 mL 2% lidocaine in the right-lateral position. 11 mL 2% lidocaine was added after observation without general spinal anesthesia and local anesthetic poisoning. The operation began when the anesthesia level having reached the T8 to S dermatomes. After 7 min, a 1,885 g live baby was delivered (Apgar score: 9-9). Hypotension occurred after the baby was delivered, and we injected 50 μg phenylephrine intravenously and her BP and HR during the surgery are shown in **Figure 2**. The operation lasted for 42 min, with 600 mL intraoperative crystalloid fluid, 200 mL bleeding. Her cardiac and renal condition was not aggravated during the surgery.

After the surgery, no complications of anesthesia were observed, the epidural catheter was removed after measuring the anesthesia level (T10-S) and the patients was transferred to the cardiology intensive care unit (CCU) for further monitoring and returned to the ward the day after the operation. Both newborns were transferred to NICU.

Both mothers returned to heparin-free dialysis on the first postoperative day. During the following days, the two women were in stable condition, and recovered without any anesthesia-related complications such as epidural hematoma occurred headache, nausea or neurological deficit. They continued regular dialysis 3 times per week after they were discharged from the hospital. **Table 1** shows their laboratory

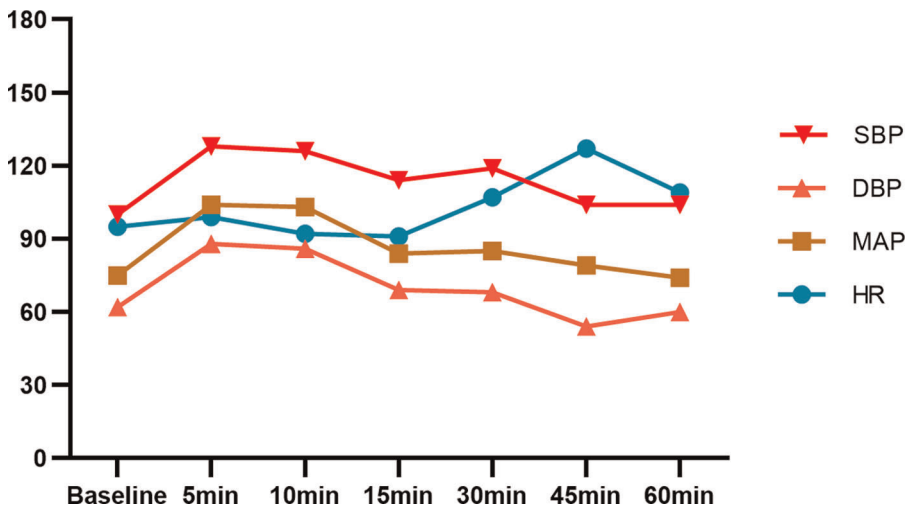

FIGURE 1 | BP and HR of case 1 after epidural anesthesia. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean artery pressure; HR, hearte rate.

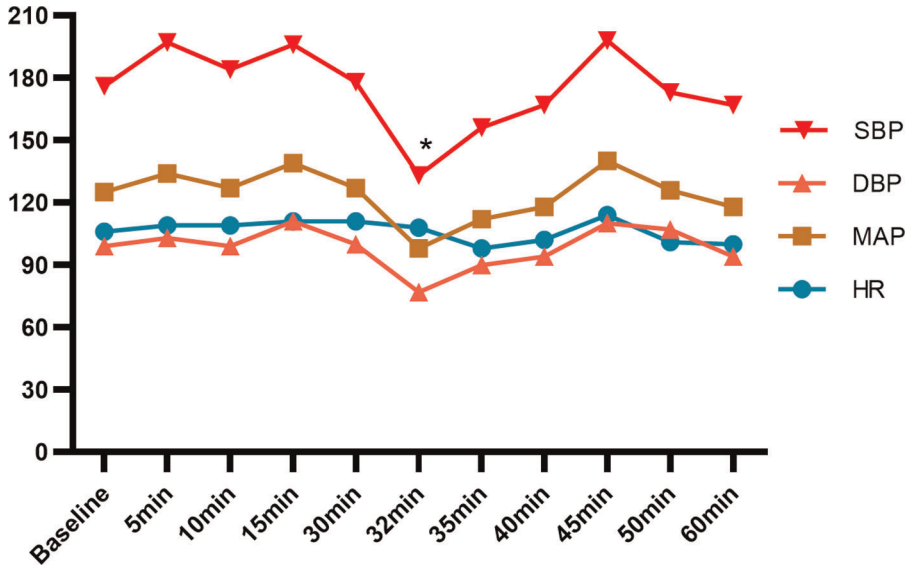

FIGURE 2 | BP and HR of case 2 after epidural anesthesia. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean artery pressure; HR, hearte rate. *intravenous injection of 50 μg phenylephrine.

TABLE 2 | Maternal and infant outcomes.

	Discharge	HD frequency	Renal function	BP and medication	Anemia and medication	Infant outcome
Case 1	The third day after operation	3/week	stable	Normal /–	Slightly lower /–	survived
Case 2	One week after operation	3/week	stable	Slightly higher / nifedipine controlled-release tablets 30 mg QD	Slightly lower /EPO	survived

HD, hemodialysis; BP, blood pressure; QD, quaque die; EPO, erythropoietin.

data for the day after the operation and the last data before discharged. After months of follow-up, their renal function has been stabilized by regular HD and their babies are growing up healthily. **Table 2** shows the maternal and infant outcomes of the two cases.

DISCUSSION

Chronic renal failure (CRF) is the common outcome of the continuous progression of all kinds of CKD. Because of the damage of renal parenchyma, the basic renal function cannot be maintained. Pregnancy is uncommon in patients with end-stage renal failure. Uremia-associated hypothalamic-pituitary dysfunction and malnutrition usually result in amenorrhea and anovulation, and thus disturbances in menstruation and fertility are commonly encountered in women with CRF, leading to a low pregnancy rate in these patients (6). In addition, due to the teratogenic effect of drugs the fertility of patients with kidney disease is reduced (3, 7). However, the number of pregnant women treated with long-term HD has been increasing recently. Even with unwanted pregnancy, achieving successful pregnancy in such patients is challenging as adverse pregnancy outcome including preeclampsia, FGR, preterm delivery and accelerated loss of maternal renal function is significantly increased with higher degrees of renal impairment (3, 8, 9). In addition, anemia, vitamin D deficiency and chronic hypertension are comorbidities that are associated with adverse pregnancy outcome and can develop secondary to underlying CKD (9). CKD may affect placental perfusion and lead to placental insufficiency (7, 10). Additionally, fetuses with placental insufficiency habitually shunt blood away from nonessential organs, such as kidneys, to decrease urine output and thus amniotic fluid volume, leading to oligohydramnios and even fetal distress (7). It is important to control anemia because it is a significant cause of left ventricular hypertrophy, heart failure and angina. As women with CKD may have insufficient capacity for a gestational increase in EPO production, supplementation with synthetic EPO may be required (9). The hematocrit should be optimized before surgery. The correction of anemia also helps to improve platelet dysfunction associated with renal failure (11). Hypertension is the most common life-threatening problem in these patients. Controlling hypertension is an

important part of CKD management during pregnancy and ideal blood pressure control should be optimized before pregnancy (3). The safety of antihypertensive drugs in pregnancy is based on historical, retrospective analyses and favours older classes of drugs, including the adrenergic receptor agonists labetalol and methyldopa and the calcium channel blocker nifedipine (9). Hyperkalemia is another important problem for patients with CRF. Hyperkalemia is usually induced by insufficient hemodialysis, acidosis, hypoxemia, and decreased body temperature. It is generally believed that preoperative fasting can reduce the level of potassium. However, a previous study found that the hormone response to fasting may transfer the potassium from the intracellular to the extracellular space (12). Therefore, close monitoring of electrolyte status during the perioperative period is necessary.

Due to presence of severe FGR and high induction rate for maternal indications like severe preeclampsia or worsening renal function, the incidence of cesarean section in pregnancy with CKD is higher (1). And the number of pregnant women with CRF requiring HD has increased recently. For patients undergoing cesarean section with HD, the choice of anesthetic methods and intraoperative management are very important. The primary task of the selection of anesthetic methods for such patients is to ensure the safety of the mother and the fetus, to minimize the adverse effects of pregnancy and kidney disease on mother and consequent effects on the fetus, and to avoid aggravating the renal failure of patients (13). Patients with CRF have a high risk of anesthesia, to help choose the appropriate anesthetic technique for such patients, a literature search of published case reports of pregnancy associated with CRF requiring HD was performed and listed in **Table 3**.

Regional anesthesia and general anesthesia are both used for cesarean delivery and both have advantages and disadvantages. It is important to clarify what type of anesthesia is more suitable for such patients. CKD may affect both the pharmacokinetics and the pharmacodynamics of a drug. In general anesthesia, there is a possibility of altered drug clearance leading to accumulation of active metabolites which could be nephrotoxic (18). And general anesthesia may lead to decreased renal blood flow in such patients, thus affecting drug clearance rate, duration of action and efficacy intensity (19). In addition, decreased gastric motility and delayed gastric emptying in parturients may increase the risk of aspiration during general anesthesia (11, 19). When general anesthesia is performed on patients with CKD, it is necessary to consider the effects of an altered clearance, the production and accumulation of active metabolites, and the risk of aggravating pre-existing kidney disease on drug administration (13). In addition, these neonates often have intrauterine growth retardation, low birth weight and premature delivery are prone to the adverse effects of anesthetic agents (13). Due to the rapid and predictable effects of general anesthesia, the majority being performed for lack of time in the setting of an emergency delivery such as severe fetal distress, or in cases of failure or contraindications of intrathecal anesthesia (20).

In cesarean delivery, regional anesthesia using spinal or epidural anesthesia is a safe technique to minimize the risk of fetal depression and aspiration pneumonia in the mother (13). Compared with general anesthesia, it is possible for regional anesthesia to establish a connection between the mother and newborn immediately after delivery. However, abnormal coagulation function in patients with CRF and long-term HD treatment may increase the risk of intrathecal anesthesia bleeding. There is no absolute contraindication to regional blocks in women with CRF undergoing HD. Some literatures have pointed out that if anticoagulants have been used during HD, at least six hours should elapse before siting a regional block (11, 16, 21). It is wise to confirm that clotting is normal by checking the APTT, PT and TEG. Spinal anesthesia is a safe technique for such women. The dosage of local anesthetic agents which are used for spinal anesthesia has been reported to exert no influence upon the baby (5). However, most cases of spinal anesthesia experience hypotension followed by decreased uterine blood flow (5), which in severe cases can cause dizziness, nausea and vomiting.

Compared with general anesthesia and spinal anesthesia, epidural anesthesia can be used for cesarean section after labor analgesia failure and for postoperative analgesia after cesarean section. In our case, B-ultrasound of both parturients

TABLE 3 | Pregnancy cases in patients with CRF requiring HD in review.

Author	Year	Gestation week	HD frequency	HD history (month)	Fetal weight(g)	Apgar Score	Anesthetic technique
Kobayashi (14)	1981	38 wk and 6 d	5/week	48	1,320	5–7	epidural anesthesia
Azuma (15)	1996	38 wk	4–6/week	120	2,575	8–9	spinal anesthesia
Masako (5)	2000	32 wk and 3 d	5/week	192	NR	8–9	general anesthesia
Dhir (10)	2007	36 wk	7/week	144	1,729	6–8	epidural anesthesia
Zencirci (11)	2010	37 wk and 5 d	3/week	36	2,220	6–8	spinal anesthesia
Fernandes (16)	2011	NR	3/week	2	2,000	–9	spinal anesthesia
Cao (17)	2018	31 wk and 4 d	3/week	48	1,700	8–10	general anesthesia
Zhang	This case	36 wk and 2 d	3/week	72	1,770	10-10	epidural anesthesia
Zhang	This case	33 wk and 5 d	5/week	72	1,885	9-9	epidural anesthesia

HD, hemodialysis; NR, not reported.

showed severe FGR, and one of the parturients was complicated with atrial septal defect. Compared with general anesthesia, epidural anesthesia can reduce venous return and alleviate the cardiac burden (22). In addition, epidural anesthesia is easier to maintain hemodynamic stability than spinal anesthesia (22). In order to avoid the effect of general anesthesia on maternal and fetal prognosis and unstable hemodynamic caused by spinal anesthesia, we chose epidural anesthesia. Previous literatures have pointed out that cesarean section under epidural anesthesia is safe for patients with heart disease (22, 23). However, before performing epidural anesthesia, attention must be paid to the coagulation function of CRF patients undergoing dialysis.

HD without heparin has long been used in maintenance dialysis patients with bleeding risk (24). In chronic HD patients with high risk of bleeding, heparin-free HD is now considered as a good option and recommended by anesthesiologists (25). In addition, thromboprophylaxis in these women was also important. The perioperative management for the two patients including thromboprophylactic agent administration was based on the collaboration of a multidisciplinary team (MDT), which was comprised of obstetrician, nephrologist, cardiologist, anesthesiologist and neonatologist. According to the suggestion of the experts in the MDT, the two patients had a relatively low risk for venous thromboembolism (VTE) during pregnancy and after surgery. Furthermore, coagulation tests and ultrasonography revealed no signs of VTE. As a result, thromboprophylactic agent was not administered during perioperative period. In our case, heparin-free dialysis was performed one day before the operation. After the preoperative examination confirmed that the blood coagulation function and internal environment were normal, the cesarean section was successfully completed under epidural anesthesia. No complications of epidural anesthesia occurred in the postoperative follow-up, and their renal function were stable. It is suggested that with careful and effective monitoring preoperatively and intraoperatively, epidural anesthesia can be safely performed for cesarean section in patients undergoing heparin-free HD.

CONCLUSION

Renal disease, either preexisting or occurring during pregnancy may impair maternal and fetal health. Although the number of pregnant women undergoing HD is rare, the risk of anesthesia is extremely high and there are multiple anesthetic considerations in such parturients. The choice of anesthesia for such patients should be made on an individual basis. Based on our cases, we consider that epidural anesthesia is safe to the patients with CRF requiring HD if there are no coagulation abnormalities. And heparin-free HD is considered as a good option for such patients to reduce the risk of bleeding during the perioperative period. However, the number of cases in this study is small, and a large number of studies are required to determine the safety of epidural anesthesia for such patients. In addition, since the condition of two patients remained stable, the central venous pressure was not monitored during the operation. if possible, it is necessary to strengthen intraoperative hemodynamic monitoring. In short, by perfecting relevant examinations before operation, correcting patient's internal environment and blood coagulation function and closely monitoring during the operation, the patient can still achieve a good outcome.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

TZ was responsible for reviewing publications and drafting of the manuscript. XX, YJ and HC were responsible for drafting of the manuscript and collecting the relevant data. JJ was responsible for the conception of the review, supervision, and critical revision of the manuscript. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Bharti J, Vatsa R, Singhal S, Roy KK, Kumar S, Perumal V, et al. Pregnancy with chronic kidney disease: maternal and fetal outcome. *Eur J Obstet Gynecol Reprod Biol.* (2016) 204:83–7. doi: 10.1016/j.ejogrb.2016.07.512
2. Confortini P, Galanti G, Ancona G. Full term pregnancy and successful delivery in a patient on chronic hemodialysis. *Proc Eur Dial Transpl Assoc.* (1971) 8:74–80.
3. Hui D, Hladunewich MA. Chronic Kidney Disease and Pregnancy. *Obstet Gynecol.* (2019) 133:1182–94. doi: 10.1097/AOG.0000000000003256
4. Kendrick J, Sharma S, Holmen J, Palit S, Nuccio E, Chonchol M. Kidney disease and maternal and fetal outcomes in pregnancy. *Am J Kidney Dis.* (2015) 66:55–9. doi: 10.1053/j.ajkd.2014.11.019
5. Otani M, Niwa H, Amaki Y. Anesthetic management of a parturient with a diagnosis of chronic renal failure for cesarean section. *J Anesth.* 14:35–7. doi: 10.1007/s005400050007
6. Hou S. Pregnancy in women treated with dialysis: lessons from a large series over 20 years. *Am J Kidney Dis Off J Natl Kidney Found.* (2010) 56:5–6. doi: 10.1053/j.ajkd.2010.05.002
7. Yu P, Diao W, Tang Q, Jiang X. A successful pregnancy and parturition in a patient with anuria undergoing maintenance hemodialysis for 6 years: a case report of a 3-year-follow-up. *BMC Pregnancy Childbirth.* (2015) 15:218. doi: 10.1186/s12884-015-0642-9
8. Davison JM. Chronic renal disease in pregnancy. *Obstet Gynaecol.* (2011) 1:29–32. doi: 10.1576/toag.1999.1.2.29
9. Wiles KS, Nelson-Piercy C, Bramham K. Reproductive health and pregnancy in women with chronic kidney disease. *Nat Rev Nephrol.* (2018) 14:165–84. doi: 10.1038/nrneph.2017.187
10. Dhir S, Fuller J. Case report: Pregnancy in hemodialysis-dependent end-stage renal disease: anesthetic considerations. *Can J Anesth.* (2007) 54:556–60. doi: 10.1007/BF03022320
11. Zencirci B. Safe spinal anesthesia in a woman with chronic renal failure and placenta previa. *Int J Gen Med.* (2010) 3:153–6. doi: 10.2147/ijgm.s11421
12. Trainor D, Borthwick E, Ferguson A. Perioperative Management of the Hemodialysis Patient. *Semin Dial.* (2011) 24:314–26. doi: 10.1111/j.1525-139X.2011.00856.x
13. Modi MP, Vora KS, Parikh GP, Shah VR, Misra V V, Jasani AF. Anesthetic management in parturients with chronic kidney disease undergoing elective

Caesarean delivery: our experience of nine cases. *Indian J Nephrol*. (2014) 24:20–3. doi: 10.4103/0971-4065.125051
14. Kobayashi H, Matsumoto Y, Otsubo O, Otsubo K, Naito T. Successful pregnancy in a patient undergoing chronic hemodialysis. *Obstet Anesth Dig*. (1981) 1:113. doi: 10.1097/00132582-198112000-00018
15. Azuma K, Nakamoto T, Terai T, Nishikawa K, Fujimori M. [Cesarean section under spinal anesthesia for a patient with chronic renal failure]. *Masui Japanese J Anesthesiol*. (1996) 45:880.
16. Fernandes SD, Suvarna D. Anesthetic considerations in a patient of autosomal dominant polycystic kidney disease on hemodialysis for emergency cesarean section. *J Anaesthesiol Clin Pharmacol*. (2011) 27:400–2. doi: 10.4103/0970-9185.83694
17. Cao Y, Zhang Y, Wang X, Zhang Y, Fan Y, Shi H, et al. Successful pregnancy and delivery in uremic patients with maintenance hemodialysis: A case report. *Med (United States)*. (2018) 97:13614. doi: 10.1097/MD.0000000000013614
18. Kapoor H, Krishnan KP, Rajeev K. Anesthetic management for cesarean section in chronic renal failure. *J Obstet Anaesth Crit Care*. (2014) 4:81. doi: 10.4103/2249-4472.143878
19. Devroe S, Van De Velde M, Rex S. General anesthesia for caesarean section. *Curr Opin Anaesthesiol*. (2015) 28:240–6. doi: 10.1097/ACO.0000000000000185
20. Palanisamy A, Mitani AA, Tsen LC. General anesthesia for cesarean delivery at a tertiary care hospital from 2000 to 2005: a retrospective analysis and 10-year update. *Int J Obstet Anesth*. (2011) 20:10–6. doi: 10.1016/j.ijoa.2010.07.002
21. Horlocker TT, Wedel DJ, Benzon H, Brown DL, Kayser Enneking F, Heit JA, et al. Regional anesthesia in the anticoagulated patient: defining the risks (The Second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). In: *Regional anesthesia and pain medicine*. W.B. Saunders. p. 172–97. doi: 10.1053/rapm.2003.50046
22. Gu J, Cai Y, Liu B, Lv S. Anesthetic management for cesarean section in a patient with uncorrected double-outlet right ventricle. *Springerplus*. (2016) 5:415. doi: 10.1186/s40064-016-2075-y
23. Aspi MTB, Ocsan PMF. The use of point-of-care assessments and advanced hemodynamic monitoring in a patient with Eisenmenger syndrome for cesarean section: a case report. *Int J Surg Case Rep*. (2021) 89:106601. doi: 10.1016/j.ijscr.2021.106601
24. Schwab SJ, Onorato JJ, Sharar LR, Dennis PA. Hemodialysis without anticoagulation. One-year prospective trial in hospitalized patients at risk for bleeding. *Am J Med*. (1987) 83:405–10. doi: 10.1016/0002-9343(87)90748-0
25. Brunot V, Serre JE, Mourad G, Klouche K, Pernin V. Heparin-free renal replacement therapy for chronic hemodialyzed patients at high risk for bleeding: a comparison of on-line predilution hemodiafiltration with conventional hemodialysis. *Hemodial Int*. (2018) 22:463–73. doi: 10.1111/hdi.12668

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Does Dysmenorrhea Affect Clinical Features and Long-Term Surgical Outcomes of Patients With Ovarian Endometriosis? A 12-Year Retrospective Observational Cohort Study

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Background: To examine and compare the differences in clinical characteristics and long-term postoperative outcomes of ovarian endometriomas (OMA) patients with and without dysmenorrhea, including data from at least 8 years of postoperative follow-up examinations.

Methods: Retrospective analysis of 334 OMA patients, including their demographic and clinical data. Long-term follow-up record was also collected. All laparoscopic cystectomy procedures were performed by the same surgeon at Peking Union Medical College Hospital between January 2009 and April 2013. Patients were divided into the dysmenorrhea and non-dysmenorrhea groups to perform the analysis of their preoperative characteristics, relevant surgical findings, and postoperative outcomes at the follow-up.

Results: Out of 334 OMA patients, 257 (76.9%) patients were allocated to the dysmenorrhea group, while the rest 77 (23.1%) patients were included in the non-dysmenorrhea group. Compared with the dysmenorrhea group, the non-dysmenorrhea group exhibited a reduced proportion of chronic pelvic pain (CPP) ($P = 0.003$), dyspareunia ($P < 0.001$), tenesmus ($P < 0.001$), concurrency of deep infiltrating endometriosis (DIE) ($P < 0.001$), and adenomyosis ($P = 0.032$). Preoperative infertility was significantly higher in the dysmenorrhea group ($P = 0.001$). The mean operating time in the dysmenorrhea vs. the non-dysmenorrhea group was 68.0 vs. 56.0 min ($P < 0.001$). According to the revised American Fertility Society (rAFS) scoring system, the mean scores of the two groups were 52.1 vs. 44.6 ($P = 0.033$). During follow-up, the dysmenorrhea group showed a higher rate of disease relapse ($P < 0.001$). A minimum postoperative follow-up period of 8 years was required to evaluate the pregnancy outcomes. Successful pregnancies were identified in 97/257 (37.7%) cases in the dysmenorrhea

group and 36/77(46.8%) cases in the non-dysmenorrhea group ($P = 0.157$), respectively. Though the dysmenorrhea group had a higher rate of postoperative infertility, differences were not significant between the two groups.

Conclusions: Compared with the dysmenorrhea group, OMA patients without dysmenorrhea exhibited lower proportions of CPP, dyspareunia, tenesmus, lower concurrency of DIE and adenomyosis, shorter mean operating time, lower mean rAFS scores, and lower infertility rates. During the long-term follow-up, a lower recurrence rate was observed in the non-dysmenorrhea group. Regarding fertility outcomes, non-dysmenorrhea patients had a higher likelihood of successful pregnancy after surgery. Postoperative management needs to be evaluated separately according to dysmenorrhea pathology.

Keywords: endometriosis, dysmenorrhea, pregnancy rate, laparoscopic cystectomy, recurrence rate, postoperative outcomes

INTRODUCTION

Endometriosis (EM), characterized by the abnormal or ectopic growth of stroma and endometrial glands outside the uterus (1), accounts for an estimated prevalence of 10–15% in females of reproductive age (2). Most EM lesions can be classified into 3 subtypes based on their locations and histological characteristics, including deep infiltrating endometriosis (DIE), cystic ovarian endometriosis/endometrioma (OMA), and superficial peritoneal endometriosis (SUP) (3). In some rare cases, endometriosis lesions can also appear in external pelvic sites such as skin and nasal cavity (4). Amongst EM lesion types, OMA is the most observed phenotype, accounting for 17–44% of EM cases. Laparoscopic cystectomy, the gold standard for OMA diagnosis, is also recommended as the first-line therapy (5–7).

Dysmenorrhea, together with infertility, constitutes the major clinical complication in OMA patients (8, 9). However, about 17–39% of OMA patients do not present any complaint of dysmenorrhea (10–12). Hence, whether dysmenorrhea symptoms would correlate with clinical characteristics and postoperative outcomes in this subset of OMA patients remain unclear.

METHODS

This study was performed in the Department of Obstetrics and Gynecology of the Peking Union Medical College Hospital (PUMCH), with prior approval from the Medical College Ethics Committee (JS-1722).

This study included OMA patients who received laparoscopic cystectomy at PUMCH between January 2009 and April 2013. All operations were performed by the same EM-specialized surgery team. The inclusion criteria were as follows: (1) patients were surgically treated in our hospital; (2) postoperative histopathological diagnosis of EM; (3) availability of complete clinical and pathological reports, and (4) participating patients were pre-menopausal. Cases, where patients had undergone similar surgeries in other hospitals were excluded from the analysis. Patients were also excluded if they were pregnant, had malignant gynecological diseases, or received any hormonal therapy (gonadotropin-releasing hormone analog, GnRHa; oral contraceptives, OCs, or levonorgestrel intrauterine system, mirena) within 3 months before the surgery.

The standard laparoscopic cystectomy surgery was executed as follows: (1) the extent of EM lesions and pelvic adhesions were identified by a thorough clinical inspection; (2) identifiable peritoneal implants were coagulated; (3) attempts were made to restore the normal anatomy as much as possible, and (4) ovarian cysts were carefully stripped off avoiding accidental damage to the surrounding healthy tissue. Regarding the surgery report of EM laparoscopy, the presence of lesions, anatomical location, the extent of subtle lesions and typical powder burns, pelvic adhesions, and the occurrence of deep infiltrating implants were recorded. The rAFS scoring system was applied to score patients along with the EM staging (13). DIE was diagnosed histologically if the lesion infiltrated >5 mm under the peritoneal surface. Visual analogique scale (VAS) was employed to evaluate the severity of pain symptom. VAS score$\geq$3 was defined as dysmenorrhea.

According to these criteria, a total of 334 patients were pathologically diagnosed with OMA. Diagnosis of adenomyosis was confirmed when at least three or more of the following ultrasound features were present–globular-appearing uterus (regular enlarged uterus), the asymmetrical thickness of the anteroposterior wall of the myometrium, heterogeneous myometrial echotexture (presence of an indistinctly myometrial area with decreased or increased echogenicity), sub endometrial echogenic linear striations (radiate pattern of thin acoustic shadowing not arising from echogenic foci), sub endometrial myometrial cysts (round anechoic areas of 1–7 mm diameter), or poor definition of the endometrial-myometrial junction, as described elsewhere (14–18). Patients who received biopsy or myomectomy during the surgery were identified to have adenomyosis by the postoperative histopathology.

The size of the OMA was defined as the largest diameter of cysts measured by ultrasound examinations. The elevated serum CA-125 level was defined as >35 U/ml, per the clinical laboratory references at PUMCH. The possibility of infertility in women

was diagnosed when the patient was unable to conceive for more than 1 year despite having a normal sex life without using any contraceptives, after ruling out any male etiological factors of infertility.

Clinical indications of eligible patients were retrospectively recorded and analyzed after thoroughly scrutinizing patients' medical records. The following demographic and medical information were retrieved: body mass index (BMI); age; parity; history of surgery; symptoms of dyschezia, dyspareunia, dysmenorrhea, dysuria; location of cysts; the size of EM lesion; serum CA-125 level; intraoperative blood loss; operating time, and rAFS stage. As the postoperative management, patients with fertility needs received a short-term GnRHa course of 3–6 injections or oral contraceptives. Furthermore, for those without fertility requirements, long-term therapy was recommended using Mirena (levonorgestrel intrauterine system) alone or a combination of GnRHa and Mirena. In the long-term therapy, it could be possible that some patients did not follow the exact time course of the treatment.

All patients were examined and followed up as per our internal protocol. A transvaginal ultrasound along with a standard gynecological examination was conducted for each patient before surgery, at 3, 6, and 12 months post-surgery, then yearly for the long-term follow-up. Menstrual fertility factors and pain symptoms were also evaluated. Patients were interviewed to reveal if they experienced any dysmenorrhea, dyspareunia, or pelvic pain symptoms during the follow-up. Pain recurrence was considered if it recurred after 3 months of surgery. Endometrioma was defined as the persistent presence of ovarian cysts with a thin wall (with a diameter of at least 2 cm), a homogenous low echogenic fluid content with scattered internal echoes regular margins, and persisted even after successive cycles of menstruation. Endometriosis recurrence was identified when pain, endometrioma, or both were noted at the follow-up ultrasound and physical examinations. The long-term postoperative follow-up information included postoperative medications, infertility and related symptoms, recurrence time, and imaging results.

Based on the diagnosis, patients were divided into either the dysmenorrhea or non- dysmenorrhea group to analyze and compare their demographic and clinical baseline characteristics, surgical observations, and postoperative outcomes during the follow-up examinations. Statistical analyses were performed using the IBM SPSS 25.0 software. The Kruskal-Wallis test was applied to analyze continuous variables, while categorical variables were analyzed using the chi-square test or Fisher's exact test. The Kaplan-Meier survival plots were constructed to measure recurrence rates. All statistical tests were two-sided, and $P < 0.05$ was set to identify the statistical significance of the result.

RESULTS

Out of 334 OMA patients participating in this study, 257 (76.9%) patients were included in the dysmenorrhea, and the remaining 77(23.1%) patients were in the non-dysmenorrhea group. Comparisons of clinical features and demographic features between these two groups are shown in **Table 1**.

TABLE 1 | Comparison of demographic and clinical characteristics.

Characteristic/group	Non-dysmenorrhea	Dysmenorrhea	*P*-value
Number (%)	77(23.1%)	257 (76.9%)	-
Mean age, y	32.69 ± 5.50	32.74 ± 5.23	0.941
BMI(Kg/m^2)	21.01 ± 2.71	21.15 ± 2.60	0.696
Gravidity	1.09 ± 1.49	0.96 ± 1.21	0.433
Parity	0.33 ± 0.50	0.33 ± 0.50	0.958
CPP (%)	4 (5.19%)	50 (19.53%)	0.003
Dyspareunia (%)	5 (6.49%)	72 (28.12%)	<0.001
Tenesmus (%)	7 (9.09%)	75 (29.30%)	<0.001
Dyschizia (%)	2 (2.60%)	23 (8.98%)	0.062
CA-125, U/ml	81.92 ± 107.67	101.80 ± 219.75	0.454
Elevated CA-125 (%)	51 (68.00%)	175 (73.22%)	0.380
Infertility			0.010
No	70 (90.91%)	200 (77.82%)	
Infertility	7 (9.09%)	57 (22.18%)	
Size of OMA, cm			-
Left	5.57 ± 2.19	5.32 ± 2.07	0.424
Right	5.67 ± 1.68	5.22 ± 1.96	0.115
Leiomyoma (%)	14 (18.18%)	46 (18.04%)	0.977
Adenomyosis (%)	22 (28.57%)	108 (42.19%)	0.032

Between the dysmenorrhea and non-dysmenorrhea groups, the mean age, mean gravidity, and mean parity were 32.74 vs. 32.69 years ($P = 0.941$), 0.96 ± 1.21 vs. 1.09 ± 1.49 ($P = 0.433$), and 0.33 ± 0.50 vs. 0.33 ± 0.50 ($P = 0.958$), respectively. The CPP symptom was diagnosed in 50 (19.53%) vs. 4 (5.19%) cases in the dysmenorrhea vs. non-dysmenorrhea group ($P = 0.003$). Menstrual tenesmus was reported in 75 (29.30%) dysmenorrhea vs. 7 (9.09%) non-dysmenorrhea patients ($P < 0.001$). Dyspareunia was observed in 72 (28.12%) vs. 5 (6.49%) cases between the groups ($P < 0.001$). Dyschizia was complained in 23 (8.98%) dysmenorrhea vs. 2 (2.60%) non-dysmenorrhea patients ($P = 0.062$). The mean levels of CA-125 were found 101.80 vs. 81.92 U/ml ($P = 0.454$) in these groups, while elevated levels of CA-125 were detected in 175 (73.22%) vs. 51 (68.00%) patients ($P = 0.380$) in the dysmenorrhea vs. non-dysmenorrhea groups. Moreover, 108 (42.19%) vs. 22 (28.57%) cases were clinically diagnosed with adenomyosis in the dysmenorrhea vs. non-dysmenorrhea group ($P = 0.032$). The pre-surgery infertility was diagnosed in 57 (22.18%) vs. 7 (9.09%) cases in the dysmenorrhea vs. non-dysmenorrhea group ($P = 0.010$).

All patients received laparoscopic cystectomy, and the diagnosis of OMA was histopathologically determined. The pelvic cavity was carefully explored to remove or coagulate any visible peritoneal implants. DIE lesions were radically removed during the procedure. Intraoperative situations are listed in **Table 2**.

Between the dysmenorrhea and non-dysmenorrhea groups, the mean surgery time was 68.0 vs. 56.0 min ($P < 0.001$), and

TABLE 2 | Surgical situations.

Characteristic/group	Non-dysmenorrhea	Dysmenorrhea	*P*-value
Operating time, min	56.0 ± 18.0	68.0 ± 21.3	<0.001
Mean bleeding volume, ml	39.7 ± 25.9	54.3 ± 57.7	0.032
DIE (%)	28 (36.4%)	150 (58.4%)	<0.001
Closed Douglas pouch (%)	43 (55.8%)	198 (77.0%)	<0.001
Multilocular (%)			-
Left	33 (70.2%)	118 (83.1%)	0.056
Right	36 (66.7%)	122 (73.5%)	0.333
rAFS score	44.6 ± 25.1	52.1 ± 25.2	0.033
Stage (%)			0.095
I	1 (1.3%)	0 (0.0%)	
II	2 (2.6%)	8 (3.1%)	
III	35 (45.5%)	90 (35.0%)	
IV	39 (50.6%)	159 (61.9%)	
Pelvic Endometriosis (%)			0.002
No	20(30.8)	33(19.0%)	
Peritoneal EM	29(44.6)	51(29.3)	
DIE	16(24.6)	81(46.6)	
Peritoneal EM+DIE	0	9(3.8)	
SUP (%)			0.857
Single	9 (26.47%)	25 (28.09%)	
Multiple	25 (73.53%)	64 (71.91%)	
SUP position (%)			
Broad ligament	5 (14.71%)	16 (17.98%)	0.666
Uterosacral ligament	22 (64.71%)	64 (71.91%)	0.436
Bladder peritoneal reflex	3 (8.82%)	11 (12.36%)	0.581
Ureter	4 (11.76%)	4 (4.49%)	0.144
Rectum	4 (11.76%)	7 (7.87%)	0.498
Uterus	5 (14.71%)	13 (14.61%)	0.989

TABLE 3 | Concurrent pelvic endometriosis conditions.

Characteristic/group	Non-dysmenorrhea	Dysmenorrhea	*P*-value
Pelvic EM (%)			
No	20(40.8)	33(39.3)	0.862
Peritoneal EM	29(49.2)	51(61.7)	
No	20(55.6)	33(28.9)	0.004
DIE	16(44.4)	81(71.1)	
No	20(100)	33(78.6)	0.025
Peritoneal EM+DIE	0	9(21.4)	
Peritoneal EM	29(64.4)	51(38.6)	0.003
DIE	16(35.6)	81(61.4)	
Peritoneal EM	29(100)	51(85)	0.028
Peritoneal EM+DIE	0	9(15)	
DIE	16(100)	81(90)	0.186
Peritoneal EM+DIE	0	9(10)	

TABLE 4 | Postoperative outcomes.

Characteristic/group	Non-dysmenorrhea	Dysmenorrhea	*P*-value
Follow-up time, m	120.64 ± 15.29	120.47 ± 14.43	0.929
Postoperative therapy (%)			0.001
No treatment	6 (7.8%)	4 (1.6%)*	
GnRHa	49 (63.6%)	187 (72.7%)	
OCs	8(10.4%)	4(1.6%)*	
Mirena	2(2.6%)	11(4.3%)	
GnRHa+Mirena	12(15.6%)	51(19.8%)	
Treatment regimen			0.40
Short-term treatment	57(80.3%)	191(75.5%)	
Long-term treatment	14(19.7%)	62(24.5%)	
Recurrence (%)	3 (3.9%)	62 (24.1%)	<0.001
Type of recurrence (%)			<0.001
No	74 (96.1%)	195 (75.9%)	
Pain	0 (0.0%)	34 (13.2%)	
Endometrioma	3 (3.9%)	18 (7.0%)	
Both	0 (0.0%)	10 (3.9%)	
Pregnancy after surgery (%)			0.051
Spontaneous Pregnant	33(42.9%)	75(29.1%)*	
Artificial Pregnant	3(3.9%)	22(8.6%)	
Failed	41 (53.2%)	160 (62.3%)	
Pregnancy outcome in infertility patients(%)			0.52
Failed	3(42.9%)	24(42.1%)	
Spontaneous	4(57.1%)	23(40.4%)	
Artificial	0	10(17.5%)	

**Indicates the proportion of two groups are significantly different from each other ($p < 0.05$).*

the mean bleeding volume was 39.7 vs. 54.3 ml ($P = 0.032$). No significant differences were noticed between the two groups ($P > 0.05$) in the mean size of cysts and their laterality, as well as the percentage of multilocular cysts. During laparoscopy, 150 (58.4%) vs. 28 (36.4%) cases were diagnosed with the DIE in the dysmenorrhea vs. non-dysmenorrhea group ($P < 0.001$). Peritoneal endometriosis was observed in 123 patients. The position and invasion quantity of SUP revealed no significant differences among groups. The mean rAFS scores were 52.1 and 44.6 ($P < 0.033$) in the dysmenorrhea and non-dysmenorrhea groups, without any significant differences in stages ($P = 0.095$).

We examined the concurrency of pelvic EM in OMA patients, excluding the influence of adenomyosis. Subgroup comparison revealed concurrent DIE had a strong effect on dysmenorrhea (**Table 3**).

For the whole study group, all patients had a minimum of 96 months of outpatient follow-up. No significant difference was seen in the follow-up time between the dysmenorrhea and non-dysmenorrhea groups (120.47 vs. 120.64 months; median: 119.45 months; $P = 0.929$). Postoperative outcomes are shown in **Table 4**.

In this study, 324 patients received postoperative medical therapy, including 253 (253/257, 98.4%) dysmenorrhea patients and 71 (71/77, 92.2%) non-dysmenorrhea patients ($P = 0.005$). The difference between treatment regimens in the two groups was non-significant ($P = 0.40$). GnRHa was the most commonly used postoperative treatment in both two groups. No significant differences were noticed between the two groups in the proportion of postoperative GnRHa administration. A higher proportion of non-dysmenorrhea patients had no postoperative medical treatment (7.8% vs. 1.6%).

Successful pregnancy cases were identified in 97/257 (37.7%) patients in the dysmenorrhea group vs. 36/77 (46.8%) patients in the non-dysmenorrhea group ($P = 0.157$) after at least 8 years of follow-up. Successful pregnancy and live births, including both *in vitro* fertilization (IVF-ET) and spontaneous pregnancy, were observed in 93/97 (95.9%) vs. 36/36 (100%) patients comparing the dysmenorrhea vs. non-dysmenorrhea groups, while spontaneous abortions were reported in the remaining patients. In all 64 patients who were preoperatively diagnosed with infertility, 37 patients got pregnant after surgery. Twenty-seven patients achieved spontaneous pregnancy while 10 patients undergone ART. In the non-dysmenorrhea group, 4 patients (57.1%) had spontaneous pregnancy after surgery, and 3 patients (42.9%) remained infertile. In dysmenorrhea group, 23 patients (40.4%) had spontaneous pregnancy, 10 patients (17.5%) conceived artificially, 24(42.1%) patients remain infertile.

The recurrence rate of the dysmenorrhea group was significantly higher than that of the non-dysmenorrhea group (24.1% vs. 3.9%, $P < 0.001$) after completion of the follow-up. Moreover, the 5-year cumulative recurrence rate was 17.9% vs. 3.9% in these two groups ($P = 0.00014$).

DISCUSSION

EM is usually diagnosed as an estrogen-dependent benign medical condition found in 10–15% of women in their reproductive ages. OMA lesions are mostly detected among all EMs. Laparoscopic cystectomy is regarded as the first line of treatment in EM management (19). Here, we investigated the clinical characteristics of EM patients with or without dysmenorrhea, involving a regular follow-up for 8–12 years, which showed women without dysmenorrhea had a lower recurrence rate.

The EM symptoms widely vary among individual subjects and disease stages (20), including pain symptoms (dysmenorrhea, dyspareunia, chronic pelvic pain), and infertility. Pain is the most important symptom in patients with EM, but underlying mechanisms remain unclear. Several pathophysiological hypotheses had been proposed in this regard, such as hormone-regulated neuro-vascular pathology (21); estrogen-dependent chronic inflammation in the presence of ectopic endometrial tissue invasions (22, 23); increased prostaglandin level, and lowered threshold of pain perception due to sensitization of nerve endings (24, 25); compression and infiltration of adjacent nerves (26), and relatively higher density of nerve fibers due to increased expressions of nerve growth factors, angiogenesis, and pathological changes leading to nerve innervation into the uterus, may contribute to the central and cross-organ sensitizations (27–30). Despite dysmenorrhea being a common clinical symptom in EM patients, we noticed that some patients diagnosed with EM did not present with dysmenorrhea. Clinical features and long-term postoperative outcomes of non-dysmenorrhea patients have not been investigated to date.

In this study, we found that 23.1% of OMA patients manifested no dysmenorrhea, which was in agreement with previous findings that 17–39% of OMA patients could be non-dysmenorrhea (10–12). According to our results, baseline characteristics such as age, BMI, parity, and gravidity showed no difference between the two groups. Patients in the dysmenorrhea group were associated with relatively higher proportions of CPP, dyspareunia, and tenesmus. The concurrency rates of adenomyosis and DIE were also higher in the dysmenorrhea group. There is accumulating evidence indicating that the presence of adenomyosis and DIE are strongly associated with dysmenorrhea (31, 32). Endometriosis, in particular DIE, was also proved to aggravate tenesmus by causing pelvic floor dysfunctions (33). It might further suggest that an increased number of patients in the dysmenorrhea group had DIE and adenomyosis, and this also explains the reason for frequently observed CPP, dyspareunia, and tenesmus symptoms in this group.

Several studies have reported that DIE patients present more severe sexual dysfunctions and dyspareunia (34), and the depth and number of infiltration are associated with the dysmenorrhea severity (32, 35, 36). We initially analyzed the location and size of the concurrent pelvic EM, including SUP and DIE. Concurrent DIE was associated with dysmenorrhea. There was no significant difference in the invasive position and number of peritoneal EM between the dysmenorrhea and non-dysmenorrhea groups. Subgroup analysis also revealed that DIE was the key factor determining the occurrence of dysmenorrhea.

Surgery is the primary treatment option for OMA patients. Our results showed that the mean operating time was significantly longer in the dysmenorrhea group. Also, the mean bleeding volume and mean rAFS score were significantly higher in the dysmenorrhea group than that in the non-dysmenorrhea group.

In this study, 324 patients received postoperative pharmacological therapy. In some centers, oral contraceptives or progesterone pills are first-line postoperative therapy to prevent endometriosis recurrence (37, 38). We noticed that GnRHa was the most commonly used postoperative treatment in our center for both patients with and without dysmenorrhea. Patients without dysmenorrhea had a higher proportion of no medical therapy after surgery. Despite the higher rate of postoperative observation, a lower recurrence rate was observed in non-dysmenorrhea patients during the long-term follow up. These results suggest that the risk of EM recurrence is affected not only by postoperative medication but also by the clinical features of the disease.

The possible reason of high recurrence rate in the dysmenorrhea group might also be the concurrence of peritoneal EM and DIE in this subset of patients. Previous research had revealed that patients who received radical surgery of rectosigmoid DIE lesions showed lower suspected recurrence rates than patients who accepted conservative surgery (39). DIE lesions are often difficult to remove completely during surgery, and invisible SUPs are almost impossible to remove by surgery, which might have contributed to higher postoperative recurrence rates in the dysmenorrhea group.

Importantly, patients in the dysmenorrhea group exhibited a higher rate of preoperative infertility compared with patients in the non-dysmenorrhea group. About one-third of women with EM suffer from infertility, which is approximately twice the rate in women without EM pathology (40). It has been suggested that the extent of disease progression and the degree of reduced spontaneous fertility in EM patients could be interrelated, but the strength of this association is not well-defined. In comparison to OMA and DIE, SUP lesions are more closely associated with infertility (41). In our study, patients in the dysmenorrhea group showed higher proportions of SUP and DIE lesions, along with higher rAFS scores, indicating the occurrence of more severe intraoperative pelvic adhesions in this group of patients. Severe pelvic adhesions may distort the dissection of fallopian tubes, thereby affecting the patient's pregnancy.

At least 8 years of the post-surgical follow-up period was required for patients to reveal the actual pregnancy outcomes. We found that non-dysmenorrhea patients had a higher postoperative pregnancy rate, especially spontaneous pregnancy rate, than dysmenorrhea patients. It suggested that non-dysmenorrhea patients had better long-term pregnancy outcomes. As previously analyzed, patients with dysmenorrhea are usually closely related to the presence of DIE and adenomyosis, and they usually have higher rAFS scores. These patients have more severe pelvic adhesions and a more common inflammatory environment in the pelvic cavity. The presence of adenomyosis also interferes with embryo implantation and endometrial receptivity, which further affects the patient's long-term pregnancy outcomes. Importantly, patients in the dysmenorrhea group exhibited a higher rate of preoperative infertility compared with patients in the non-dysmenorrhea group. It could also be explained by the higher proportion of pelvic adhesions and adenomyosis in the dysmenorrhea group. As for postoperative long-term pregnancy outcomes, over half of the patients with a preoperative diagnosis of infertility had pregnancy after surgical procedure. Although there was no significant difference, patients in the non-dysmenorrhea group demonstrated a higher proportion of spontaneous pregnancies than those with dysmenorrhea. Previous studies had revealed that endometrioma cystectomy may have benefits on the chances of spontaneous conception (42). Cystectomy for endometrioma has certain effect on ovarian reserve function. Nevertheless, these negative effects of endometriosis do not reflect on pregnancy and delivery rates, which remain fully comparable and overlap with other causes of infertility (43, 44). Our result is consistent with previous research and further illustrates the relationship between postoperative pregnancy outcomes and dysmenorrhea.

As far as we are aware, the major strength of our study is that compared with previous studies, our data were collected after a real long-term follow-up, which was 8–12 years. For our patients, all the surgeries were performed primarily by one surgeon, which can eliminate many inherent confounding factors like introducing selection bias. This study also has some limitations. As a retrospective study, the main limitations of our study were recall bias. An observational design means that causal relationships cannot be established between factors and outcomes. At the same time, as a retrospective study of patients with a single surgeon in a single-center, some results may not be generalizable to a larger population. Considering the limitations of this study, in future investigations, multiple prospective studies involving non-dysmenorrhea patients are warranted to develop predictive models for clinicians toward a better understanding of the treatment strategies and prognosis.

CONCLUSIONS

In this study, we summarized the clinical characteristics, surgical findings, and postoperative outcomes of OMA patients without dysmenorrhea in a long-term follow-up. Compared with dysmenorrhea, non-dysmenorrhea was significantly correlated with a lower proportion of CPP, dyspareunia, tenesmus, lower concurrency of DIE, adenomyosis, shorter operating time, a lower rAFS score, and lower infertility rate.

Also, non-dysmenorrhea patients exhibited a significantly lower rate of recurrence during the long-term follow-ups. Therefore, gynecologists should pay special attention to the clinical features of OMA patients. Non-dysmenorrhea patients have milder surgical difficulties and lower postoperative recurrence rates. The postoperative treatments need to be discussed separately.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Peking Union Medical College Hospital Review Board, reference number: JS-1532. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Material preparation and data collection were completed by YW and XL. Data analysis was performed by

YW. The first draft of the manuscript was written by YW and XL. All authors commented on previous versions of the manuscript, contributed to the study conception and design, and approved publication of the final version.

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REFERENCES

1. Berveiller P, Ropert S, Mir O. Endometriosis. *N Engl J Med.* (2020) 383:193–4. doi: 10.1056/NEJMc2013221
2. Zondervan KT, Becker CM, Missmer SA. Endometriosis. *N Engl J Med.* (2020) 382:1244–56. doi: 10.1056/NEJMra1810764
3. Chapron C, Marcellin L, Borghese B, Santulli P. Rethinking mechanisms, diagnosis and management of endometriosis. *Nat Rev Endocrinol.* (2019) 15:666–82. doi: 10.1038/s41574-019-0245-z
4. Mignemi G, Facchini C, Raimondo D, Montanari G, Ferrini G, Seracchioli R, et al. case report of nasal endometriosis in a patient affected by Behcet's disease. *J Minim Invasive Gynecol.* (2012) 19:514–6. doi: 10.1016/j.jmig.2012.03.005
5. Giudice LC. Clinical practice. *Endometriosis N Engl J Med.* (2010) 362:2389–98. doi: 10.1056/NEJMcp1000274
6. Falcone T, Flyckt R. Clinical management of endometriosis. *Obstet Gynecol.* (2018) 131:557–71. doi: 10.1097/AOG.0000000000002469
7. Peiris AN, Chaljub E, Medlock D. Endometriosis. *JAMA*. (2018) 320:2608. doi: 10.1001/jama.2018.17953
8. Brawn J, Morotti M, Zondervan KT, Becker CM, Vincent K. Central changes associated with chronic pelvic pain and endometriosis. *Hum Reprod Update.* (2014) 20:737–47. doi: 10.1093/humupd/dmu025
9. Ziegler D, Borghese B, Chapron C. Endometriosis and infertility: pathophysiology and management. *Lancet.* (2010) 376:730–8. doi: 10.1016/S0140-6736(10)60490-4
10. Ye M, Guo H, Han J, He H, Zhang K, Xiong G, et al. Relationship between endometriosis stage, characteristics of enodmetriotic lesions and severity of dysmenorrhoea. *Zhonghua Yi Xue Za Zhi.* (2015) 95:685–8. doi: 10.3760/cma.j.issn.0376-2491.2015.09.012
11. Hao M, Zhao WH, Wang YH. [Correlation between pelvic adhesions and pain symptoms of endometriosis]. *Zhonghua Fu Chan Ke Za Zhi*. (2009) 44:333–6.
12. Kotowska M, Urbaniak J, Falecki WJ, Łazarewicz P, Masiak M, Szymusik I. Awareness of endometriosis symptoms-a cross sectional survey among polish women. *Int J Environ Res Public Health.* (2021) 18:9919. doi: 10.3390/ijerph18189919
13. Revised American society for reproductive medicine classification of endometriosis: 1996. *Fertil Steril.* (1997) 67:817–21. doi: 10.1016/S0015-0282(97)81391-X
14. Dueholm M. Transvaginal ultrasound for diagnosis of adenomyosis: a review. *Best Pract Res Clin Obstet Gynaecol*. (2006) 20:569–82. doi: 10.1016/j.bpobgyn.2006.01.005
15. Lazzeri L, Di Giovanni A, Exacoustos C, Tosti C, Pinzauti S, Malzoni M, et al. Preoperative and postoperative clinical and transvaginal ultrasound findings of adenomyosis in patients with deep infiltrating endometriosis. *Reprod Sci*. (2014) 21:1027–33. doi: 10.1177/1933719114522520
16. Cunningham RK, Horrow MM, Smith RJ, Springer J. Adenomyosis: a sonographic diagnosis. *Radiographics*. (2018) 38:1576–89. doi: 10.1148/rg.2018180080
17. Bazot M, Darai E. Role of transvaginal sonography and magnetic resonance imaging in the diagnosis of uterine adenomyosis. *Fertil Steril*. (2018) 109:389–97. doi: 10.1016/j.fertnstert.2018.01.024
18. Naftalin J, Hoo W, Pateman K, Mavrelos D, Holland T, Jurkovic D. How common is adenomyosis? a prospective study of prevalence using transvaginal ultrasound in a gynaecology clinic. *Hum Reprod*. (2012) 27:3432–9. doi: 10.1093/humrep/des332
19. Rolla E. Endometriosis: advances and controversies in classification, pathogenesis, diagnosis, and treatment. *F1000Res*. (2019) 8:F1000 Faculty Rev-529. doi: 10.12688/f1000research.14817.1
20. Sinaii N, Plumb K, Cotton L, Lambert A, Kennedy S, Zondervan K, et al. Differences in characteristics among 1,000 women with endometriosis based on extent of disease. *Fertil Steril.* (2008) 89:538–45. doi: 10.1016/j.fertnstert.2007.03.069
21. Stratton P, Berkley KJ. Chronic pelvic pain and endometriosis: translational evidence of the relationship and implications. *Hum Reprod Update.* (2011) 17:327–46. doi: 10.1093/humupd/dmq050
22. Harel Z. Dysmenorrhea in adolescents and young adults: an update on pharmacological treatments and management strategies. *Expert Opin Pharmacother.* (2012) 13:2157–70. doi: 10.1517/14656566.2012.725045
23. Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, et al. European society of human reproduction and embryology. ESHRE guideline: management of women with endometriosis. *Hum Reprod.* (2014) 29:400–12. doi: 10.1093/humrep/det457
24. Ruoff G, Lema M. Strategies in pain management: new and potential indications for COX-2 specific inhibitors. *J Pain Symptom Manage.* (2003) 25:21–31. doi: 10.1016/S0885-3924(02)00628-0
25. Harel Z. Cyclooxygenase-2 specific inhibitors in the treatment of dysmenorrhea. *J Pediatr Adolesc Gynecol.* (2004) 17:75–9. doi: 10.1016/j.jpag.2004.01.002
26. Vercellini P, Vigano P, Somigliana E, Fedele L. Endometriosis: pathogenesis and treatment. *Nat Rev Endocrinol.* (2014) 10:261–75. doi: 10.1038/nrendo.2013.255
27. Kajitani T, Maruyama T, Asada H, Uchida H, Oda H, Uchida S. Possible involvement of nerve growth factor in dysmenorrhea and dyspareunia associated with endometriosis. *Endocr J.* (2013) 60:1155–64. doi: 10.1507/endocrj.EJ13-0027
28. Arnold J, Barcena de Arellano ML, Rüster C, et al. Imbalance between sympathetic and sensory innervation in peritoneal endometriosis. *Brain Behav Immun.* (2012) 26:132–41. doi: 10.1016/j.bbi.2011.08.004
29. Payne LA, Rapkin AJ, Seidman LC, et al. Experimental and procedural pain responses in primary dysmenorrhea: a systematic review. *J Pain Res.* (2017) 10:2233–46. doi: 10.2147/JPR.S143512
30. Carey ET, Till SR, As-Sanie S. Pharmacological management of chronic pelvic pain in women. *Drugs.* (2017) 77:285–301. doi: 10.1007/s40265-016-0687-8
31. Leng JH, Lang JH, Dai Y, Li HJ, Li XY. [Relationship between pain symptoms and clinico-pathological features of pelvic endometriosis]. *Zhonghua Fu Chan Ke Za Zhi.* (2007) 42:165–8. doi: 10.3760/j.issn:0529-567x.2007.03.006
32. Liu X, Yuan L, Wang Y, Shen F, Guo SW. Risk factors for dysmenorrhea and its severity in women with ovarian endometriomas. *Gynecol Obstet Invest.* (2008) 66:169–77. doi: 10.1159/000140513
33. Mabrouk M, Raimondo D, Del Forno S, Baruffini F, Arena A, Benfenati A, et al. Pelvic floor muscle assessment on three- and four-dimensional transperineal ultrasound in women with ovarian endometriosis with or without retroperitoneal infiltration: a step towards complete functional assessment. *Ultrasound Obstet Gynecol.* (2018) 52:265–8. doi: 10.1002/uog.18924
34. Orr NL, Noga H, Williams C, Allaire C, Bedaiwy MA, Lisonkova S, et al. Deep Dyspareunia in Endometriosis: Role of the Bladder and Pelvic Floor. *J Sex Med.* (2018) 15:1158–66. doi: 10.1016/j.jsxm.2018.06.007
35. Wang YY, Leng JH, Shi JH, Li XY, Lang JH. [Relationship between pain and nerve fibers distribution in multiple endometriosis lesions]. *Zhonghua Fu Chan Ke Za Zhi*. (2010) 45:260–3.
36. Perper MM, Nezhat F, Goldstein H, Nezhat CH, Nezhat C. Dysmenorrhea is related to the number of implants in endometriosis patients. *Fertil Steril.* (1995) 63:500–3. doi: 10.1016/S0015-0282(16)57416-0
37. Chen I, Veth VB, Choudhry AJ, Murji A, Zakhari A, Black AY, et al. Pre- and postsurgical medical therapy for endometriosis surgery. *Cochrane Database Syst Rev.* (2020) 11:CD003678. doi: 10.1002/14651858.CD003678.pub3
38. Mabrouk M, Frascà C, Geraci E, Montanari G, Ferrini G, Raimondo D, et al. Combined oral contraceptive therapy in women with posterior

deep infiltrating endometriosis. *J Minim Invasive Gynecol*. (2011) 18:470–4. doi: 10.1016/j.jmig.2011.04.008
39. Mabrouk M, Raimondo D, Altieri M, Arena A, Del Forno S, Moro E, et al. Surgical, clinical, and functional outcomes in patients with rectosigmoid endometriosis in the gray zone: 13-year long-term follow-up. *J Minim Invasive Gynecol*. (2019) 26:1110–6. doi: 10.1016/j.jmig.2018.08.031
40. Prescott J, Farland LV, Tobias DK, et al. A prospective cohort study of endometriosis and subsequent risk of infertility. *Hum Reprod*. (2016) 31:1475–82. doi: 10.1093/humrep/dew085
41. Santulli P, Lamau MC, Marcellin L, Gayet V, Marzouk P, Borghese B, et al. Endometriosis-related infertility: ovarian endometrioma per se is not associated with presentation for infertility. *Hum Reprod*. (2016) 31:1765–75. doi: 10.1093/humrep/dew093
42. Ban FrangeŽ H, Vrtacnik Bokal E, Štimpfel M, Divjak Budihna T, Gulino FA, Garzon S, et al. Reproductive outcomes after laparoscopic surgery in infertile women affected by ovarian endometriomas, with or without *in vitro* fertilisation: results from the SAFE (surgery and ART for endometriomas) trial. *J Obstet Gynaecol*. (2021) 29:1–8. doi: 10.1080/01443615.2021.1959536
43. Ro ustan A, Perrin J, Debals-Gonthier M, Paulmyer-Lacroix O, Agostini A, Courbiere B. Surgical diminished ovarian reserve after endometrioma cystectomy versus idiopathic DOR: comparison of in vitro fertilization outcome. *Hum Reprod*. (2015) 30:840–7. doi: 10.1093/humrep/dev029
44. Yu HT, Huang HY, Tseng HJ, Wang CJ, Lee CL, Soong YK. Bilaterality of ovarian endometriomas does not affect the outcome of in vitro fertilization/intracytoplasmic sperm injection in infertile women after laparoscopic cystectomy. *Biomed J*. (2017) 40:295–9. doi: 10.1016/j.bj.2017.06.009

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SYSTEMATIC REVIEW
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Intrauterine Hematoma in the First Trimester and Pregnancy Complications: A Systematic Review and Meta-Analysis

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Background: Studies evaluating the relationship between intrauterine hematoma in the first trimester and prenatal complications are conflicting.

Objectives: To evaluate whether intrauterine hematoma identified in the first trimester in women with singleton pregnancies is associated with adverse perinatal outcomes.

Search Strategy: A comprehensive literature search of three databases (Embase, PubMed, and Web of Science) was performed up to September 2021.

Selection Criteria: Cohort and case-control studies that have evaluated the relationship between intrauterine hematoma identified before 14 gestational weeks and the risk of prenatal complications, in women with a singleton pregnancy.

Data Collection and Analysis: Two members of our team independently assessed the studies for inclusion, collected the data of interest, and assessed the risk of bias, and calculated pooled odds ratios (ORs) using random-effects models.

Main Results: Nine studies, including 1,132 women with intrauterine hematoma and 11,179 controls met the inclusion criteria. Intrauterine hematoma increased the risk of spontaneous abortion [OR 2.15, 95% confidence interval (CI) 1.23–3.75], preterm birth (OR 1.83, 95% CI 1.37–2.43), fetal growth restriction (OR 2.33, 95% CI 1.13–4.83) and placental abruption (OR 3.16, 95% CI 1.23–8.13). No statistically significant association was found between intrauterine hematoma and preeclampsia (OR 1.30, 95% CI 0.87–1.94).

Conclusion: Intrauterine hematoma in the first trimester of pregnancy increases the risk of spontaneous abortion, preterm birth, placental abruption, and fetal growth restriction.

Systematic Review Registration: https://www.crd.york.ac.uk/PROSPERO/.

Keywords: intrauterine hematoma, singleton pregnancy, first trimester, prenatal complications, spontaneous abortion

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INTRODUCTION

Intrauterine hematomas (IUHs) are commonly found on routine obstetric ultrasonography during the first trimester, however, they can be randomly observed throughout the pregnancy (1, 2). In ultrasound imaging, IUH often appears as a hypoechoic area between the uterine wall and chorionic

membrane (2, 3). According to the literature, the incidence of IUH varies from 1 to 39.5% among previous studies, and this huge variation is mainly attributed to the heterogeneity in the study cohorts, definitions, ultrasonic equipment employed, and timing of diagnosis (4–8).

It was first proposed by Mantoni and Pedersen in 1981 (9), and several studies have sought to clarify the relationship between IUH and prenatal complications; however, the association remains uncertain and inconsistent. Some authors thought that compared with pregnant women who did not have IUH, women with IUH were not at a higher risk of adverse prenatal complications (10, 11). However, other researchers have contrasting opinions. They concluded that for women with IUH identified by ultrasonography, the risk of prenatal complications, including spontaneous abortion, premature labor, and fetal growth restriction (FGR) increases dramatically (12–14).

In 2011, Tuuli et al. (15) performed a systematic review and meta-analysis focus on the relationship between IUH and pregnancy complications. Seven studies, including 1,735 women with IUH and 70,703 controls, were included in their study. They reported that IUH significantly increased the risk of spontaneous abortion, stillbirth, placental abruption, preterm labor, and preterm premature rupture of membranes (PPROM) (15). They also found that IUH detected by ultrasound imaging during the first and second trimesters did not cause an increase in the incidence of FGR and preeclampsia (15). However, some limitations of this meta-analysis should be discussed. A major limitation of their study was the significant clinical heterogeneity among the included studies. Among these studies they included, the diagnosis time of IUH varied from 5 to 24 weeks of gestational age. In addition, the diagnostic criteria for IUH and definitions of the outcomes of interest were heterogeneous across studies. Following their systematic review, some high-quality studies on this topic have been published (4–6, 16–18).

Briefly, we believe that it is of clinical significance and necessary to conduct an updated literature review on this topic.

MATERIALS AND METHODS

This systematic review and meta-analysis were conducted following the recommendations of "The PRISMA 2020 statement: an updated guideline for reporting systematic reviews" (19) and "meta-analyses and systematic reviews of observational studies in epidemiology (MOOSE) group" (20). The protocol of this study was registered in PROSPERO (Registration no. CRD42020183315).

The literature search, eligibility identification, quality assessment, and data collection were performed independently by two or three members of our team. Any disagreements in these processes were resolved through discussion or, if necessary, consultation with a third senior researcher (Ai Zheng).

Literature Search

Three electronic databases (Embase, PubMed, and Web of Science) were searched for eligible studies (database inception to 14 September 2021). Given our limited linguistic proficiency, the searches were limited to studies published in English journals. Studies that have reported the results of interest, regardless of the type, were included. Medical subject headings, keywords, and search strategies were tailored for each electronic database by Yu Xu, who specializes in medical literature retrieval. Gray literature resources, such as conference summaries identified by database searches and the reference lists of eligible studies, were reviewed and searched for potentially eligible studies. Step-by-step search strategies for Embase, PubMed, and Web of Science are presented in **Supplementary Material 1**.

Study Selection

Retrieved records from the database and manual searches were managed using EndNote (version X9). The study selection process was independently conducted by two members (Zhaojuan Qin and Yu Xu) of our team. First, duplicate studies were excluded. Subsequently, an initial assessment of relevance was made by reviewing the titles and abstracts of the remaining records. Finally, the full text of the remaining records was reviewed for eligibility.

Observational studies (cohort studies, or case-control studies) were included if they met the following inclusion criteria: enrolled adult women (aged >18 years) with singleton intrauterine pregnancy; patients of the case-cohort had IUH identified by ultrasound imaging in the first trimester, and the women in the control cohort had normal pregnancies; pregnancy outcomes and complications were compared between the two cohorts; results were reported in the form of odds ratios (ORs) with 95% confidence intervals (CIs). The first trimester was defined as the time between the 1st day of the last menstrual period and the end of the 13th week of pregnancy. Gestational age was identified based on ultrasound biometric measurement (crown-rump length) of the fetus when the last menstrual period was unknown (21).

Studies were excluded for the following reasons: results were not reported in a peer-reviewed journal; results were reported in languages other than English; the study population was duplicated in another study included in final results analysis; the study cohort included women with multiple pregnancies; or the study cohort only included women whose pregnancy was achieved by assisted reproductive technology. When studies with duplicate cohorts were found, studies with more participating centers or larger sample sizes were included in our meta-analysis.

Quality Assessment

The risk of bias of each eligible study was assessed using the guidelines of the "Newcastle-Ottawa Scale (NOS) for the assessment of the quality of non-randomised studies in meta-analysis" (22). The NOS estimates the risk of bias by assigning points to eight items that which are categorized into the following three domains: "selection of participants, measures of exposure and outcome variables, and appropriate control of confounding" (22). A star system was employed to enable a semi-quantitative assessment of the risk of bias (22). As is commonly accepted in previous studies (23–25), the risk of bias in a particular study is thought to be low if the NOS score is at least 7 points. Otherwise, the risk of bias was considered to be high. The quality assessment of this study was independently performed by Yi Du and Ya-li Chen, and any dispute was resolved by discussion.

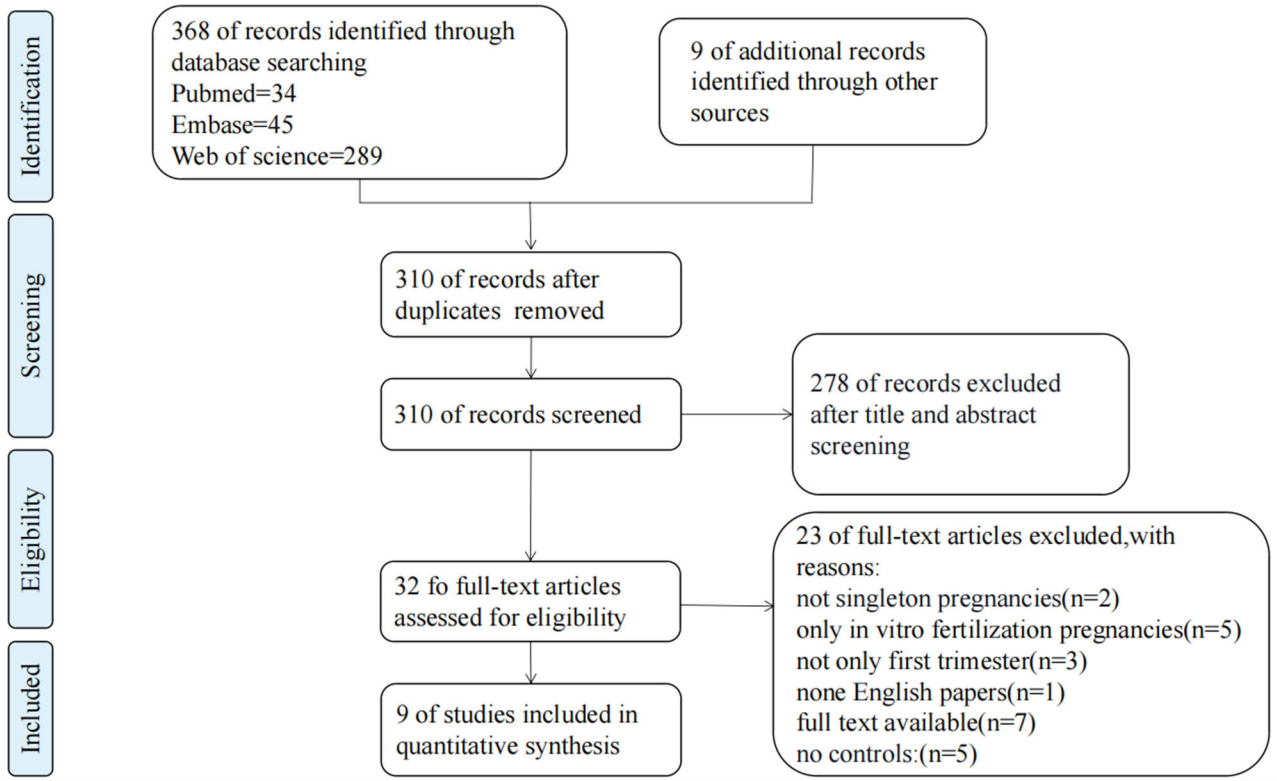

FIGURE 1 | The flow chart of study selection.

Data Extraction and Synthesis

A pre-designed spreadsheet was used for data extraction, and Zhao-juan Qin and Liang Sun independently collected the data collection step. The name of the first author, study design, size of the study cohort, year of publication, timing of IUH identification, IUH definition, number of events of interest, and ORs were extracted from all included studies. The collected data were reviewed and validated by a third investigator (Yu Xu). When data were unavailable in a publication, we made efforts to contact the corresponding author to obtain the missing details.

The pregnancy complications or outcomes of interest in this study were spontaneous abortion, preterm birth, FGR, placental abruption, and preeclampsia. Spontaneous abortion was defined as loss of pregnancy without external intervention before 28 weeks of gestation (26). Preterm birth was defined as delivery after 28 weeks of gestation but <37 weeks (27). FGR was defined as a birth weight less than the 10th percentile for gestational age, according to population norms. Placental abruption was defined as the removal of the placenta from the endometrium before delivery of the fetus (28). Preeclampsia was defined as blood pressure ≥140/90 mmHg intervals of more than 4 h apart, with proteinuria simultaneously, quantified by 24 h urine collection (> 3 g protein/24 h), after 20 weeks of gestation in a woman with previously normal blood pressure (29).

Separate meta-analyses were performed for each of the prenatal adverse outcomes, where possible. Heterogeneity was assessed statistically using the χ^2 test and I^2 value, and χ^2 test for heterogeneity, and the extent of heterogeneity was quantified using the I^2 value. An I^2 statistic ≥50% and $P < 0.1$ indicated a high risk of heterogeneity. Random-effects models were used to combine ORs from different studies owing to the possibility of clinical heterogeneity. If there was significant heterogeneity among the included studies, possible sources of heterogeneity were investigated *via* sensitivity analysis. If the results of some original studies could not be statistically pooled by meta-analysis, they were presented in a tabular.

RESULTS

Selection and Characteristics of Studies

Through literature searches, 377 records were identified in total. After duplicate studies were excluded, 310 literatures were reviewed the titles and abstracts, 32 literatures were screened in full text, and nine studies (4–6, 14, 16–18, 30, 31) with 12,311 patients involved were eventually included in data analysis. Characteristics of the 9 included articles are shown in **Table 1**. The study selection process is presented in **Figure 1**. These studies were published since 1996 to 2020,

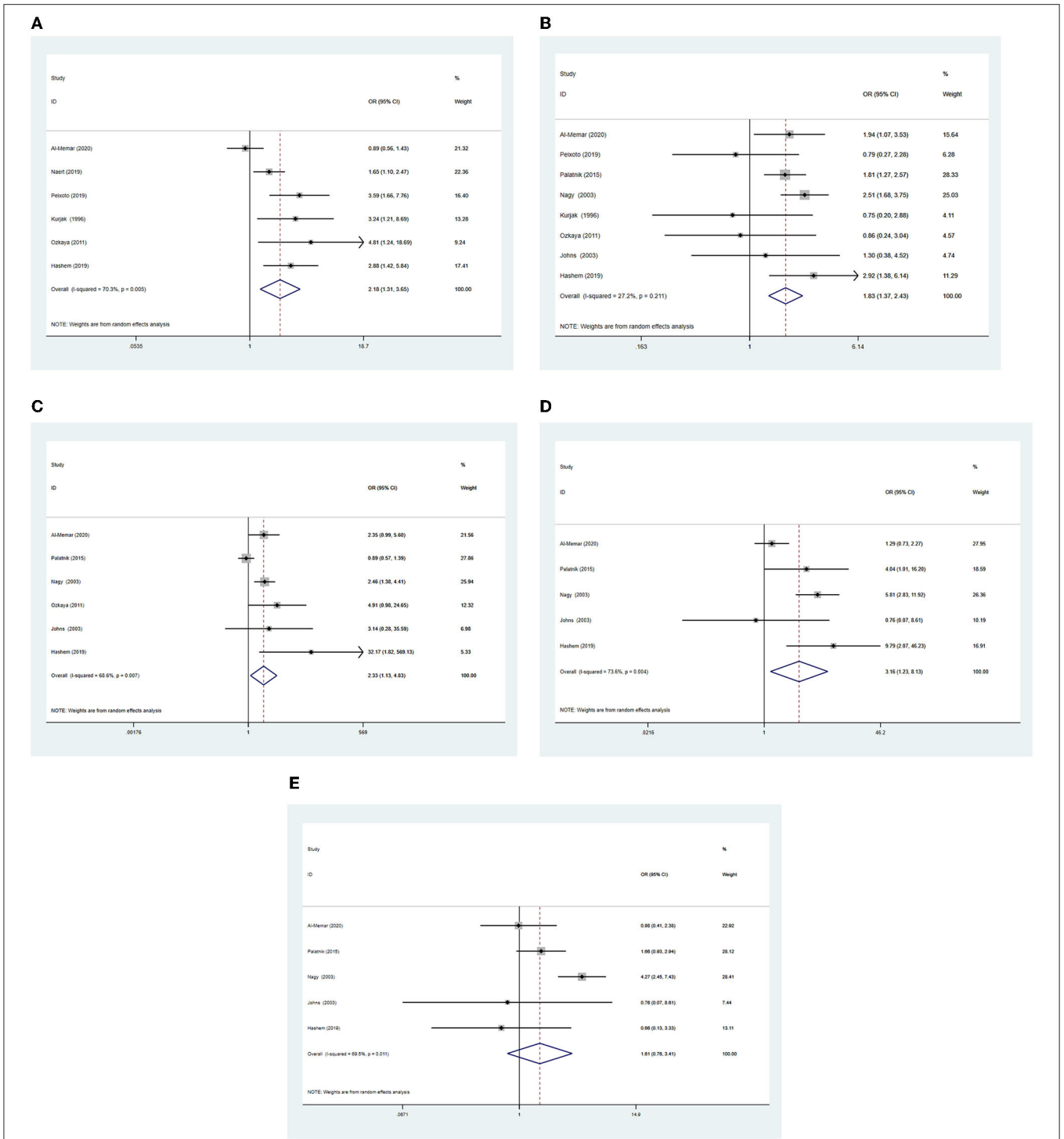

FIGURE 2 | Forest plots of outcomes comparing the intrauterine hematoma group with the control group **(A)**, spontaneous abortion **(B)**, preterm birth **(C)**, fetal growth restriction **(D)**, placenta abruption **(E)**, pre-eclampsia.

number of included samples ranged from 88 to 6,675. Among them, five studies were cohort studies and four were case-control studies.

Assessment of Bias Risk

The overall quality of the studies included was acceptable, as shown in **Table 2**. Five of the studies had a medium risk of bias,

TABLE 1 | Characteristics of the studies included in the review.

References	Study design	IUH	Control	Study participants	Exclusion criteria
Al-Memar et al. (4)	Prospective cohort	268	678	Singleton intrauterine pregnancy; 5–14weeks	Women aged under 16 and over 50 years
Peixoto et al. (5)	Retrospective cohort	35	748	Singleton pregnancies with GA; the presence of IUH, 6–11weeks	Non-viable embryos without a detectable heartbeat and embryos with pathological features
Naert et al. (6)	Retrospective cohort	389	1,783	Singleton pregnancies; before 14 weeks	Women with pregnancy loss before 20 weeks of gestation. multiple gestations, a vanishing twin, or a fetal heart rate <100 beats per minute
Nagy et al. (14)	Prospective cohort	187	6,488	The presence of a viable, singleton gestation and delivery after 24 weeks' gestation	A non-viable fetus, multifetal pregnancy, or fetal abnormality diagnosed by ultrasonography
Palatnik et al. (16)	Retrospective cohort	512	1,024	Had a singleton non-anomalous gestation, before 14 weeks	Women with multifetal gestation, cerclage, or a uterine anomaly
EOzkaya et al. (17)	Case-contorl	43	45	Pregnancy between 7 and 14 weeks' gestation with vaginal bleeding	Patients with possible risk factors for primary end-points
Hashem et al. (18)	Case-contorl	100	200	Singleton viable intrauterine pregnancy, gestation, 6–14 weeks	Patients with a non-viable fetus, multifetal pregnancy, fetal abnormality, patients with history of recurrent miscarriage and with scarred uterus
Kurjak et al. (30)	Case-contorl	59	135	Vaginal bleeding, closed cervix, and ultrasonic findings of a living embryo and subchorionic hematoma	None
Johns et al. (31)	Case-contorl	51	78	Women with vaginal bleeding or lower abdominal pain at <12 weeks of gestation with SCH on ultrasound	multiple gestations, women with vaginal bleeding or referred for nuchal translucency measurement

and four had a low risk of bias. All cohort studies and case-control studies had a low risk of bias in terms of selection and comparability. All included studies had scores above 7 points, with a maximum score of 9 points.

Pooled Estimates of Outcomes of Interest

Spontaneous Abortion

Six studies (4–6, 17, 18, 30) reported the risk of spontaneous abortion in pregnant women diagnosed with IUH before 14 gestational weeks. The meta-analysis showed that for IUH in the first trimester of pregnancy, increases the likelihood of spontaneous abortion [odds ratio (OR) 2.17, 95% confidence interval (CI) 1.29–3.63] (**Figure 2A**). Significant heterogeneity was observed ($\chi^2 = 20.90$, $P = 0.001$, $I^2 = 75\%$). Accordingly, sensitivity analysis was performed to explore the influence of a single study on the pooled results of the meta-analysis. The results of the sensitivity analyses showed that the study by Al-Memar et al. (4) had a great influence on the results of the pooled synthesis. After excluding that study, the meta-analysis of the remaining five studies revealed that IUH was still associated with an increased risk of spontaneous abortion (OR 2.57, 95% CI 1.67–3.95), with low heterogeneity ($I^2 = 39\%$).

Preterm Birth

Eight studies (4, 5, 14, 16–18, 30, 31) reported the risk of preterm birth in pregnant women with IUH identified in the first trimester, and the pooled ORs using random-effects models revealed an increased risk of preterm birth (OR 1.83, 95% CI 1.37–2.43; **Figure 2B**) in women with IUH when compared to women with normal pregnancies. No significant heterogeneity was noted among these studies ($\chi^2 = 9.62$, $P = 0.21$, $I^2 = 27\%$).

Fetal Growth Restriction

Six studies (4, 14, 16–18, 31) reported FGR as an outcome. IUH was increased the likelihood of FGR (OR 2.33, 95% CI 1.13–4.83; **Figure 2C**). There was statistical heterogeneity among the studies ($\chi^2 = 15.92$, $P = 0.007$, $I^2 = 69\%$). Similarly, for the outcome of FGR, the pooled OR was unchanged when Palatnik's study (16) was excluded (OR 2.90, 95% CI 1.93–4.37), showing low heterogeneity ($I^2 = 0\%$).

Placental Abruption

Five studies (4, 14, 16, 18, 31) reported placental abruption as an outcome. IUH was also significantly increased the likelihood of placental abruption (OR 3.16, 95% CI 1.23–8.13; **Figure 2D**). Statistical heterogeneity was noted in placental abruption ($\chi^2 = 15.12$, $P = 0.004$, $I^2 = 74\%$). For the outcome of placental abruption, the pooled OR was unchanged when Al-Memar's study (4) was excluded (OR 5.13, 95% CI 2.71–9.71), demonstrating low heterogeneity $I^2 = 9\%$.

Preeclampsia

Five studies (4, 14, 16, 18, 31) reported preeclampsia as an outcome. However, no statistically association was observed between IUH and preeclampsia (OR 1.30, 95% CI 0.87–1.94; **Figure 2E**). There was statistical heterogeneity in preeclampsia

TABLE 2 | Risk of bias in the studies.

	Study design	Selection				Comparability	Outcome			
	Cohort	**Representative-ness of the exposed cohort**	**Non-exposed cohort**	**Ascertainment of exposure**	**Outcome of interest not present at start**	**Comparability of cohorts based on design or analysis**	**Assessment of outcome**	**Follow-up duration sufficient**	**Adequacy of follow-up**	**Risk of bias[a]**
Al-Memar et al. (4)	1	1	1	1	1	1	1	1	1	Low
Peixoto et al. (5)	1	1	1	1	1	1	1	1	0	Medium
Naert et al. (6)	1	1	1	1	1	1	0	1	1	Medium
Nagy et al. (14)	1	1	1	1	1	1	0	1	1	Medium
Palatnik et al. (16)	1	1	1	1	1	1	1	1	1	Low
	Case-control	**Adequate case definition**	**Representative-ness of cases**	**Selection of controls**	**Definition of controls**	**Definition of controls**	**Ascertainment of exposure**	**Same method of ascertainment for cases and controls**	**Non-response rate**	
Ozkaya et al. (17)	1	1	1	1	1	1	0	1	1	Medium
Hashem et al. (18)	1	1	1	1	1	1	1	1	1	Low
Kurjak et al. (30)	1	1	1	1	1	1	0	1	0	Medium
Johns et al. (31)	1	1	1	1	1	1	1	1	1	Low

[a] *Low, ≥7; medium, 5–7; high, ≤4.*

($\chi^2 = 13.12$, $P = 0.01$, $I^2 = 70\%$). Regarding the outcome of preeclampsia, the pooled OR was unchanged when Nagy's study (14) was excluded (OR 1.31, 95% CI 0.83–2.06), presenting low heterogeneity $I^2 = 0\%$.

DISCUSSION

Before the placenta structure has been formed, the exchange barrier between mother and fetus is the chorion. IUH is another common term for intrauterine bleeding. In IUH, ultrasound imaging detects a hematoma or hypoechoic hemorrhage between the uterine wall and the gestational sac, which is the separation of fetal membranes in the first trimester, also known as subchorionic hemorrhage. Most women present with mild vaginal bleeding, but some are asymptomatic on ultrasound imaging. In general, IUH is relatively common in clinical practice, with an incidence of 2.8% (14) to 28.3% (4) among the nine studies included in our meta-analysis. This may be due to the use of more advanced ultrasound equipment during the first trimester, which provides higher-quality images. The gestational age at the initial prenatal examination is earlier than in the past, and many asymptomatic IUH cases are detected early. In clinical practice, pregnant women with IUH are prone to anxiety. However, there is a lack of consensus on whether IUH found in the first trimester by ultrasonography increases the risk of prenatal adverse events in ongoing singleton pregnancies, for example, among studies assessing whether IUH increases the likelihood of spontaneous abortion in the first-trimester, some show an increased risk of spontaneous abortion (16, 18), whereas others elaborate no increased risk (4, 6, 31). For obstetricians, when dealing with counseling for pregnant women with IUH, the research conclusions of the current studies may be confusing. However, the present meta-analysis suggests that an IUH during the first trimester significantly increased the likelihood of spontaneous abortion in pregnant women, compared with normal pregnancy. In addition, IUH also increased the likelihood of preterm birth, placental abruption and FGR. The present study shows that IUH was not associated with the occurrence of preeclampsia.

According to current research results, there have been three systematic reviews on this topic (2, 15, 32). Pearlstone et al. (2) reported that a small IUH was common in the first trimester and did not increase the risk of pregnancy complications during pregnancy. While Tuuli et al. (15) concluded that IUH increased the risk of spontaneous abortion, stillbirth, preterm delivery, and PPROM. The latest one demonstrated that a retroplacental, posterior or subchorionic in the fundus of uterus, and/or persistent IUH is associated with adverse outcomes in the ongoing pregnancy (32). However, they included women in both the first trimester and second trimester of pregnancy. Xiang et al. (32) even inclusive the series case report, the case-control studies and cohort studies, and synthesis the results of different types of studies.

The strength of our study is that this is the first study to generalize the available evidence evaluating the relationship between prenatal complications of singleton pregnancies and IUH in the first trimester. In addition, previous systematic reviews identified and collected literature before January 2014. By contrast, the present review was based on an exhaustive search of high-quality research until September 2021. In comparison, our study had a larger number of participants, including pregnant women with IUH detected only on ultrasound examinations performed before 14 weeks of pregnancy. Therefore, we believe our results are more reliable than those obtained when comparing prenatal complications of singleton pregnancies with those of IUH in the first trimester.

Importantly, the conclusions of our study have significant health care practice implications, and we may provide information to obstetricians for future clinical practice decisions. Therefore, this meta-analysis can guide the clinical decision-making. Women with IUH before 14 weeks of gestation can be counseled about that they are at increased risk of spontaneous abortion. They should also be informed that they may develop placental abruption, FGR, an increased risk of preterm birth, and possibly receive more surveillance during pregnancy.

This study also has some limitations. A considered heterogeneity is estimated between studies, because of differences in diagnostic methods, criteria, and sampling frames. Regarding the influence of IUH on pregnancy outcomes, the diagnosis was made by transvaginal sonography or abdominal sonography. The location, volume, and duration of IUH, combined with threatened abortion symptoms such as vaginal bleeding and abdominal pain, may affect the pregnancy outcomes, and there may be mixed bias in related studies. Heller et al. (3) evaluated and compared several grading systems of IUH size in a study population of first-trimester pregnancies, and estimated IUH size in relation to the gestational sac size was superior to other methods of IUH quantification. Therefore, the size of the hematoma relative to the gestational sac size is considerably remarkable. There may be no complications in cases with small hematomas, but important complications may occur in those with larger hematomas. Hashem et al. (18) demonstrated that spontaneous abortion was more likely to occur with large hematomas than small-sized IUH, this was also supported by Ozkaya et al. (17). Due to the inconsistent grading standards of IUH size in our included literatures, we did not have enough data to discuss the impact of IUH size on prenatal complications. There may be differences in exposure and outcomes in terms of diagnostic methods and criteria. We only included literatures publications in English. Therefore, we minimized potential bias by having two independent reviewers screen eligible studies, extract data, and assess the quality of included studies.

At present, the research on the etiology of IUH is still unclear. Part of the reasons may be the external impact on the abdomen in the early pregnancy, or gestational hypertension during pregnancy, which may lead to the separation of part of the fetal membranes from the uterine wall. In addition, IUH may be more common in *in-vitro* fertilization pregnancies and multiple pregnancies (33). The length of the cervical canal also influences the separation of the fetal membranes. Taken together, our study suggests that women with IUH have an increased the likelihood of having adverse prenatal complications such as preterm birth, spontaneous abortion, placental abruption, and FGR, in the first trimester.

In addition, further research is needed to investigate the possible mechanisms by which IUH is associated with antenatal adverse events.

CONCLUSION

To the best of our knowledge, this is the first study to assess the association between prenatal complications in a single pregnancy and IUH in the first trimester of pregnancy. These results indicate that IUH in the first trimester of pregnancy increases the risk of preterm birth, spontaneous abortion, placental abruption, and FGR. Nonetheless, further studies are required to confirm this finding.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

Z-jQ, YX, and AZ: conceptualization. YX and Z-jQ: methodology and writing—original draft. Z-jQ, YX, YD, Y-lC, and LS: data collection. YX and AZ: project administration and supervision. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.892146/full#supplementary-material

REFERENCES

1. Ott J, Pecnik P, Promberger R, Pils S, Binder J, Chalubinski KM. Intra- versus retroplacental hematomas: a retrospective case-control study on pregnancy outcomes. *BMC Pregnancy Childbirth.* (2017) 17:366. doi: 10.1186/s12884-017-1539-6
2. Pearlstone M, Baxi L. Subchorionic hematoma: a review. *Obstet Gynecol Surv.* (1993) 48:65–8. doi: 10.1097/00006254-199302000-00001
3. Heller HT, Asch EA, Durfee SM, Goldenson RP, Peters HE, Ginsburg ES, et al. Subchorionic hematoma: correlation of grading techniques with first-trimester pregnancy outcome. *J Ultrasound Med.* (2018) 37:1725–32. doi: 10.1002/jum.14524
4. Al-Memar M, Vaulet T, Fourie H, Bobdiwala S, Farren J, Saso S, et al. First-trimester intrauterine hematoma and pregnancy complications. *Ultrasound Obstet Gynecol.* (2020) 55:536–45. doi: 10.1002/uog.20861
5. Peixoto AB, Caldas TMRDC, Petrini CG, Romero ACP, Júnior LEB, Martins WP, et al. The impact of first-trimester intrauterine hematoma on adverse perinatal outcomes. *Ultrasonography.* (2018) 37:330–6. doi: 10.14366/usg.18006
6. Naert MN, Khadraoui H, Muniz Rodriguez A, Naqvi M, Fox NS. Association between first-trimester subchorionic hematomas and pregnancy loss in singleton pregnancies. *Obstet Gynecol.* (2019) 134:276–81. doi: 10.1097/AOG.0000000000003360
7. Sukur YE, Goc G, Kose O, Acmaz G, Ozmen B, Atabekoglu CS, et al. The effects of subchorionic hematoma on pregnancy outcome in patients with threatened abortion. *J Turk Ger Gynecol Assoc.* (2014) 15:239–42. doi: 10.5152/jtgga.2014.14170
8. Norman SM, Odibo AO, Macones GA, Dicke JM, Crane JP, Cahill AG. Ultrasound-detected subchorionic hemorrhage and the obstetric implications. *Obstet Gynecol.* (2010) 116:311–5. doi: 10.1097/AOG.0b013e3181e90170
9. Mantoni M, Pedersen JF. Intrauterine haematoma. An ultrasonic study of threatened abortion. *Br J Obstetric Gynaecol.* (1981) 88:47–51. doi: 10.1111/j.1471-0528.1981.tb00936.x
10. Leite J, Ross P, Rossi AC, Jeanty P. Prognosis of very large first-trimester hematomas. *J Ultrasound Med.* (2006) 25:1441–5. doi: 10.7863/jum.2006.25.11.1441
11. van Oppenraaij RH, Jauniaux E, Christiansen OB, Horcajadas JA, Farquharson RG, Exalto N. Predicting adverse obstetric outcome after early pregnancy events and complications: a review. *Hum Reprod Update.* (2009) 15:409–21. doi: 10.1093/humupd/dmp009
12. Jauniaux E, Van Oppenraaij RH, Burton GJ. Obstetric outcome after early placental complications. *Curr Opin Obstet Gynecol.* (2010) 22:452–7. doi: 10.1097/GCO.0b013e32834 04e44
13. Maso G, D'Ottavio G, De Seta F, Sartore A, Piccoli M, Mandruzzato G. First-trimester intrauterine hematoma and outcome of pregnancy. *Obstet Gynecol.* (2005) 105:339–44. doi: 10.1097/01.AOG.0000152000.71369.bd
14. Nagy S, Bush M, Stone J, Lapinski RH, Gardó S. Clinical significance of subchorionic and retroplacental hematomas detected in the first trimester of pregnancy. *Obstet Gynecol.* (2003) 102:94–100. doi: 10.1097/00006250-200307000-00019
15. Tuuli MG, Norman SM, Odibo AO, Macones GA, Cahill AG. Perinatal outcomes in women with subchorionic hematoma: a systematic review and meta-analysis. *Obstet Gynecol.* (2011) 117:1205–12. doi: 10.1097/AOG.0b013e31821568de
16. Palatnik A, Grobman WA. The relationship between first-trimester subchorionic hematoma, cervical length, and preterm birth. *Am J Obstet Gynecol.* (2015) 213:403e401–4. doi: 10.1016/j.ajog.2015.05.019
17. Ozkaya E, Altay M, Gelisen O. Significance of subchorionic haemorrhage and pregnancy outcome in threatened miscarriage to predict miscarriage, preterm labour and intrauterine growth restriction. *J Obstet Gynaecol.* (2011) 31:210–2. doi: 10.3109/01443615.2010.545899
18. Hashem A, Sarsam SD. The impact of incidental ultrasound finding of subchorionic and retroplacental hematoma in early pregnancy. *J Obstet Gynaecol India.* (2019) 69:43–9. doi: 10.1007/s13224-017-1072-6
19. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* (2021) 372:n71. doi: 10.1136/bmj.n71
20. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *J Am Med Assoc.* (2000) 283:2008–12. doi: 10.1001/jama.283.15.2008
21. Cooper S, Somerset D. Determination of gestational age by ultrasound. *J Obstetr Gynaecol Canada.* (2016) 38:337. doi: 10.1016/j.jogc.2016.03.007
22. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* (2010) 25:603–5. doi: 10.1007/s10654-010-9491-z
23. Nitecki R, Ramirez PT, Frumovitz M, Krause KJ, Tergas AI, Wright JD, et al. Survival after minimally invasive vs open radical hysterectomy for early-stage cervical cancer: a systematic review and meta-analysis. *J Am Med Assoc Oncol.* (2020) 6:1019–27. doi: 10.1001/jamaoncol.2020.1694
24. Zhang T, Sidorchuk A, Sevilla-Cermeño L, Vilaplana-Pérez A, Chang Z, Larsson H. et al. Association of cesarean delivery with risk of neurodevelopmental and psychiatric disorders in the offspring: a systematic review and meta-analysis. *J Am Med Assoc Netw*

Open. (2019) 2:e1910236. doi: 10.1001/jamanetworkopen.2019.10236
25. Mohammed SH, Habtewold TD, Birhanu MM, Sissay TA, Tegegne BS, Abuzerr S, et al. Neighbourhood socioeconomic status and overweight/obesity: a systematic review and meta-analysis of epidemiological studies. *BMJ Open.* (2019) 9:e028238. doi: 10.1136/bmjopen-2018-028238
26. Griebel CP, Halvorsen J, Golemon TB, Day AA. Management of spontaneous abortion. *Am Fam Physician.* (2005) 72:1243–50.
27. Vogel JP, Chawanpaiboon S, Moller AB, Watananirun K, Bonet M, Lumbiganon P. The global epidemiology of preterm birth. *Best Pract Res Clin Obstet Gynaecol.* (2018) 52:3–12. doi: 10.1016/j.bpobgyn.2018.04.003
28. Nkwabong E, Tiomela Goula G. Placenta abruption surface and perinatal outcome. *J Matern Fetal Neonatal Med.* (2017) 30:1456–9. doi: 10.1080/14767058.2016.1219988
29. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. *Lancet.* (2016) 387:999–1011. doi: 10.1016/S0140-6736(15)00070-7
30. Kurjak A, Schulman H, Zudenigo D, Kupesic S, Kos M, Goldenberg M. Subchorionic hematomas in early pregnancy: clinical outcome and blood flow patterns. *J Matern Fetal Med.* (1996) 5:41–4. doi: 10.1002/(SICI)1520-6661(199601/02)5:1<41::AID-MFM10>3.0.CO;2-Q
31. Johns J, Hyett J, Jauniaux E. Obstetric outcome after threatened miscarriage with and without a hematoma on ultrasound. *Obstet Gynecol.* (2003) 102:483–7. doi: 10.1097/00006250-200309000-00010
32. Xiang L, Wei Z, Cao Y. Symptoms of an intrauterine hematoma associated with pregnancy complications: a systematic review. *PLoS ONE.* (2014) 9:e111676. doi: 10.1371/journal.pone.0111676
33. Capriglione S, Ettore C, Terranova C, Plotti F, Angioli R, Ettore G, et al. Analysis of ultrasonographic and hystopathologic features of placental invasiveness *in vitro* Fertilization (IVF) pregnancies: a prospective study. *J Matern Fetal Neonatal Med.* (2021) 2021:1–8. doi: 10.1080/14767058.2021.1888917

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Decreased Risk of Low Back Pain During Pregnancy Associated With the Use of Orthopedic Manual Therapy: A Nested Case-Control Study

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Chang W-C, Livneh H, Yen C-T, Hsieh M-C, Lu M-C, Chen W-J and Tsai T-Y (2022) Decreased Risk of Low Back Pain During Pregnancy Associated With the Use of Orthopedic Manual Therapy: A Nested Case-Control Study. Front. Med. 9:887877. doi: 10.3389/fmed.2022.887877

Background: Recent evidence suggests that the use of orthopedic manual therapy (OMT) may lessen the subsequent risk of low back pain (LBP), but this association has not been examined among pregnant women who are at higher risk of LBP. This study aims to determine whether the addition of OMT to conventional LBP treatment before pregnancy could decrease the subsequent risk of LBP during pregnancy.

Methods: From Taiwan's National Health Insurance Research Database, we identified 68,960 women, 20–55 years of age, with first pregnancy between 2001 and 2012. We then performed a nested case-control study in which 3,846 women with newly diagnosed LBP were matched to 3,846 controls according to age and cohort entry year. Multivariate conditional logistic regression was employed to estimate the association between OMT use before pregnancy and LBP during pregnancy.

Results: OMT users had a lower risk of LBP than did non-users, with an adjusted OR of 0.86 (95% CI, 0.78–0.93). Subgroup analysis showed that women with high intensity use of OMT treatment prior to pregnancy reported the lowest level of LBP during pregnancy by nearly 30%.

Conclusion: The pre-pregnancy use of OMT treatment significantly decreased LBP risk during pregnancy, especially with high-intensity use. Thus, clinicians may consider recommending OMT for pregnant women to avoid possible obstetric complications during the pregnancy.

Keywords: low back pain, orthopedic manual therapy, pregnancy, nested case-control study, risk

INTRODUCTION

Low back pain (LBP) is increasingly common worldwide. Epidemiological surveys from different centuries put LBP figures, during lifetime, at between 377.5 million in 1990 and 577.0 million in 2017, translating to an increase by nearly 53% (1). LBP affects all age groups, especially women during pregnancy, affecting 7 out of 10 pregnant women (2). Extreme LBP places the affected women at increased risk of developing perinatal depression, thus compromising both maternal and pediatric health (3). Despite the high prevalence of pregnancy-related LBP and its significant impact on women's quality of life, the physiological and biomechanical processes underlying the development of pregnancy-related LBP remain unclear (4). The extra weight and body changes in pregnancy along with loosened joints and ligaments due to hormonal changes are implicated in this condition. A recent study suggests that morphometric differences in the paraspinal muscle before pregnancy may be associated with subsequent clinical symptoms, particularly LBP (5).

Acetaminophen and non-steroidal anti-inflammatory drugs are common treatments for LBP. However, such medications can cause neurological and renal problems (6). A recent cohort study in the US reports that pregnant women receiving NSAIDs experienced a 60% higher risk of miscarriage than did those who did not (7). Thus, shifting the approach to managing LBP, from treatment to early prevention, is imperative, particularly for such groups (8).

Orthopedic manual therapy (OMT), an important branch of traditional Chinese medicine, has recently become a popular form of treatment for pain (9). A randomized sham-controlled trial showed that adding OMT to conventional treatment resulted in a greater decrease in LBP and functional disability than did conventional care without OMT (8). OMT treatment was reported to have favorable therapeutic outcomes among patients with inflammatory conditions and was proposed to act *via* regulation of specific circulating cytokines and leukocytes (10, 11). In view of the growing body of evidence suggesting that abnormal inflammatory responses may contribute to a predisposition to LBP (12, 13), the use of OMT prior to or early in pregnancy might lessen the risk of having LBP in later pregnancy. Accordingly, this study aims to determine whether adding OMT to conventional treatment for LBP before pregnancy could lessen the subsequent risk of LBP during the pregnancy period.

METHODS

Data Source and Identification of Participants

Taiwan's NHI program, launched in 1995, is a single-payer government-operated compulsory health insurance program. As of 2015, up to 99.6% of Taiwan's population was enrolled in the NHI program (14). The Longitudinal Health Insurance Database (LHID), the database for the NHI program, is made up of one million randomly beneficiaries under the NHI and contain registration profiles that cover (i) enrollees' demographic information; (ii) health insurance claims data; (iii) diagnostic codes; (iv) contracted pharmacies; and (v) medical examination information from the NHI program. Due to the use of a multistage stratified systematic sampling design, it ensures no significant deviations in the distribution of sex and age between the LHID enrollees and the general population. This study was approved by the local institutional review board and ethics committee of Buddhist Dalin Tzu Chi Hospital (No. B10803015-1).

In this nested case-control study, the relevant disease designation was defined by using the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) code in the medical record diagnosis field. First, we recruited pregnant women 20–55 years of age who had a first-time diagnosis of pregnancy as V22, V23, or 640–648 in the outpatient dataset or as operation code 74 in the inpatient dataset for cesarean delivery between 2001 and 2012 ($n = 70{,}638$). The patients were divided into two groups according to whether they have, or have not, sought ambulatory healthcare services for LBP during their pregnancy (ICD-9-CM codes 721.3, 722.1, 724.02, 724.09, 724.2, 724.3, 724.5, 724.9) (15). To minimize the potential for disease misclassification, LBP was defined as at least three consensus diagnoses during outpatient visits, within 1 year, or hospital admission with a primary diagnosis, all with the required diagnostic code for LBP. The first LBP diagnosis was defined as the index date. The control group comprised patients randomly selected from the remaining insured pregnant women without LBP. For each patient, one matched control was selected using frequency matching for age and entry date. Each control was assigned the index date of the corresponding patient. After matching, we then analyzed the history of OMT use for LBP before pregnancy in both groups (**Figure 1**).

Definition of Exposure

From the medical claims data, we defined history of OMT use as the code "C4" in records of ambulatory care visits dating from 1996, when computerized claims data from the LHID became available, until the index date. For inclusion, we required that OMT services were provided by a certified Chinese medicine physician to ensure diagnostic validity and to avoid any potential misclassifications. Under the NHI program in Taiwan, only certified Chinese medicine physicians are allowed to provide OMT therapy that contains high-velocity/low-amplitude (HVLA) and myofascial release (MFR).

Inclusion of Potential Confounders

Potential confounders included age, monthly income (for estimating insurance payment), urbanization level of the enrollee's residential area, and previous comorbidities. Monthly income was separated into 3 classes, from lowest income (class 1) to highest income (class 3). A previous study classified urbanization into 7 levels, with a higher number indicating a more urban environment (16). In this study, we classified urbanization into 3 levels: high (metropolitan cities), medium (small cities and suburban areas), and low (rural areas). Baseline comorbidities for each woman were determined based on claims data for 1 year before index date, all of which were assessed by the established Charlson-Deyo comorbidity index (CCI) (17). It

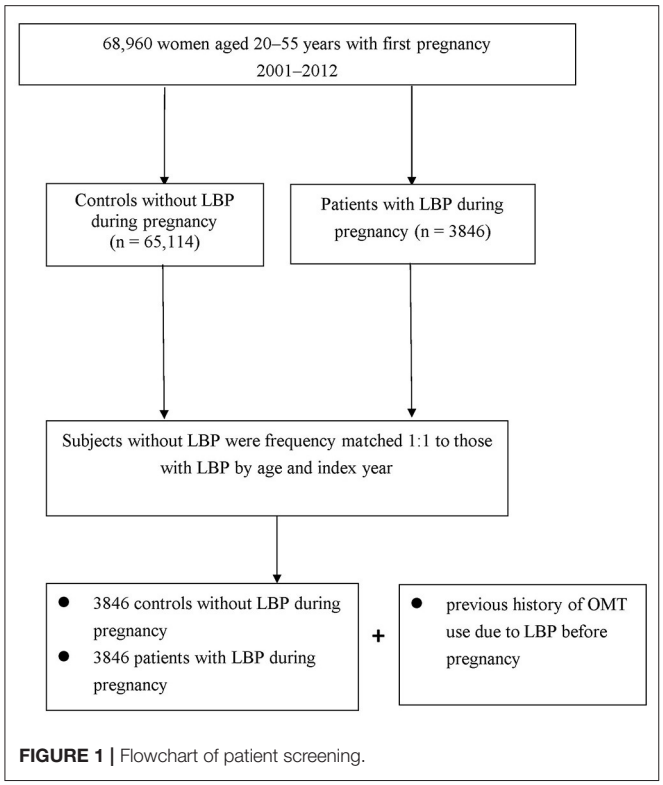

FIGURE 1 | Flowchart of patient screening.

is a commonly used method of categorizing comorbid conditions of patients based on the diagnostic codes found in administrative data. Higher scores on the CCI are indicative of a more severe impact of the concomitant comorbidities.

Statistical Modeling

All statistical analyses were carried out using SAS version 9.3 software (SAS Institute Inc., Cary, NC, USA). We used the Chi-square test and independent *t*-test to compare demographic characteristics between the patients and controls. Univariate conditional logistic regression analysis was used to estimate the crude association between each covariate and LBP during pregnancy. Multivariate conditional logistic regression analysis was used to evaluate the association between a previous history of OMT use and LBP. All multivariate models were adjusted for patient comorbidities and demographic data. Furthermore, to ensure robustness of the findings herein, we conducted a sensitivity analysis that further divided all subjects into 2 groups, according to their placement of either above and below the 50th percentile for the frequency of OMT use. This procedure allowed us to directly estimate the effect of OMT on LBP prevention. The associations are presented as odds ratio (OR) with 95% confidence interval (CI). The statistical test results were considered significant with a 2-sided $p < 0.05$.

RESULTS

From the original cohort, we identified 3,846 women with newly diagnosed LBP and 3,846 controls who did not experience LBP during pregnancy. The baseline characteristics of the two groups are shown in **Table 1**. The age distribution between them were well-matched, with a mean age of 29.60 ± 6.21 years for all enrollees (**Table 1**). The majority of participants had a monthly income of NTD 17,881–43,900 (81.6%) and lived in urbanized areas (58.4%). For comorbidities, the mean CCI score was 0.42 (±1.96). Collectively, no significant differences were observed between the two groups with respect to age, monthly income, location of residence, or CCI score after random matching, indicating that the two groups were comparable in baseline characteristics.

TABLE 1 | Subject demographic data and comorbidities.

	Total subjects (n = 7,692)	Patients n = 3,846 (%)	Controls n = 3,846 (%)	p
Age				0.90
Mean (SD)	29.60 (6.21)	29.60 (6.23)	29.59 (6.18)	
Monthly income				0.72
Low	6,278 (81.6)	3,135 (81.5)	3,143 (81.7)	
Median	1,342 (17.4)	678 (17.6)	664 (17.3)	
High	72 (0.9)	33 (0.9)	39 (1.0)	
Residential area				0.68
Urban	4,494 (58.4)	2,238 (58.2)	2,256 (58.7)	
Suburban	1,432 (18.6)	716 (18.6)	716 (18.6)	
Rural	1,766 (23.0)	892 (11.6)	874 (22.7)	
CCI				
Mean (SD)	0.42 (1.96)	0.43 (1.99)	0.42 (1.94)	0.82

SD, standard deviation.

We next used multivariable logistic regression models to identify the association of previous OMT use with the sequent risk of LBP during pregnancy (**Table 2**). Those who ever used OMT had a lower risk of LBP than those who did not (adjusted OR, 0.86; 95% CI, 0.78–0.93). Notably, high-intensity OMT was associated with a nearly 30% lower risk of LBP, which suggests a dose-dependent inverse relationship between OMT use and the risk of LBP during pregnancy (adjusted OR, 0.72; 95% CI, 0.64–0.84).

DISCUSSION

This is the first study to our knowledge to report the OMT use prior to the pregnancy may lessen the subsequent risk of LBP during the pregnant period. We discovered that the rate of LBP throughout pregnancy was significantly lower among women who ever underwent OMT for LBP before pregnancy than among those who did not. Notably, those receiving high intensity OMT treatment had a nearly 30% lower risk of LBP than did non-OMT users. No earlier research findings have shown this relationship, rendering a comparison of results impossible. Yet, the findings obtained herein are consistent with earlier research findings and add to the growing body of knowledge on the beneficial effects of OMT for patients with chronic diseases (11, 18, 19).

While the underlying mechanisms of OMT are still not well-understood, several hypotheses have been proposed to explain the positive effect of OMT on reducing LBP. First, one study

TABLE 2 | The association between LBP onset and use of OMT before pregnancy.

OMT use before pregnancy	Subjects [*n* (%)]				Crude OR (95% CI)	Adjusted OR* (95% CI)
	Patients *n* = 3,846		Controls *n* = 3,846			
No OMT	1,852	48.2	1,710	44.5	1	1
OMT users	1,994	51.8	2,136	55.5	0.86(0.79–0.94)	0.86 (0.78–0.93)
Low intensity	1,501	39.0	1,522	39.6	0.91(0.83–0.99)	0.91 (0.83–0.98)
High intensity	493	12.8	614	16.0	0.73 (0.65–0.85)	0.72 (0.64–0.84)

*Model adjusted for age, residential area, monthly income, and CCI.

notes that use of OMT was helpful for normalizing paraspinal muscle activity and side-to-side balance, as determined by muscle functional magnetic resonance imaging (mfMRI). This treatment relieved pain and functional disability caused by lumbar muscle asymmetry, thus lessening the recurrence of LBP (20). Second, women affected by LBP are reported to have a tendency toward higher levels of pro-inflammatory cytokines such as interlukin-1 beta (IL-1), interlukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), both locally and systemically (12, 13). As of now, OMT is gaining acceptance among pregnant women, with medical professionals reporting that they adopt OMT for treating chronic LBP because of its beneficial anti-inflammatory effects (8). An *in vivo* study of patients with chronic LBP showed that the inflammatory response significantly decreased after implementation of a 6-session regimen of OMT (10). Recent studies also indicated that regulation of the autonomic nervous system functions may underlie the benefits of OMT, thus resulting in the reduction of pro-inflammatory substances (11, 21). Immune cells and inflammatory responses are affected by both parasympathetic and sympathetic efferent nerves (22), with the latter implicated in the earlier stages of the inflammatory process and the former playing a decisive role in regulating innate immune responses and cytokine function in chronic process (23, 24).

While the clinical success of OMT observed in this study may support the hypothesis that OMT modulates biomechanical function and reduces LBP onset, several limitations should be considered. First, our findings were derived from analysis of retrospective claim data based on ICD-9-CM diagnostic codes. Thus, relevant cases may have been misclassified. To improve diagnostic accuracy and minimize overestimation of the prevalence of conditions of interest, we enrolled only women with a first-time diagnosis of pregnancy or LBP. LBP classification required either: (a) at least three outpatient visits reporting consistent diagnoses in 1 year or (b) at least one inpatient admission. In addition, the NHI Administration randomly reviews the records of 1 in 100 ambulatory care visits, and 1 in 20 in-patient claims to verify the accuracy of the diagnosis. Also, a certain degree of exposure misclassification is inevitable. However, because the coding approach and data set were similar, regardless of case/control status, we believe this bias to be non-differential to cause an underestimate of the association. Second, the LHID lacks information on variables such as social network relationships, family history, laboratory data, and fetal weight. Accordingly, residual confounding might occur in the observed association. Third, the records of OMT are administratively integrated and are only available in a single location, thus precluding further examination of the initial database. It is, therefore, impossible to directly identify which specific OMT was applied to each patient. As a result, data are not available to directly compare specific therapeutic effects across diverse forms of OMT. Future research to address this concern, by using clinical survey in diverse groups of individuals, is warranted. Finally, despite our balanced study design, in which several confounding factors were adequately controlled, data derived from a retrospective nested case-control study are generally of lower statistical rigor than those derived from randomized trials because of potential biases. Therefore, well-designed randomized controlled trials are needed to minimize confounding by covariates not explicitly accounted for in the present design, thus paving the way for further *in vivo* studies on the effect of OMT on patients with other chronic disorders. These limitations notwithstanding, this investigation has several strengths. A major strength of this study is that it included a large, population-based sample that is highly representative, leaving little room for selection bias. Moreover, compared with former studies, our outcomes were based on administrative codes instead of patient self-report, and our multivariate model included adjustment for several potentially significant covariates, all of which could strengthen the validity of the study findings.

CONCLUSION

To our knowledge, this study is the first large-scale investigation of the effect of OMT on the risk of pregnancy-related LBP based on nationwide figures. We found that high-intensity use of OMT prior to the pregnancy indeed ameliorated LBP risk in later pregnancy by nearly 30%. These findings suggest that clinicians might consider recommending OMT to pregnant women to minimize subsequent obstetric complications and negative effects on pediatric health throughout the pregnancy period.

DATA AVAILABILITY STATEMENT

The data supporting the conclusion of this study are available from the authors, but the raw data (NHIRD) need to be obtained from the National Health Research Institute of Taiwan through an application process upon approval.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board and Ethics Committee of Buddhist Dalin Tzu Chi Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

Study concept and design and writing: W-CC, W-JC, HL, C-TY, M-CH, and T-YT. Acquisition of data: W-JC, M-CL, and T-YT. Data analysis: HL and T-YT. Project management: W-CC, W-JC, and T-YT. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Wu A, March L, Zheng X, Huang J, Wang X, Zhao J, et al. Global low back pain prevalence and years lived with disability from 1990 to 2017: estimates from the Global Burden of Disease Study 2017. *Ann Transl Med.* (2020) 8:299. doi: 10.21037/atm.2020.02.175
2. Wang SM, Dezinno P, Maranets I, Berman MR, Caldwell-Andrews AA, Kain ZN. Low back pain during pregnancy: prevalence, risk factors, and outcomes. *Obstet Gynecol.* (2004) 104:65–70. doi: 10.1097/01.AOG.0000129403.54061.0e
3. Long G, Yao ZY, Na Y, Ping Y, Wei S, Mingsheng T. Different types of low back pain in relation to pre- and post-natal maternal depressive symptoms. *BMC Pregn Childb.* (2020) 20:551. doi: 10.1186/s12884-020-03139-9
4. Daneau C, Abboud J, Marchand A-A, Houle M, Pasquier M, Ruchat SM, et al. Mechanisms underlying lumbopelvic pain during pregnancy: a proposed model. *Front Pain Res.* (2021) 2:773988. doi: 10.3389/fpain.2021.773988
5. Long G, Fang ZY, Xiang-Sheng T, Feng Y, Hao-ning M, Qing-ying H, et al. Symmetry in paraspinal muscles as a predictor of the development of pregnancy-related low back and pelvic pain: a prospective study. *Orthop Surg.* (2021) 13:2255–62. doi: 10.1111/os.13126
6. Ystrom E, Gustavson K, Brandlistuen RE, Knudsen GP, Magnus P, Susser E, et al. Prenatal exposure to acetaminophen and risk of ADHD. *Pediatrics.* (2017) 140:e20163840. doi: 10.1542/peds.2016-3840
7. Li DK, Ferber JR, Odouli R, Quesenberry C. Use of nonsteroidal antiinflammatory drugs during pregnancy and the risk of miscarriage. *Am J Obstet Gynecol.* (2018) 219:275.e1–275.e8. doi: 10.1016/j.ajog.2018.06.002
8. Licciardone JC, Aryal S. Prevention of progressive back-specific dysfunction during pregnancy: an assessment of osteopathic manual treatment based on Cochrane Back Review Group criteria. *J Am Osteopath Assoc.* (2013) 113:728–36. doi: 10.7556/jaoa.2013.043
9. Koukoulithras I Sr, Stamouli A, Kolokotsios S, Plexousakis M Sr, Mavrogiannopoulou C. The effectiveness of non-pharmaceutical interventions upon pregnancy-related low back pain: a systematic review and meta-analysis. *Cureus.* (2021) 13:e13011. doi: 10.7759/cureus.13011
10. Licciardone JC, Kearns CM, Hodge LM, Bergamini MV. Associations of cytokine concentrations with key osteopathic lesions and clinical outcomes in patients with nonspecific chronic low back pain: results from the OSTEOPATHIC Trial. *J Am Osteopath Assoc.* (2012) 112:596–605. doi: 10.7556/jaoa.2012.112.9.596
11. Cerritelli F, Cardone D, Pirino A, Merla A, Scoppa F. Does osteopathic manipulative treatment induce autonomic changes in healthy participants? A thermal imaging study. *Front Neurosci.* (2020) 14:887. doi: 10.3389/fnins.2020.00887
12. Sainoh T, Orita S, Miyagi M, Inoue G, Yamauchi K, Suzuki M, et al. Single intradiscal injection of the interleukin-6 receptor antibody tocilizumab provides short-term relief of discogenic low back pain; prospective comparative cohort study. *J Orthop Sci.* (2016) 21:2–6. doi: 10.1016/j.jos.2015.10.005
13. Ren K, Torres R. Role of interleukin-1β during pain and inflammation. *Brain Res Rev.* (2009) 60:57–64. doi: 10.1016/j.brainresrev.2008.12.020
14. National Health Insurance Database, Taiwan. *LHID 2000.* 2012. Available online at: http://nhird.nhri.org.tw/en/index.htm (accessed February 8, 2022).
15. Chia YY, Lo Y, Chen YB, Liu CP, Huang WC, Wen CH, et al. Risk of chronic Low back pain among parturients who undergo cesarean delivery with neuraxial anesthesia: a nationwide population-based retrospective cohort study. *Medicine.* (2016) 95:e3468. doi: 10.1097/MD.0000000000003468
16. Liu CY, Hung YT, Chuang YL, Chen YJ, Weng WS, Liu JS. Incorporating development stratification of Taiwan townships into sampling design of large scale health interview survey. *J Health Manag.* (2006) 4:1–22. doi: 10.29805/JHM.200606.0001
17. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* (1992) 45:613–9. doi: 10.1016/0895-4356(92)90133-8
18. Montrose S, Vogel M, Barber KR. Use of osteopathic manipulative treatment for low back pain patients with and without pain medication history. *J Osteopath Med.* (2021) 121:63–9. doi: 10.1515/jom-2019-0193
19. Turkistani A, Shah A, Jose AM, Melo JP, Luenam K, Ananias P, et al. Effectiveness of manual therapy and acupuncture in tension-type headache: a systematic review. *Cureus.* (2021) 13:e17601. doi: 10.7759/cureus.17601
20. Clark BC, Walkowski S, Conatser RR, Eland DC, Howell JN. Muscle functional magnetic resonance imaging and acute low back pain: a pilot study to characterize lumbar muscle activity asymmetries and examine the effects of osteopathic manipulative treatment. *Osteopath Med Prim Care.* (2009) 3:7. doi: 10.1186/1750-4732-3-7
21. Cicchitti L, Martelli M, Cerritelli F. Chronic inflammatory disease and osteopathy: a systematic review. *PLoS ONE.* (2015) 10:e0121327. doi: 10.1371/journal.pone.0121327
22. Wei Y, Liang Y, Lin H, Dai Y, Yao S. Autonomic nervous system and inflammation interaction in endometriosis-associated pain. *J Neuroinflammation.* (2020) 17:80. doi: 10.1186/s12974-020-01752-1
23. Pongratz G, Straub RH. The sympathetic nervous response in inflammation. *Arthritis Res Ther.* (2014) 16:504. doi: 10.1186/s13075-014-0504-2
24. Chobanyan-Jürgens K, Jordan J. Autonomic nervous system activity and inflammation: good ideas, good treatments, or both? *Am J Physiol Heart Circ Physiol.* (2015) 309:H1999–2001. doi: 10.1152/ajpheart.00826.2015

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Huge vaginal stone: Case report and review of the literature

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Primary vaginal stones have been rarely reported; the reports that do exist are usually case reports. Because of their low incidence, they are often misdiagnosed. This case report and literature review of a primary vaginal stone presents an assessment of symptoms and common risk factors for vaginal stone formation. A 28-year-old woman with spastic quadriplegia who had been bedridden for most of her life presented to the emergency department for abdominal distension and fever. She had chronic constipation, recurrent urinary tract infections (UTIs), and vaginal discharge. Abdominopelvic computed tomography (CT) was performed and a large stone observed. The vaginal stone was completely removed through the vaginal stump after hysterectomy. Differential diagnoses of vesicovaginal fistula, urethrovaginal fistula, genital anomaly, and ectopic ureter were made by performing several tests using indigo-carmine dye. She recovered from surgery without any complications. There was no recurrence of vaginal stones after 3 months. A biochemical analysis reported that the vaginal stone was 100% struvite. Vaginal stones are caused by repeated infections in an environment in which urine collects gradually. Patients with recurrent UTIs who are bedridden should be able to prevent vaginal stones with periodic gynecological examinations for early diagnosis and management.

KEYWORDS

vaginal stone, spastic quadriplegia, primary vaginal calculus, struvite, recurrent urinary tract infections (rUTIs)

Introduction

Vaginal stones are rare and have been presented only in case reports (1). Stones can occur in the kidney, ureter, bladder, gallbladder, and salivary glands; however, they are commonly found in the urinary system (2). Vaginal stones, also called vaginal calculus, are formed by a mechanism similar to that of urinary stones (3). They are classified as primary or secondary depending on the presence or absence of nidus. Primary vaginal stones result from urine stasis in the vagina; however, secondary vaginal stones form as urine crystalizes around foreign bodies in the vagina (4, 5).

There have been several case reports of vaginal stones; however, they have been found sporadically over the course of approximately 80 years. Therefore, we conducted a review of case reports published in English after the 2000s. While reviewing these case reports, paralyzed patients who spent most of their time

bedridden accounted for a high proportion of vaginal stone cases. We aimed to contribute to the knowledge of the origin of vaginal stones among bedridden patients and to prevent this disease by reviewing the literature and sharing our case.

Case presentation

A 28-year-old woman presented with fever and abdominal distension to our tertiary hospital emergency department. Abdominopelvic contrast-enhanced computed tomography (CECT) was performed to find the cause of the fever, and a large, hard mass was observed in the vagina (**Figure 1**). Therefore, she was referred to the gynecology department. The patient was living in a social welfare facility because she had no relatives. Therefore, her caregiver, who was a staff member at the facility, had limited knowledge of the patient's family history and medical history. The caregiver told us that the patient had chronic constipation, recurrent urinary tract infections (UTIs), and vaginal discharge with odor for a prolonged time. The patient had quadriplegia as a result of cerebral palsy when she was young and had undergone laparotomy for peritonitis at approximately 7 years of age. She had severe mental and motor disabilities, joint contractures involving the lower and upper limbs, and spasticity. She spent most of her time bedridden in a supine position and defecating in diapers. Both ovaries and the uterus were normal according to CECT, and there was a 9.3 cm × 8 cm × 6 cm mass compressing the rectum between the bladder and colon; therefore, we suspected that the stone was inside the vagina (**Figure 1**). During physical examination, her abdomen was distended, her external genitalia was normal, and her hymen was intact. Vaginal discharge was mucoid, yellowish-gray, and had an unpleasant odor. During the speculum examination, a stone-like mass was found within the vagina. Because of her fever, bacteriuria, and pyuria, our diagnosis was UTI accompanied by a vaginal calculus. *Proteus vulgaris* and *Streptococcus anginosus* were found in her urine culture. The UTI was treated antibiotics. We consulted with a urologist and decided to use Holmium laser lithotripsy to cut the vaginal stone into pieces so it could be removed through the vaginal opening. Under general anesthesia, we placed her in the lithotomy position and tried to cut into the vaginal stone with Holmium laser lithotripsy for about 6 h and 45 min; however, the stone was too hard. Consequently, surgery was ended without removing the vaginal stone. She recovered well from surgery and was discharged approximately 1 week later. However, during her follow-up examination at the clinic, it was observed that an edge of the broken stone had stabbed the vaginal wall, resulting in bleeding and inflammation. The secretion worsened and the UTI recurred. After discussion with one of her caregivers, we decided to remove the vaginal stone by performing hysterectomy through laparotomy after treating UTI with antibiotics and daily vaginal irrigation. Under general anesthesia, hysterectomy was performed with a low-midline incision in the lithotomy position. After hysterectomy, the stone was carved out of the vaginal stump using a small drill for approximately 1 h (**Figure 2**). The vaginal stone was completely removed (**Figure 3**). To rule out other causes of vaginal stone formation during surgery, the vaginal wall was inspected closely after injection of intravenous indigo-carmine dye. We did not find an ectopic ureter or fistula. The patient was discharged without complications 10 days after surgery. Her caregiver was instructed to maintain the patient's posture upright at least twice per day and to visit the gynecology clinic periodically to prevent the recurrence of vaginal stones. Three

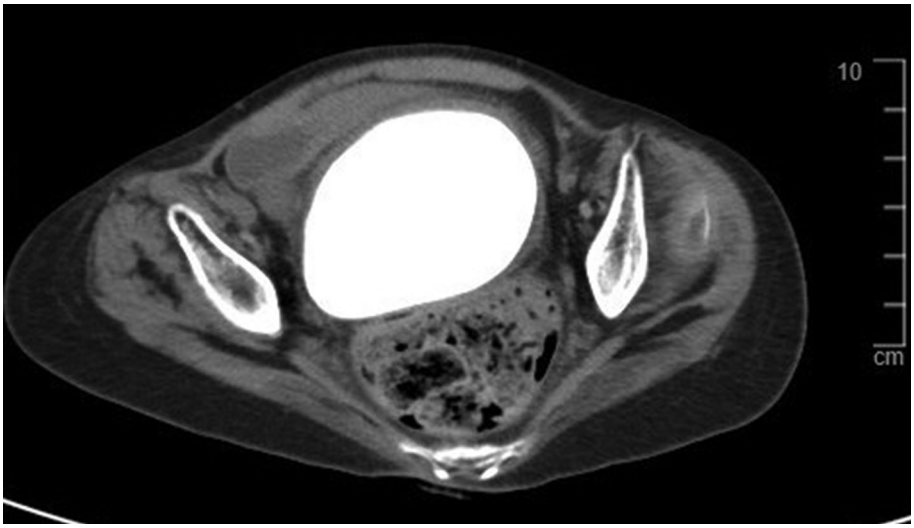

FIGURE 1
Computed tomography (axial view) show 9.3 cm × 8.0 cm high density mass with smooth margin between bladder and rectum.

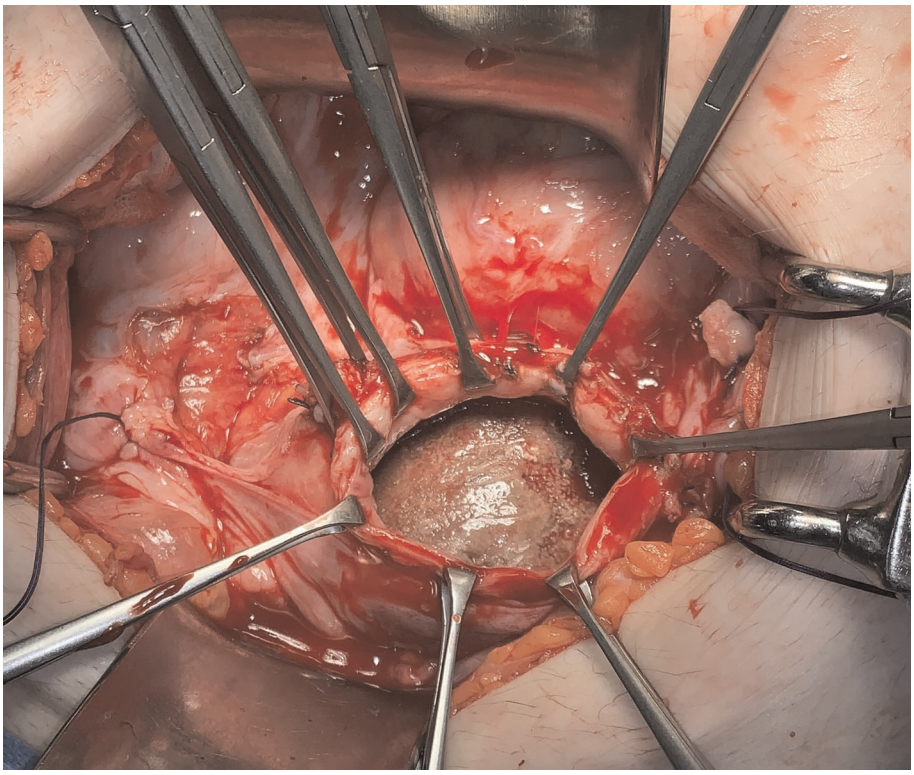

FIGURE 2
After hysterectomy, stone can see through stump during surgery.

months after surgery, the patient had no vaginal stone or UTI recurrence. The vaginal stone weighted 600 g. The biochemical analysis indicated that it comprised 100% struvite.

Literature review

We searched PubMed and EMBASE for primary vaginal stones and primary vaginal calculus. The search was limited to articles published from January 1, 2000 to March 30, 2022. We included pediatric articles; however, we excluded articles related to secondary vaginal stones. The relevant data summarized in **Table 1** were extracted from the case report descriptions. The ages of the patients ranged was from 4 to 69 years. Of a total of 24 patients, 14 presented with urogenital defects or anomalies such as vesicovaginal fistula, urethrovaginal fistula, and vaginal outlet obstruction. Ten out of 24 patients were bedridden with paraplegia or tetraplegia (42%). The periods when patients were bedridden ranged from 5 years to 42 years. The correlation between the length of the bedridden period and the vaginal stone size was not significant. Most case reports included urinary incontinence and recurrent UTIs. Nonspecific symptoms such as fever and stone passage were observed in children and paralyzed individuals. The main causes of vaginal stones are described in **Table 1**. In 22 of the 24 case reports, urine stagnation was the main cause of vaginal stones. The two excluded case reports, which included vaginal outlet obstruction, assumed that the cause of the vaginal stone was of hematic origin. Among the 24 case reports, six did not describe the stone composition. Forteen of the eighteen case reports that described the composition of the vaginal stones reported that they contained struvite. Other reported components of the stones were carbonate apatite, calcium phosphate, oxalate, and hemosiderine. They were found simultaneously with struvite in three case reports. Four of the 18 case reports that described the composition of vaginal stones did not indicate that the stones contained struvite. In three of the 24 case reports, vaginal stones were removed transperitoneally; in the remaining 21 case reports, episiotomy or hymenectomy was performed to remove the stones vaginally.

Discussion

The occurrence of vaginal stones is rare and has been reported only in case reports since 1926 (6). Most of the vaginal stones reported so far comprised struvite. Struvite is composed of magnesium ammonium phosphate. It is formed by a combination of two factors: decreased urine volume and

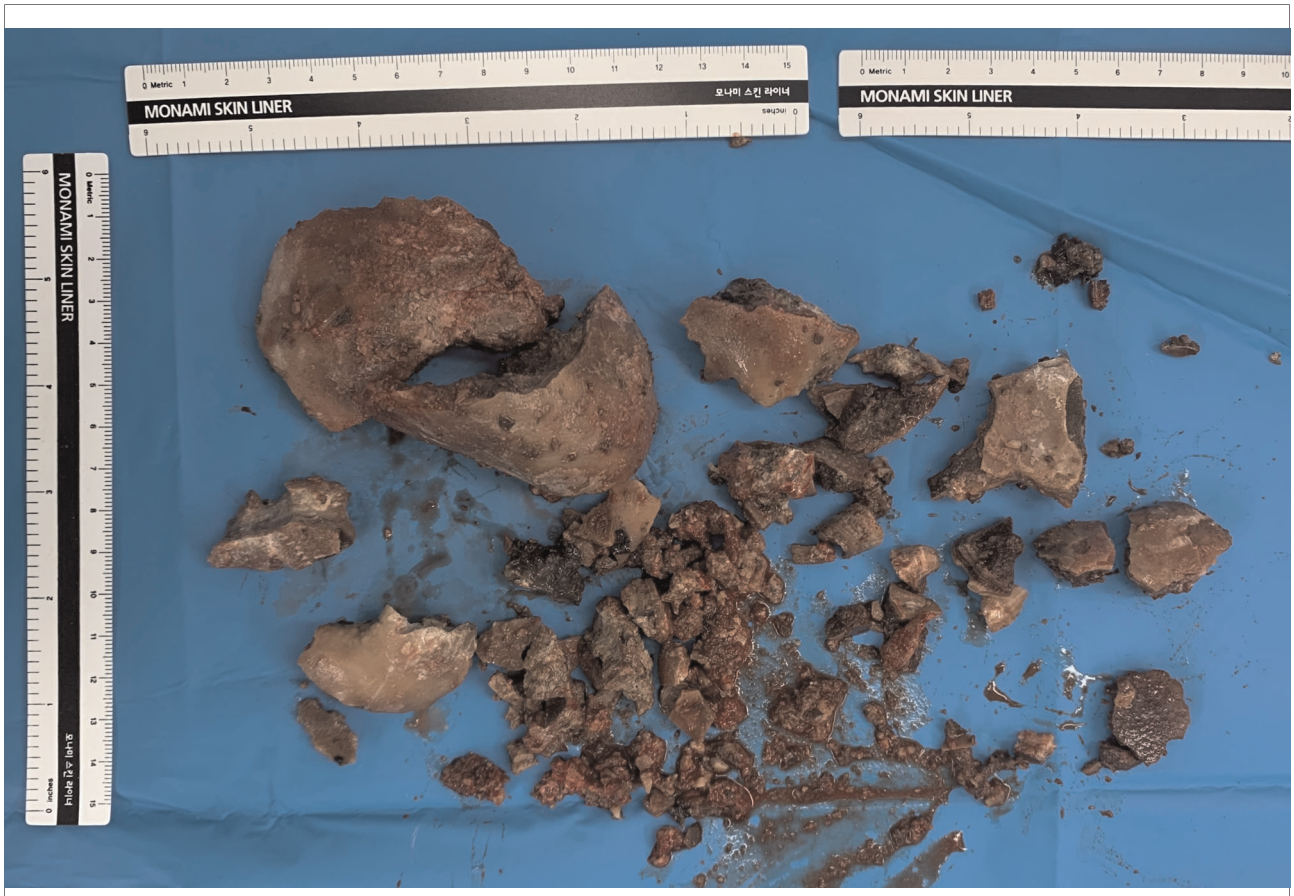

FIGURE 3
Round laminated vaginal stone was removed through stump after grinding.

infection with bacterial species such as *Proteus*, *Staphylococcus*, *Pseudomonas*, and *Klebsiella*, which increase the urine pH by producing urease (7, 8). Many of the case reports classified vaginal stones as primary or secondary according to the presence or absence of a nidus (6). Secondary vaginal stones are caused by repeated infections caused by foreign bodies such as an intrauterine device (5), surgical gauze (9), or mesh (10) that act as the nidus and promote mineral accumulation. In contrast, primary vaginal stones do not have a nidus. Related case reports are listed in **Table 1**.

We reviewed the case reports of primary vaginal stones published since 2000. The majority of the case reports described urine stasis in the vagina and recurrent UTIs, which might be important risk factors for the formation of vaginal stones. Vesicovaginal fistula, urethrovaginal fistula, urogenital sinus anomaly, and genital anomaly cause urinary retention in the vagina. Of 25 cases reports (including our case report), 14 cases involved a urogenital anatomic abnormality such as a vaginal outlet obstruction, fistula, or urogenital sinus anomaly. Notably, 11 of the 24 patients reported (including our patient) were bedridden for a long period of time because of disability. In other words, patients with a vaginal stone seem to be bedridden for long periods or have a genitourinary malformation. In particular, the lying position can result in urine retention that is severe enough to form a fistula. During surgery of our patient, we found that the bladder capacity was approximately 50 ml, which is approximately 10-times smaller than that of the adult bladder. Presumably, dissonance between contraction of the bladder detrusor muscle and the urethral sphincter causes decreased bladder capacity and leads to urine leakage. Leaked urine passes through the vaginal wall and stagnates in the vaginal cavity, thus leading to bacterial colonization in the stagnant urine. Because *Proteus* species proliferate in urine, and because the urine pH was 9 in our patient, the infected urine passed to the vagina, resulting in urease production and an alkaline vaginal environment. Ureolysis caused by urease increases ammonia and bicarbonate, thus creating a supersaturated state and resulting in struvite crystal formation (8). Because the enlarged vaginal stone pressed the bladder, the bladder became atrophied, and urine leakage became more frequent. Because the stone remained in the vagina, more frequent UTIs occurred. The patient had no history of child birth, and the stump was expected to be too small after hysterectomy to remove the

TABLE 1 Reports of primary vaginal stones.

Author/year	Age	Immobility/ years	Urogenital anatomy	Symptoms	Cause of the stone	Size/component	Treatment
Yoshimura et al., 2000 (11)	11	Yes/11 years	Normal	Vaginal passage of stone, recurrent UTI	Urine retention and infection	4 × 3 cm^2 /struvite	Transvaginal extraction
Bar-Moshe et al., 2000 (12)	26	No	PVO	Urinary incontinence	Urine retention	5 × 6 cm^2/not described	Transperitoneal approach
PLAIRE et al., 2000 (13)	4	No	PVO	Urinary incontinence	Urine retention	Not described/ probably struvite	Transvaginal extraction
PLAIRE et al., 2000 (13)	13	No	PVO	Recurrent UTI	Recurrent infection	Not described/ calcium phosphate	Transvaginal extraction
Cetinkurşun et al., 2001 (14)	13	Yes/ 13 years	Normal	Urinary incontinence	Urine retention	4 × 3 cm^2/struvite (85%) + micronate apatite (15%)	Transvaginal extraction
Ergün et al., 2002 (15)	23	No	PVO	Apareunia	Hematocolpos	1 × 1 cm^2/hemosiderine + oxalate + Phosphate + carbonate + ammonium	Transvaginal extraction
Malhotra et al., 2004 (3)	21	No	PVO	Apareunia	Hematocolpos	8 × 8 cm^2/struvite	Transvaginal extraction
Lin et al., 2005 (16)	43	Yes/40 years	Normal	Urinary incontinence	Urine retention	10 × 8 cm^2/ not described	Transperitoneal approach
Ho and Lin, 2008 (17)	24	No	Transvaginal septum, hypospadias	Dyspareunia	Urine retention	4 × 3 cm^2/carbonate apatite	Transvaginal extraction
Liu et al., 2008 (18)	14	No	PVO, urethrovaginal fistula	Urinary incontinence, recurrent UTI	Urine retention	2 × 2 cm^2/struvite	Transperitoneal approach
Oguzkurt et al., 2009 (4)	6	No	Imperforated hymen, urethrovaginal fistula	Abdominal pain, fever	Urine retention	2.5 × 1.5 cm^2/struvite	Transvaginal extraction
Urbanowicz et al., 2010 (19)	11	Yes/11 years	PVO	Urinary incontinence, recurrent UTI	Urine retention and infection	6.5 × 3 cm^2/struvite	Transvaginal extraction
Jaspers et al., 2010 (20)	5	Yes/5 years	Normal	Recurrent UTI	Urine retention and infection	3 × 2 cm^2/struvite	Transvaginal extraction
Chen et al., 2011 (21)	12	No	PVO, vesicovaginal fistula	Dysuria	Urine retention and infection	8 × 7 cm^2/struvite	Transvaginal extraction
Avsar et al., 2013 (22)	22	Yes/22 years	Normal	Chronic pelvic pain	Urine retention and infection	9 × 7 cm^2/struvite	Transvaginal extraction
Ikeda et al., 2013 (23)	42	Yes/42 years	Normal	No symptoms	Urine retention	2 × 1.5 cm^2/struvite (98%) + calcium phosphate (2%)	Transvaginal extraction
Gunes and Uygun, 2014 (24)	11	No	Wide vaginal orifice	Vaginal passage of stone	Urine retention	1.5 × 1.5 cm^2/struvite	Transvaginal extraction
Castellan et al., 2017 (1)	34	Yes/34 years	Normal	Fever	Urine retention and infection	5.1 × 3.7 cm^2/struvite	Transvaginal extraction
Tokgöz et al., 2018 (25)	14	Yes/9 years	Normal	Poor appetite	Urine retention and infection	3.8 × 2 cm^2/struvite	Transvaginal extraction
Wei et al., 2019 (26)	28	No	Urethrovaginal fistula	Frequency, dyspareunia	Urine retention and infection	6 × 5 cm^2/not described	Transvaginal extraction
Xu and Zou, 2020 (27)	23	No	Urogenital sinus anomaly	Recurrent abdominal pain amenorrhea	Urine retention	8 × 7 cm^2/not described	Transvaginal extraction
Fedrigon et al., 2020 (28)	61	Yes/15 years	Normal	Vaginal bleeding	Urine retention	10.6 × 8.8 cm^2/struvite (60%) + calcium phosphate (40%)	Transvaginal extraction
Ranawaka et al., 2020 (29)	12	No	Urogenital sinus anomaly	Recurrent abdominal pain	Urogenital sinus anomaly	1.4 × 0.8 cm^2/not described	Transvaginal extraction
Kurmanov et al., 2022 (30)	69	No	Vesicovaginal fistula	Vaginal discharge	Urine retention	5 × 0.5 cm^2/not described	Transvaginal extraction

PVO, Partial vaginal outlet obstruction.

vaginal stone through laparotomy; therefore, we attempted to remove it through vaginal extraction. However, Holmium laser lithotripsy was unsuccessful because the stone was difficult to break. The second surgery confirmed that our prediction was wrong. The stump and vaginal wall, which were exposed after hysterectomy, were sufficiently dilatated; therefore, the vaginal stone was cut into pieces (**Figures 2**, **3**).

This case report and literature review had several limitations. The vaginal stone in this case did not undergo culture testing; hence, it was inferred through urine culture testing that it was not the primary cause of bacteria. Because only case reports were reviewed and there was no control group for comparison, we could not estimate the general incidence of vaginal stones among nonimmobilized patients or accurately define the risk factors for vaginal stones.

Vaginal stones are rare and have been described only by reports. Therefore, we reviewed other case reports to contribute to the knowledge of vaginal stones in immobilized patients. These patients present to the hospital with nonspecific symptoms because they are not able to express their discomfort or pain. If patients with immobility have recurrent UTIs, then clinicians should perform simple radiography or consult a gynecologist to confirm or dismiss the diagnosis of vaginal stones and prevent their complications.

Conclusion

When treating bedridden patients, especially those with recurrent UTIs, it is necessary to consider the possibility of vaginal stones because their symptoms are not specific. For women, a gynecologic examination and simple radiography should be considered.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the patients and caregiver for the publication of any potentially identifiable images and data included in this article.

Author contributions

JJ drafted the work, obtained the data, performed searches and analyses, and completed most of the writing. SL and WC prepared radiographic images. JS contributed to the conception and substantively revised the manuscript. IC was responsible for revising the manuscript and its knowledge content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Castellan P, Nicolai M, De Francesco P, Di Tizio L, Castellucci R, Bada M, et al. Primary vaginal calculus in a woman with disability: case report and literature review. *J Endourol Case Rep*. (2017) 3(1):182–5. doi: 10.1089/cren.2017.0100

2. Rodgers AL, Spector M. Human stones. *Endeavour*. (1981) 5(3):119–26. doi: 10.1016/0160-9327(81)90044-2

3. Malhotra N, Kumar S, Roy KK, Agarwal R, Verma V. Vaginal calculus secondary to vaginal outlet obstruction. *J Clin Ultrasound*. (2004) 32(4):204–6. doi: 10.1002/jcu.20015

4. Oguzkurt P, Ince E, Ezer SS, Temiz A, Demir S, Hicsonmez A. Primary vaginal calculus secondary to urethrovaginal fistula with imperforate hymen in a 6-year-old girl. *J Pediatr Surg*. (2009) 44(7):e11–3. doi: 10.1016/j.jpedsurg.2009.03.040

5. Aronson SL, Hovius MC, Janszen EWM. Large primary vaginal stone in a woman with multiple sclerosis. *BMJ Case Rep*. (2020) 13(10):e235103. doi: 10.1136/bcr-2020-235103

6. Navani S, Tessier PA. A primary vaginal stone. *Br J Radiol*. (1970) 43 (507):222–3. doi: 10.1259/0007-1285-43-507-222

7. Vella M, Karydi M, Coraci G, Oriti R, Melloni D. Pathophysiology and clinical aspects of urinary lithiasis. *Urol Int*. (2007) 79(Suppl. 1):26–31. doi: 10.1159/000104438

8. Griffith DP. Struvite stones. *Kidney Int*. (1978) 13(5):372–82. doi: 10.1038/ki.1978.55

9. Patankar S, Dobhada S, Bhansali M. Vesicovaginal fistula with secondary vaginal stones. *J Laparoendosc Adv Surg Tech*. (2006) 16(4):386–9. doi: 10.1089/lap.2006.16.386

10. Griffiths KM, Towers GD, Yaklic JL. Vaginal urinary calculi formation secondary to vaginal mesh exposure with urinary incontinence. *Case Rep Obstet Gynecol*. (2017) 2017:1–3. doi: 10.1155/2017/8710315

11. Yoshimura T, Nagata Y, Matsuura K, Okamura H. Primary vaginal stone in an 11-year-old recumbent girl. *Gynecol Obstet Invest*. (2000) 50(1):64–6. doi: 10.1159/000010283

12. Bar-Moshe O, Oboy G, Assi J. Vaginal calculi in a young woman. *Eur Urol*. (2000) 37(4):505–7. doi: 10.1159/000020176

13. Plaire JC, Snodgrass WT, Grady RW, Mitchell ME. Vaginal calculi secondary to partial vaginal outlet obstruction in pediatric patients. *J Urol*. (2000) 164(1):132–3. doi: 10.1016/S0022-5347(05)67478-2

14. Cetinkurşun S, Surer I, Demirbag S, Oztürk H. A primary vaginal stone in a disabled child. *Obstet Gynecol*. (2001) 98(5 Pt 2):978–9. doi: 10.1097/00006250-200111001-00038

15. Ergün SS, Babalioglu R, Aydin S, Ozmen N, Sidal B, Koser RM. Vaginal stones with a pinpoint hymenal opening. *Arch Gynecol Obstet*. (2002) 266 (1):58–9. doi: 10.1007/pl00007503

16. Lin C-J, Chen C-P, Wu C-H, Chen H-Y, Hsu H-H. Huge primary vaginal stone in a recumbent woman. *Taiwan J Obstet Gynecol*. (2005) 44(1):80–2. doi: 10.1016/S1028-4559(09)60114-5

17. Ho TC, Lin IL. Primary vaginal stone in a young active woman. *Taiwan J Obstet Gynecol*. (2008) 47(4):457–9. doi: 10.1016/s1028-4559(09)60019-x

18. Liu B, Huang X, Lu J, Zhang Z, Wang P, Huang Z. Vaginal calculi secondary to urethrovaginal fistula with vaginal stenosis in a 14-year-old girl. *Urol Res*. (2008) 36(1):73–5. doi: 10.1007/s00240-007-0129-x

19. Urbanowicz W, Szymik-Kantorowicz S, Sulisławski J, Wolnicki M. Primary vaginal stone in a disabled child. *Cent European J Urol*. (2010) 63(4):187–9. doi: 10.5173/ceju.2010.04.art4

20. Jaspers JW, Kuppens SM, van Zundert AA, de Wildt MJ. Vaginal stones in a 5-year-old girl: a novel approach of removal. *J Pediatr Adolesc Gynecol*. (2010) 23 (1):e23–5. doi: 10.1016/j.jpag.2009.05.006

21. Chen S, Ge R, Zhu L, Yang S, Wu W, Yang Y, et al. Giant primary vaginal calculus secondary to vesicovaginal fistula with partial vaginal outlet obstruction in a 12-year-old girl. *Urology*. (2011) 78(4):908–10. doi: 10.1016/j.urology.2011.01.026

22. Avsar AF, Keskin HL, Catma T, Kaya B, Sivaslioglu AA. A large primary vaginal calculus in a woman with paraplegia. *J Low Genit Tract Dis*. (2013) 17 (1):61–5. doi: 10.1097/LGT.0b013e31824d6f9c

23. Ikeda Y, Oda K, Matsuzawa N, Shimizu K. Primary vaginal calculus in a middle-aged woman with mental and physical disabilities. *Int Urogynecol J*. (2013) 24(7):1229–31. doi: 10.1007/s00192-012-1902-0

24. Gunes A, Uygun I. Is every stone urinary stone? A rare case of stone. *Pediatr Urol Case Rep*. (2014) 1(2):18–20. doi: 10.14534/PUCR.201424453

25. Tokgöz Y, Erdem AO, Özbey BC, Terlemez S. A rare reason in a child with feeding intolerance: intravaginal struvite stone. *Turk J Pediatr*. (2018) 60(1):86–8. doi: 10.24953/turkjped.2018.01.013

26. Wei D, Xie Y, Niu X. Vaginal stones caused by urethrovaginal fistula: a case report. *Medicine (Baltimore)*. (2019) 98(47):e18003. doi: 10.1097/md.0000000000018003

27. Xu Q, Zou Y. Primary vaginal calculus in a woman with urogenital sinus anomaly: a case report. *BMC Urol*. (2020) 20(1):142. doi: 10.1186/s12894-020-00708-0

28. Fedrigon D, Bretschneider CE, Muncey W, Stern K. Removal of large primary vaginal calculus using the nephroscope and endoscopic ultrasonic lithotrite: a case report. *J Endourol Case Rep*. (2020) 6(2):92–5. doi: 10.1089/cren.2019.0099

29. Ranawaka RS, Goyal A, Shabani A, Hennayake S, Dickson AP, Cervellione RM. Novel approach to vaginal calculus in a girl with urogenital sinus anomaly. *J Pediatr Surg*. (2020) 55(9):e4–5. doi: 10.1016/j.jpedsurg.2012.07.033

30. Kurmanov TA, Kulkayeva GU, Shakirova AF, Shalekenov SB, Mugalbekov S, Mustafinov DD. Primary vaginal stone associated with vesicovaginal fistula: a case report. *Urol Case Rep*. (2022) 40:101917. doi: 10.1016/j.eucr.2021.101917

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ORIGINAL RESEARCH
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A Survey on Current Practices of Umbilical Cord Clamping in Malaysia

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Background: Delayed cord clamping (DCC) has been demonstrated to have significant benefits in reducing the incidence of intraventricular hemorrhage, blood transfusion and neonatal mortality in preterm neonates and improving hemodynamic and long-term neurodevelopment among term infants. There is no clear guideline on umbilical cord clamping (UCC) practices in Malaysia.

Objective: The aim of this survey was to assess the knowledge and practice of DCC among obstetric doctors and midwives in Malaysia, and pediatric colleagues who witness the delivery.

Method: This is a cross-sectional survey conducted in childbirth facilities in Malaysia from October 2020 to January 2021. A convenient snowball sampling was adopted. A validated questionnaire was disseminated to practicing obstetric and pediatric doctors and midwives electronically via email and WhatsApp using Google Form. The data were analyzed using descriptive and analytical statistics.

Results: A total of 327 respondents completed the questionnaires, comprising 206 obstetric doctors, 72 pediatric doctors and 49 midwives. The majority of respondents were specialists or higher in rank (53.2%). Only 29% reported the existence of guidelines on UCC in their place of work. Midwives ($P = 0.003$) and staff of lower ranks and level of education ($P < 0.001$) appeared to be more aware of the existence of a UCC guideline. Most respondents had positive knowledge of DCC for both term and preterm neonates. A large proportion (82%) of respondents agreed that DCC helped increase neonatal iron stores, and was good for both preterm (70.7%) and term (76.2%) neonates not requiring positive pressure ventilation. Doctors, specialists, those who are 40 years old and above, and those who have been in service for at least 10 years were found to have better knowledge regarding DCC ($P < 0.05$).

Conclusion: The awareness and practice of obstetric, pediatric and midwifery staff of guidelines on UCC were less than satisfactory. Even though most respondents have good knowledge and positive perception regarding benefits of DCC, these were not translated into their routine practice. Hence, a national guideline emphasizing the benefits of DCC should be made available in all childbirth facilities.

Keywords: obstetricians, midwives, pediatricians, umbilical cord clamping, practices and knowledge

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INTRODUCTION

Delayed cord clamping (DCC) has been demonstrated to reduce the incidence of intraventricular hemorrhage and the need for neonatal blood transfusion in preterm neonates (1). This practice has also reduced neonatal mortality compared to early clamping in preterm infants (1, 2). The World Health Organization (WHO) recommends DCC >1 min after birth (3) as it can significantly improve hemodynamic and long-term neurodevelopment in term infants (4, 5).

Early or immediate cord clamping (ECC or ICC) is generally defined as clamping of the cord within the first 60 s after birth, and late or DCC is performed more than 60 s after birth or upon cessation of cord pulsation (4, 5).

Although the American College of Obstetricians and Gynecologists (ACOG) recommends a DCC in vigorous term and preterm infants for at least 30–60 s after birth (6), a few studies on DCC practices among healthcare professionals in different countries showed that there are variations in the management of umbilical cord clamping (UCC) and cord milking during normal births (7, 8).

Nevertheless, despite a set time of UCC recommended by WHO and ACOG, some healthcare workers used cessation of cord pulsation or waited until the expulsion of placenta as a set time for UCC (9, 10).

The extent to which this procedure is being practiced in Malaysia is unknown. The aim of this study was to assess the knowledge and practice of DCC among obstetric doctors and midwives in Malaysia, as reported by themselves or by pediatric colleagues who witness the delivery.

MATERIALS AND METHODS

We conducted a cross-sectional survey involving healthcare setups with childbirth facilities, including private hospitals and maternity centers, government hospitals and teaching hospitals in Malaysia over a period of 3 months from October 2020 to January 2021.

The inclusion criteria were obstetric doctors and midwives who conducted deliveries, and pediatric doctors who witnessed deliveries. Doctors and midwives who were not actively conducting or witnessing childbirths, e.g., retired professionals, were excluded from this survey.

This study was approved by the Universiti Kebangsaan Malaysia (UKM) Research Ethics Committee (Approval Code: JEP-2020-580).

A validated questionnaire in English on UCC practice and knowledge toward DCC from a published survey (11) was used with permission from the previous researcher. The questionnaire was sent to members of the Perinatal Society of Malaysia (PSM) and the Malaysian Pediatric Association (MPA), as well as to individual practicing obstetric and pediatric doctors and midwives in Malaysia via email or WhatsApp using Google Form. A convenient snowball sampling method was deployed.

The questionnaire covered three domains: (1) demographic data, (2) existing UCC practice, and (3) knowledge about DCC. Consent was obtained from all respondents who were provided with information regarding the survey within the Google Form.

Sample Size

The sample size was calculated using Statcalc based on a study done by Ibrahim et al. on current UCC practices and knowledge of obstetricians and midwives toward DCC in Saudi Arabia (11). Based on this study, 70% of the respondents have good knowledge toward DCC. By using Statcalc application version 7.2.4.0, with a confidence interval of 95% and margin of error of 5%, we estimated a sample size of 323. Considering 20% dropouts, we aimed to recruit 388 respondents.

Statistical Analyses

The data were analyzed using the Statistical Package for Social Sciences version 22 (IBM SPSS Statistics 22) for Windows. Results were expressed in percentages. Analyses of comparison of the percentages were conducted using the chi-square test or Fisher's exact test (for non-parametric data). In all analyses, $p < 0.05$ was taken to indicate statistical significance.

RESULTS

Study Flow Chart

The questionnaire was sent to 367 and 788 members of PSM and MPA respectively (**Figure 1**). It was also disseminated to individual practicing obstetric and pediatric doctors and midwives in Malaysia via email or WhatsApp using Google Form.

Out of a total of 348 respondents who answered the questionnaire, 327 respondents completed it. This number comprised 206 obstetric doctors, 72 pediatric doctors and 49 midwives. Meanwhile, 21 respondents did not complete the questionnaire. The completed survey rate was therefore 94%.

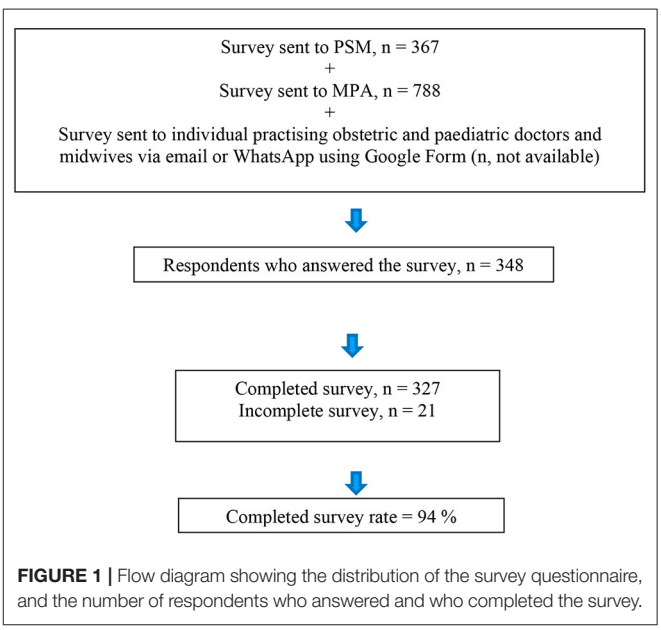

FIGURE 1 | Flow diagram showing the distribution of the survey questionnaire, and the number of respondents who answered and who completed the survey.

Demographic Background of Respondents

The majority of the respondents were females (72%), specialists, fellows or consultants (53%), aged between 30–39 years old (53%), and practicing at Government Hospitals (57%). Most respondents had tertiary educational background (99%) and about a third of the respondents were senior staff with working experience of more than 15 years (33.3%) (**Table 1**).

Existing Umbilical Cord Clamping Practice/Guideline

The majority of respondents (71%) reported no existing UCC guideline in their workplace. Among 29% of respondents who reported the presence of UCC guideline in their practice, only 44 and 50% reported always practicing or practicing most of the time, respectively.

Umbilical Cord Clamping for Term Neonates

About a third of the respondents (35%) reported setting UCC time for term neonates. Among those, the majority (62%) reported setting UCC time at 1–3 min. About one third (35%) reported no reason for this routine UCC practice, 29% followed local UCC protocol, 20% clamped the umbilical cord early to prevent polycythemia or hyperbirubinemia, and 15% clamped the cord when the cord pulsations ceased.

Most respondents (77%) applied earlier UCC or immediate cord clamping when the neonates have poor Apgar scores. Other reasons for earlier UCC were increased vaginal blood loss (41%) and presence of nuchal cord (32%). A fifth (20%) of them reported occasions when early UCC took place without any specific reason.

On the other hand, among occasions for later UCC, most of the respondents (40%) reported no specific reason for practicing that. One third (33%) performed later UCC to fulfill the wish of the parents and 16% waited for cessation of umbilical cord pulsation.

Umbilical Cord Clamping for Preterm Neonates

In preterm neonates, only 26% of the respondents reported a set UCC time. Half of these respondents (49%) reported a set UCC time of 1–3 min. About a third (35 and 32% respectively) of the respondents reported that DCC benefits or ECC benefits to pediatricians (especially when resuscitation is needed) were important for their routine UCC in preterm neonates.

UCC Time in Cesarean Section

During elective cesarean section, 22% of respondents practiced UCC at the same time as vaginal delivery and 20% reported cord milking. Most of them (61%) reported UCC time of 30–59 s. On the other hand, during emergency cesarean section, 20% of the respondents practiced UCC as soon as possible, 17 and 15%, respectively, reported cord milking or practiced UCC at the same time as performed in vaginal delivery. Out of those who reported a specific UCC time during this procedure, 40% carried out UCC at 30–59 s (**Table 2**).

Existing UCC Practices With Demographic Characteristic

There was a significantly higher rate of reporting the existence of a UCC guideline among midwives compared to doctors (47

TABLE 1 | Demographic and characteristics of respondents ($n = 327$).

Demographic and characteristics	*n* (%)
Profession	
Obstetric	206 (63.0)
Pediatric	72 (22.0)
Midwife	49 (15.0)
Level of expertise among doctors	
Houseman	6 (2.2)
Medical Officer	86 (30.9)
Registrar	38 (13.7)
Specialist	53 (19.0)
Fellow	13 (4.7)
Consultant	82 (29.5)
Gender	
Male	90 (27.5)
Female	237 (72.5)
Age (years old)	
20–29	22 (6.7)
30–39	172 (52.6)
40–49	70 (21.4)
50–59	54 (16.5)
>60	9 (2.8)
Place of practice	
Private hospital/Maternity Center	87 (26.6)
Government hospital (KKM)	187 (57.2)
University/Academic hospital	53 (16.2)
State of Malaysia where you practice	
Federal Territory of Kuala Lumpur	73 (22.3)
Federal Territory of Labuan	4 (1.2)
Federal Territory of Putrajaya	49 (15)
Johor	28 (8.6)
Kedah	7 (2.2)
Kelantan	8 (2.4)
Malacca	3 (0.9)
Negeri Sembilan	17 (5.2)
Pahang	8 (2.4)
Perak	15 (4.6)
Perlis	1 (0.3)
Penang	32 (9.8)
Sabah	10 (3.1)
Sarawak	8 (2.4)
Selangor	61 (18.7)
Terengganu	3 (0.9)
Education level	
High school	5 (1.5)
Diploma	35 (10.7)
Bachelor	129 (39.5)
Master	153 (46.8)
PhD	5 (1.5)
Years of service	
<1 year	7 (2.1)
1–5 years	66 (20.2)
6–10 years	96 (29.4)
11–15 years	49 (15.0)
>15 years	109 (33.3)

Values are number and percentage.

TABLE 2 | Existing umbilical cord clamping practices ($n = 327$).

Item	Options	Number of responses, *n*	%
Existing guidelines for UCC	Yes	95	29.0
	No	232	71.0
UCC practice following existing guideline (If answer YES)	Always	42	44.2
	Most of the time	48	50.5
	Sometimes	5	5.3
	Never	0	0.0
Set UCC time for term neonate	Yes	116	35.5
	No	211	64.5
Time of UCC in term neonate if answer YES	0–29 s	13	11.2
	30–59 s	28	24.1
	1–3 min	72	62.1
	4–10 min	2	1.7
	Others	1	0.9
Time of UCC in term neonate if answer NO	0–29 s	64	30.3
	30–59 s	85	40.3
	1–1 min 59 s	34	16.1
	2–3 min 59 s	7	3.3
	4–10 min	2	1.0
	>10 min	0	0
	Until pulsations have ceased	14	6.6
	Until the placenta detached	1	0.5
	Other	4	1.9
UCC routine*	No reason	114	34.9
	UCC according to a protocol	96	29.4
	UCC to prevent polycythemia or hyperbilirubinemia	64	19.6
	Wait as long as possible; not worried about polycythemia or hyperbilirubinemia	33	10.1
	Wait until the pulsations have ceased to optimize blood supply	50	15.3
	Wait until normal neonatal breathing to optimize blood supply	31	9.5
	Administration of meds (e.g., oxytocin) during AMTSL	16	4.9
	Other	24	7.3
Occasions for earlier UCC *	No reason	67	20.5
	Low APGAR score	252	77.1
	Excessive vaginal blood loss	134	41.0
	Short umbilical cord	54	16.5
	Neonate has Hypothermia	36	11.0
	Nuchal cord	106	32.4
	Wish of the parents	18	5.5
	Pulsations have already ceased	32	9.8
	Placental detachment from the uterine wall	52	15.9
	Administration of oxytocin/other uterotonics	14	4.3
	Low position of the infant	13	4.0
	To prevent polycythemia/hyperbilirubinemia	37	11.3
	Other	8	2.5
Occasions for later UCC*	No reason	132	40.4
	Umbilical cord is still pulsating	51	15.6
	Placenta is still attached to the uterine wall	32	9.8
	The mother is breastfeeding	9	2.7
	No vaginal blood loss	67	20.5
	Wish of the parents	109	33.3
	Other	13	4.0
Set UCC time in preterm neonate	Yes	84	25.7
	No	243	74.3
Time of UCC in preterm neonate if answer YES	0–29 s	10	11.9
	30–59 s	30	35.7
	1–3 min	41	48.8
	4–10 min	2	2.4
	>10 min	0	0.0
	Others	1	1.2
Time of UCC in preterm neonate if answer NO	0–29 s	105	43.2
	30–59 s	77	31.7
	1–1 min 59 s	30	12.4
	2–3 min	9	3.7
	4–10 min	1	0.4
	> 10 min	1	0.4
	Until pulsations have ceased	13	5.3
	Until the placenta detached	1	0.4
	Others	6	2.5
Reason of UCC when neonate is preterm	No reason	14	4.3
	ECC benefits are important to pediatricians	106	32.4
	DCC benefits are important	115	35.1
	Condition of baby is important	15	4.6
	Others	77	23.6
UCC time in elective cesarean section	Same time as in vaginal delivery	73	22.3
	As soon as possible	25	7.6
	Cord stripping or milking	64	19.6
	Specific UCC time	44	13.5

(Continued)

TABLE 2 | Continued

Item	Options	Number of responses, n	%
	Not applicable (not obstetrician/ O&G trainee)	121	37.0
If have specific UCC time in elective cesarean section	0–29 s	2	4.5
	30–59 s	27	61.4
	1–3 min	6	13.6
	4–10 min	0	0.0
	>10 min	1	2.3
	Other	8	18.2
UCC time in emergency cesarean section	Same time as in vaginal delivery	49	15.0
	As soon as possible	66	20.2
	Cord stripping or milking	56	17.1
	Specific UCC time	35	10.7
	Not applicable (not obstetrician/ O&G trainee)	121	37.0
If have specific UCC time in emergency cesarean section	0–29 s	1	2.9
	30–59 s	14	40.0
	1–3 min	9	25.7
	4–10 min	0	0
	>10 min	0	0
	Other	11	31.4

*More than one response allowed.
ATMSL, active third stage of labor.

vs. 26%, $P = 0.003$), respondents practicing in government hospital compared to private hospitals (35 vs. 14%, $P < 0.001$) and lower education compared to higher education (60 vs. 25%, $P < 0.001$). Government hospitals were hospitals under the Ministry of Health (MOH) while teaching hospitals were governed under the Ministry of Higher Education (MOHE). Lower education comprised secondary education and diploma, while higher education included bachelor's degree, master and PhD. One factor that was significantly associated with a higher rate of reporting of a set time of UCC for term neonates was lower education (50%) compared to 33% among staff with high level of education ($P = 0.04$). Meanwhile, for preterm neonates, significantly higher rates of reporting of a set time of UCC were found among respondents from Klang Valley (34%), compared to 20% among non-Klang Valley residents ($P = 0.006$). Similar associations were observed among those with lower education (45 vs. 23% in higher, $P = 0.003$). The Klang Valley comprises mainly urban areas in Kuala Lumpur and Selangor in the central west coast of the Malaysian peninsular (**Table 3**).

Knowledge on Delayed Cord Clamping

More than two thirds (71% and 76%) of the respondents agreed that DCC was good for both preterm and term neonates not requiring PPV, respectively. The majority of the respondents (82%) agreed that DCC increased iron stores during the neonatal period in both preterm and term babies. Nearly three quarters (73%) respondents agreed that DCC has valuable effects that extend beyond the neonatal period including better long-term neurodevelopment while 67% agreed that DCC helped stabilize the transition of circulation, lessening the need for inotropic medications and reducing blood transfusion, necrotizing enterocolitis and intraventricular hemorrhage in preterm babies (**Table 4**).

Among the respondents, doctors, specialists, males, those who are 40 years old and above, those who have been in service for at least 10 years were found to have better knowledge regarding DCC ($P < 0.05$) (**Table 5**).

DISCUSSION

Our study revealed the state of practice of UCC and level of knowledge regarding DCC among obstetric and pediatric doctors, and midwives in Malaysia. The majority (71%) of respondents were not aware of any formal guideline on UCC in their place of practice. Similar findings were seen in previous studies by Ibrahim et al. (11) and Jelin et al. (12). Despite published evidence on the benefits associated with DCC (1–3, 6, 13, 14), only 29% of respondents reported that their institution have a UCC guideline. This was contrary to obstetric practice in a developed country, where DCC is considered a standard of care (6, 13).

One statistically significant finding in reporting the existence of a UCC guideline in the workplace was the significant disparity between midwives (47%) and doctors (26%) ($P = 0.003$). This was contrary to the observation in the study by Ibrahim et al. (11) where doctors were more aware of the availability of a UCC guideline compared to midwives.

Another survey conducted among midwives in Irish hospitals (14) reported 64.7% of the midwives were aware of the guideline on DCC in their place of practice. Our study also found a statistically significant difference in the reporting of the existence of a set time for UCC for term neonates between staff with lower education vs. those with higher education (60 vs. 25%, $P = <$ 0.001 and 50 vs. 33%, $P = 0.04$, respectively). Lower education included high school and diploma, indicating midwives. These findings were consistent with the findings of studies by Boerre et al. (9) and Mercer et al. (15). Furthermore, some midwifery institutions such as the American College of Nurse-Midwives (ACNM) have adopted DCC as a standard practice for both preterm and term newborns (16).

Midwives have slightly higher rates of having a set time for UCC for both term and preterm neonates than doctors (39 vs. 35% and 31 vs. 25%, respectively), although the differences were not statistically significant ($P = 0.600$ and 0.392 respectively). Similar findings were seen in a study by Boerre et al. (9). Interestingly, the UCC practice among midwives was said to be based more on belief, experience and clinical training rather than scientific rationale (15). This possibly explains the disparity between knowledge and practice in our survey, with better DCC

TABLE 3 | Existing UCC practices with demographic characteristic.

Characteristics	Total number	Number with characteristics	%	*P*
Existence of UCC guidelines/ protocols (*n* = 95)				
Profession				
Doctor	278	72	25.9	0.003*
Midwife	49	23	46.9	
Level of expertise among doctors (*n* = 72)				
Specialist	148	42	28.4	0.314
Non specialist	130	30	23.1	
Gender				
Male	90	28	31.1	0.613
Female	237	67	28.3	
Age				
<40 years old	194	61	31.4	0.250
≥40 years old	133	34	25.6	
Place of practice				
Government hospital	240	83	34.6	<0.001*
Private hospital	87	12	13.8	
State of Malaysia where you practice				
Klang Valley	134	45	33.6	0.133
Outside Klang Valley	193	50	25.9	
Education level				
Low	40	24	60.0	<0.001*
High	287	71	24.7	
Years of service				
<10 years	169	52	30.8	0.479
≥10 years	158	43	27.2	
Existence of set time for UCC for term neonates (*n* = 116)				
Profession				
Doctor	278	97	34.9	0.600
Midwife	49	19	38.8	
Level of expertise among doctors (*n* = 97)				
Specialist	148	55	37.2	0.397
Non-specialist	130	42	32.3	
Gender				
Male	90	39	43.3	0.067
Female	237	77	32.5	
Age				
<40 years old	194	74	38.1	0.223
≥40 years old	133	42	31.6	
Place of practice				
Government hospital	240	88	36.7	0.454
Private hospital	87	28	32.2	
State of practice in Malaysia				
Klang Valley	134	49	36.6	0.731
Outside Klang Valley	193	67	34.7	
Education level				
Low	40	20	50.0	0.040*
High	287	96	33.4	
Years of service				
<10 years	169	60	35.5	0.991
≥10 years	158	56	35.4	

(Continued)

TABLE 3 | Continued

Characteristics	Total number	Number with characteristics	%	*P*
Existence of set time for UCC for preterm neonates (*n* = 84)				
Profession				
Doctor	278	69	24.8	0.392
Midwife	49	15	30.6	
Level of expertise among doctors (*n* = 69)				
Specialist	148	37	25.0	0.941
Non-specialist	130	32	24.6	
Gender				
Male	90	28	31.1	0.167
Female	237	56	23.6	
Age				
<40 years old	194	48	24.7	0.636
≥40 years old	133	36	27.1	
Place of practice				
Government hospital	240	11	4.6	0.350
Private hospital	87	2	2.3	
State of Malaysia where you practice				
Klang Valley	134	45	33.6	0.006*
Outside Klang valley	193	39	20.2	
Education level				
Low	40	18	45.0	0.003*
High	287	66	23.0	
Years of service				
<10 years	169	42	24.8	0.720
≥10 years	158	42	26.6	

Data presented as n (%) and analyzed by Chi-square test.
Specialist includes fellow and consultant. Non-specialist consists of houseman, medical officer and registrar.
Government hospital includes all hospitals under MOH and MOE.
Low education consists of high school and diploma. High education includes bachelor, master and PhD.
*Klang valley consists of areas in Kuala Lumpur and Selangor. *Statistically significant difference.*

practice among midwives, despite poorer knowledge. At the level of diploma education, the emphasis is on technicalities and practice, rather than deep knowledge and scientific evidence. This is the level of education of the vast majority of midwives in Malaysia.

DCC for at least 30–60 s for vigorous term and preterm newborns who do not require resuscitation at birth was incorporated into the curriculum of Neonatal Resuscitation Program (NRP) 7th edition (17). In fact, umbilical cord management plan has been included as one of the 4 important pre-birth questions to the obstetric provider in the NRP 8th edition which was launched in 2021 (18). One of the possible explanation for the above observation in the UCC in Malaysia is that NRP is a mandatory course funded by the government for all the pediatric and obstetrics house officers, medical officers and midwives in Malaysian public and teaching hospitals (19). These categories of providers had the opportunities to learn about the latest information of the DCC guidelines in their NRP training compared to their more senior colleagues, e.g., the fellows and the consultants as well as their counterparts in the private sectors.

A systematic review demonstrated that there were no significant differences between ECC and DCC with regard to adverse neonatal outcomes such as low Apgar score and admission to special care nursery (SCN) or neonatal intensive care unit (NICU), and adverse maternal outcomes such as severe postpartum hemorrhage (4). Having said that, majority of the respondents (77% and 41%) applied ECC to neonates with poor Apgar scores and where mothers had increased vaginal loss, respectively, in this study. Such practices were usually performed in order to assist in neonatal resuscitation or to prevent postpartum hemorrhage (20).

Among the respondents who reported a set UCC time, (26% in preterm and 35% in term neonates), most of them reported a set UCC time of 1–3 min (49% in preterm and 62% in term). This practice is consistent with the recommendation by WHO (3), whereby in both preterm and term neonates who do not require PPV, the cord should not be clamped earlier than 1 min after birth. DCC (no earlier than 1 min after birth) is recommended to improve both maternal and infant health and nutritional outcomes.

The majority of respondents (71 and 76%, respectively) agreed that DCC was good for preterm and term neonates not requiring PPV. These findings are consistent with the study done by Ibrahim et al. (11) where the majority of respondents agreed that DCC is beneficial for both term (69%) and preterm (71%) neonates not requiring PPV. In fact, DCC in preterm neonates who require PPV can now be facilitated by providing a mobile resuscitation trolley before UCC (21) and this was proven to be feasible as demonstrated by Lapcharoensap et al. (22) and Joshi et al. (23). Having said that, only 30% of the respondents agreed that DCC was good for neonates who require PPV. Similar findings were reported by Leslie et al. (13). This may be due to its safety concern and acceptability to clinician and parents of DCC in a newborn who requires PPV is still being investigated (21).

Like previous studies (9, 11), majority of the respondents (82%) agreed that DCC increases iron stores during the neonatal period in both preterm and term babies. Most (73%) respondents agreed that DCC has valuable effects that extend beyond the neonatal period, including better long term neurodevelopment. Two thirds (67%) agreed that DCC helped stabilize the transition of circulation, lessening the need for inotropic medications and reducing blood transfusion, necrotizing enterocolitis and intraventricular hemorrhage in preterm babies. These findings are consistent with a previous systematic review and meta-analyses, which supports current guidelines recommending DCC in preterm infants (4, 24).

TABLE 4 | Attitude and knowledge toward delayed cord clamping (Likert items).

Item	Mean	SD	Percentage agree/strongly agree
DCC is good for preterm neonates who do not require PPV	3.82	0.88	70.7
DCC is good for term neonates who do not require PPV.	3.94	0.86	76.2
DCC can help to increase iron stores in term and preterm babies.	3.98	0.66	82.0
DCC has valuable effects that extend beyond the neonatal period by increasing the iron stores, which include improvements in long term neurodevelopment.	3.84	0.70	72.8
DCC helps in stabilizing the transition of circulation, lessening the need for inotropic medications and reducing blood transfusions, necrotizing enterocolitis and intraventricular hemorrhage in preterm babies.	3.80	0.71	67.3

Coding: 1 = strong disagree, 2 = disagree, 3 = not sure, 4 = agree, 5 = strongly agree.

TABLE 5 | Number and percentage of respondents with positive attitude and good knowledge toward DCC by demographic characteristics.

Characteristic	Total number	Number with good knowledge (n = 151)	%	P
Profession				
Doctor	278	137	49.3	0.007*
Midwife	49	14	28.6	
Level of expertise among doctors (n = 137)				
Specialist	148	90	60.8	<0.001*
Non-specialist	130	47	36.2	
Gender				
Male	90	53	58.9	0.004*
Female	237	98	41.4	
Age				
<40 years old	194	80	41.2	0.030*
≥40 years old	133	71	53.4	
Place of practice				
Government hospital	187	80	42.8	0.154
Private hospital	140	71	50.7	
State in Malaysia where you practice				
Klang Valley	134	60	44.8	0.672
Outside Klang valley	193	91	47.2	
Education level				
Low	40	16	40.0	0.403
High	287	135	47.0	
Years of service				
<10 years	169	68	40.2	0.026*
≥10 years	158	83	52.5	

*Positive attitude and good knowledge is defined by selecting strongly agree and agree for all 5 statements about DCC as shown in **Table 4**. Data presented as n (%) and analyzed by Chi-square test. *Statistically significant difference.*

In our study, doctors, specialists, males, those who are 40 years old and above, and those who have been in service for at least 10 years have better knowledge regarding DCC. This is quite similar to the findings in the study by Ibrahim et al. (11), where males and those with more than 16 years of practice in obstetrics had good knowledge of DCC. The relatively lower level of knowledge regarding delayed cord clamping among midwives and non-specialists is a matter of concern, because in Malaysia the majority of deliveries in public facilities are conducted by midwives and medical officers who are not specialists yet, and calls for more efforts to educate these two groups of healthcare workers on this issue. The older age and seniority are probably confounded by the specialist status of those who scored well on knowledge assessment.

The strength of this study was the high completed survey rate of 94%. Besides, this study utilized a widely-used validated questionnaire to measure the practice of UCC and knowledge regarding DCC. Furthermore, this was the first study that assessed obstetric and pediatric doctors and midwives on UCC practices and knowledge regarding DCC in Malaysia. It is also the first such survey in the South East Asia region. We hope to alert not only our fellow Malaysian healthcare workers in the related fields, but also regional healthcare professionals, especially in our neighboring developing countries. Similarly, we hope to raise awareness in other Low to Moderate Income Countries (LMICs) elsewhere in the world.

One limitation of this study was that the participants were selected by convenient snowball sampling through email and WhatsApp using Google form, hence not all hospitals in Malaysia participated. We were unable to capture the actual numbers of invitation sent to the potential respondents because of the overlap in membership among the three professional societies, namely the Perinatal Society of Malaysia (PSM), the Malaysian Paediatric Association (MPA), and the Obstetrical and Gynaecological Society of Malaysia (OGSM). Although we were able to send the invitation to more than 1,000 members from PSM ($n = 367$) and MPA ($n = 788$) however only about one third ($n = 348$) of them returned the survey form.

CONCLUSION

Awareness of the existence of guidelines on UCC was still markedly lacking among Malaysian professionals handling childbirth. Even though most respondents had good knowledge of DCC, this did not translate into their routine practice. Hence, a national guideline emphasizing the benefits of DCC should be made available in Malaysia. This may also help create awareness of the existence of international UCC guidelines.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Universiti Kebangsaan Malaysia (UKM) Research Ethics Committee (Approval Code: JEP-2020-580). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceptualization by KP who steered the project and critically edited the manuscript. NP prepared the first draft of this manuscript, created the survey, analyzed and collated the data, statistics from the survey, contributed in the writing, created the table and figure, accessed the statistics from sources, ensured editorial accuracy of the manuscript, and reference compilation. ZM critically edited, primarily involved in re-structuring, and re-writing and re-formatting the manuscript into the final form. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.917129/full#supplementary-material

REFERENCES

1. Rabe H, Gyte GML, Díaz-Rossello JL, Duley L. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database Syst Rev*. (2019) 9:CD003248. doi: 10.1002/14651858.CD003248.pub4
2. Tarnow-Mordi W, Morris J, Kirby A, Robledo K, Askie L, Brown R, et al. Delayed versus Immediate Cord Clamping in Preterm Infants. *N Engl J Med*. (2017) 377:2445–55. doi: 10.1056/NEJMoa1711281
3. WHO. Delayed umbilical cord clamping for improved maternal and infant health and nutrition outcomes. *World Heal Organ*. (2014) 59:46–9.

4. Mcdonald SJ, Middleton P, Dowswell T, Morris PS. Cochrane in context: Effect of timing of umbilical cord clamping in term infants on maternal and neonatal outcomes. *Evidence-Based Child Heal.* (2014) 9:347–9. doi: 10.1002/ebch.1965
5. Mercer JS. Current best evidence: a review of the literature on umbilical cord clamping. *J Midwifery Womens Heal.* (2001) 46:402–12. doi: 10.1016/S1526-9523(01)00196-9
6. ACOG. Delayed umbilical cord clamping after birth. Committee opinion no 684. *Am J Obstet Gynecol*. (2017) 684:e5–10.
7. Mivšek AP, Petročnik P, Skubic M, Zakšek TŠ, Došler AJ. Umbilical cord management and stump care in normal childbirth in Slovenian and Croatian maternity hospitals. *Acta Clin Croat.* (2017) 56:773–80. doi: 10.20471/acc.2017.56.04.27
8. Al-Wassia H, Shah PS. Efficacy and safety of umbilical cord milking at birth: A systematic review and meta-analysis. *JAMA Pediatr.* (2015) 169:18–25. doi: 10.1001/jamapediatrics.2014.1906
9. Boere I, Smit M, Roest AAW, Lopriore E, Van Lith JMM, Te Pas AB. Current practice of cord clamping in the Netherlands: a questionnaire study. *Neonatology.* (2015) 107:50–5. doi: 10.1159/000365836
10. The ROM, Of O, Statement IJ, Stage T, Haemorrhage PP. Joint statement: Management of the third stage of labour to prevent post-partum haemorrhage. *J Midwifery Womens Heal.* (2004) 49:76–7. doi: 10.1016/j.jmwh.2003.11.005
11. Ibrahim NO, Sukkarieh HH, Bustami RT, Alshammari EA, Alasmari LY, Al-Kadria HM. Current umbilical cord clamping practices and attitudes of obstetricians and midwives toward delayed cord clamping in Saudi Arabia. *Ann Saudi Med.* (2017) 37:216–24. doi: 10.5144/0256-4947.2017.216
12. Jelin AC, Kuppermann M, Erickson K, Clyman R, Schulkin J. Obstetricians' attitudes and beliefs regarding umbilical cord clamping. *J Matern Neonatal Med.* (2014) 27:1457–61. doi: 10.3109/14767058.2013.864275
13. Leslie MS, Greene J, Schulkin J, Jelin AC. Umbilical cord clamping practices of U. S. obstetricians. *J Neonatal Perinatal Med.* (2018) 11:51–60. doi: 10.3233/NPM-181729
14. Devin J, Larkin P. Delayed cord clamping in term neonates: Attitudes and practices of midwives in Irish hospitals. *Int J Childbirth.* (2018) 8:4–17. doi: 10.1891/2156-5287.8.1.4
15. Mercer JS, Nelson CC, Skovgaard RL. Umbilical cord clamping: beliefs and practices of American nurse-midwives. *J Midwifery Womens Heal.* (2000) 45:58–66. doi: 10.1016/S1526-9523(99)00004-5
16. American College of Nurse Midwives. *Position Statement: Delayed umbilical cord clamping.* (2014). Available online at: http://www.midwife.org/ACNM/files/ACNMLibraryData/UPLOADFILENAME/000000000290/Delayed-Umbilical-Cord-Clamping-May-2014.pdf (accessed April 10, 2022).
17. Wyckoff MH, Aziz K, Escobedo MB, Kapadia VS, Kattwinkel J, Perlman JM, et al. Part 13: Neonatal resuscitation: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* (2015) 132:S543–60. doi: 10.1161/CIR.0000000000000267
18. Aziz K, Lee HC, Escobedo MB, Hoover A V., Kamath-Rayne BD, Kapadia VS, et al. Part 5: neonatal resuscitation: 2020 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*. (2020) 142:S524–50. doi: 10.1161/CIR.0000000000000902
19. Pong KM, Teo JTR, Cheah FC. Simulation-based education in the training of newborn care providers—a Malaysian perspective. *Front Pediatr*. (2021) 9:1–8. doi: 10.3389/fped.2021.619035
20. Garofalo M, Abenhaim HA. Early versus delayed cord clamping in term and preterm births: a review. *J Obstet Gynaecol Canada.* (2012) 34:525–31. doi: 10.1016/S1701-2163(16)35268-9
21. Weeks AD, Watt P, Yoxall CW, Gallagher A, Burleigh A, Bewley S, et al. Innovation in immediate neonatal care: development of the Bedside Assessment, Stabilisation and Initial Cardiorespiratory Support (BASICS) trolley. *BMJ Innov.* (2015) 1:53–8. doi: 10.1136/bmjinnov-2014-000017
22. Lapcharoensap W, Cong A, Sherman J, Schwandt D, Crowe S, Daniels K, et al. Safety and ergonomic challenges of ventilating a premature infant during delayed cord clamping. *Children.* (2019) 6:59. doi: 10.3390/children6040059
23. Joshi NS, Padua K, Sherman J, Schwandt D, Sie L, Gupta A, et al. A feasibility study of a novel delayed cord clamping cart. *Children.* (2021) 8:357. doi: 10.3390/children8050357
24. Hutton EK, Hassan ES. Late vs early clamping of the umbilical cord in full-term neonates: systematic review and meta-analysis of controlled trials. *J Am Med Assoc.* (2007) 297:1241–52. doi: 10.1001/jama.297.11.1241

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The Role of Amnioreduction in Emergency Cervical Cerclage with Bulging Membranes: A Retrospective Comparative Study

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The purpose of this study was to investigate the role of amnioreduction in patients who underwent emergency cervical cerclage (ECC) with bulging membranes during the second trimester. This retrospective comparative study included 46 singleton pregnant women who had cervical dilation at least 1 cm with bulging membranes beyond the external cervical os and underwent ECC at the Third Affiliated Hospital of Sun Yat-sen University between December 2016 and December 2021. Cases were categorized as amnioreduction group ($n = 16$) and non-amnioreduction group ($n = 30$) according to whether amnioreduction was performed prior to ECC. The gestational age and cervical dilation at cerclage, operative time, prolongation of pregnancy, and outcomes of pregnancy were compared between the two groups. All 46 patients underwent successful ECC excepted one case with intraoperative rupture of membrane in non-amnioreduction group. In the amnioreduction group, the cervical dilation at cerclage was larger than that in the non-amnioreduction group (4.5 ± 2.2 vs. 2.2 ± 1.2 cm, $P < 0.001$), and had more patients with cervical dilation ≥4 cm (50.0% vs. 10.0%, $P = 0.004$). However, the gestational age at cerclage, operative time, prolongation of pregnancy, gestational age at delivery were not significantly different between the two groups (22.9 ± 2.8 vs. 22.9 ± 3.2 weeks, 31.1 ± 9.2 vs. 27.9 ± 11.4 min, 21.3 ± 21.5 vs. 38.7 ± 40.2 days, 25.9 ± 4.5 vs. 28.4 ± 6.1 weeks; $P > 0.05$). The rates of delivery ≥28 weeks, ≥32 weeks, and live birth were 20.0% vs. 80.0%, 12.5% vs. 26.7%, 56.3% vs. 66.7% ($P > 0.05$) in amnioreduction group and non-amnioreduction group, respectively. In conclusion, even in cases with larger cervical dilation, the application of amnioreduction with ECC is possible to get the acceptable pregnancy outcomes. These findings suggested that amnioreduction may be a safe and feasible option to be applied before ECC, especially for those with advanced cervical dilation and bulging membranes.

Keywords: emergency cervical cerclage, prolongation of pregnancy, amnioreduction, cervical dilation, bulging membranes

INTRODUCTION

The loss of mid-term pregnancy and premature birth are major problems in obstetrical fields, which brings great burden to the society and family [1]. Cervical incompetence is a status of pregnancy in which the cervix begins to dilate and efface before the term of pregnancy [2, 3]. It has been shown that the rate of preterm birth before 37 gestational weeks in patients with cervical incompetence is 3.3 times higher than those without cervical incompetence, accounting for 8–9% of all preterm births [4]. The live birth rate is estimated to be 23% at 23 weeks of gestation, 38% at 24 weeks of gestation and 54% at 25 weeks of gestation [5, 6], suggesting that prolonging gestational age can significantly improve the live birth rate of premature infants. According to the ACOG (American College of Obstetricians and Gynecologists) guideline on cerclage for the management of cervical insufficiency, the diagnosis of cervical insufficiency mainly depends on the past medical history [3]. For women with a history of cervical insufficiency, preventive cervical cerclage is an effective surgical method for treating cervical insufficiency, which can effectively prolong the gestational age and reduce the adverse perinatal outcomes[3, 7–10]. However, for women with the first pregnancy, or those without a history of mid-trimester pregnancy loss or spontaneous preterm birth, emergency cervical cerclage (ECC) is a salvage procedure when cervical dilation with bulging fetal membranes but no signs of labor and infection in mid-trimester, in an attempt to prolong the pregnancy to a viable gestation [11–14]. However, compared to the elective cervical cerclage, ECC is a technically challenging procedure, as the protruding membranes in the cervix making it difficult to place the cervical suture properly and carry the risk of iatrogenic rupture of the membranes during surgery [11–13, 15]. In addition, ECC is also associated with worse pregnancy outcomes including the earlier gestation age at delivery, lower birth weight, lower live birth rate, and higher intra-amniotic infection rate, especially for women with advanced cervical dilation [11, 16–20]. Moreover, ECC is not always successful in all patients with cervical dilation, especially when dilation is completely [3, 7, 10, 14].

In 1979, Robert C. Goodwin reported for the first time the application of amnioreduction before ECC to reduce the tension of the protruding amniotic sac in the vagina [21]. Since then, several studies have reported on amnioreduction prior to ECC for bulging membranes, however, the pregnancy outcomes were inconsistent due to the heterogeneity of cases [22–26]. To improve the success of ECC procedure and pregnancy outcomes among patients with large bulging membranes, our hospital started to adopt amnioreduction prior to ECC since December 2016. In this study, we retrospectively compared the clinical features and pregnancy outcomes of patients who underwent ECC with bulging membranes between 16 cases with amnioreduction and 30 cases without amnioreduction and evaluated the safety and effectiveness of amnioreduction in ECC during the second trimester.

METHODS

Study Design and Subjects

This retrospective cohort study recruited pregnant women who had painless cervical dilation with bulging membranes beyond the external cervical os and underwent ECC during the second trimester at the Third Affiliated Hospital of Sun Yat-sen University between December 2016 and December 2021. Inclusion criteria were: (1) singleton pregnancy. (2) gestational age between 14^{+0} and 27^{+6} weeks. (3) cervical dilatation of at least 1 cm and bulging membranes were confirmed by transvaginal ultrasound and speculum examination. (4) ECC were performed within 24 h after cervical dilation diagnosed, not waiting for the results of vaginal microbiotic smear. Exclusion criteria included: (1) premature rupture of membranes. (2) persistent or active vaginal bleeding (3) regular uterine contractions that occurred before operation. (4) clinical chorioamnionitis (maternal body temperature $\geq$38° C, with fetal heart rate $\geq$160 beats/min or maternal peripheral blood leukocyte count $\geq 15 \times 10^9$/L. (5) severe pregnancy complications and disease. (6) fetal structural abnormalities.

From December 2016, amnioreduction was applied prior to ECC at our hospital when cervical dilation is $\geq$3 cm or difficult to replace the bulging membranes unless the patients refuse amnioreduction, or the deepest vertical pocket of amniotic fluid is less than 30 mm, or it is difficult to avoid puncturing placenta. This study was approved by the institutional review board of the Third Affiliated Hospital of Sun Yat-sen University and written informed consent was obtained from each patient.

ECC and Amnioreduction

At admission, after extensive counseling on the potential risk of miscarriage and failure of the operation, all pregnant women had signed informed consent for ECC with or without amnioreduction. The patients were placed in a lithotomy position with steep Trendelenburg tilt under spinal anesthesia. Vaginal speculum examination reconfirmed the cervical dilation and the tension of bulging membranes. The protruding membranes were gradually retracted into the uterus by inflated Foley catheter or cervical cook balloon, or moistened gauze ball according to the size of cervical dilation and discretion of operator. Cervical cerclage was performed using the McDonald techniques. If the cervical dilation is larger than 3 cm or prolapsed amniotic sac is hard to repositioned, a transabdominal amnioreduction would be needed before ECC unless the placental penetration could not be avoided. After emptying the bladder, ultrasound-guided freehand techniques were conducted with 22G needle punctured into the amniotic cavity. The amount of amniotic fluid reduction was determined by the distension of the bulging sac, usually from 50 to 250 ml. If having the indication of prenatal diagnosis, the obtained amniotic fluid was sent for fetal chromosomal karyotyping with or without microarray analysis under the consent of the pregnant women.

Perioperative and Postoperative Treatment

During the perioperative period, all the patients were given treatment regimen consisting of five schemes, included: bed rest until 34 gestational weeks, intravenous broad-spectrum antibiotics (cephalosporins or azithromycin + metronidazole) for 5 to 7 days after the operation, tocolytics (including indomethacin + ritodrine hydrochloride, or atosiban) for at least 48 h, prophylactic venous thromboembolism with low molecular weight heparin until 34 gestational weeks with normal physical activity or presenting the following indication for removal sutures, and dexamethasone for fetal lung maturation (after 24 gestational weeks). However, the specific course of tocolytic treatment was individualized at the discretion of senior obstetrician, mainly based on uterine contractions, gestational age and whether presenting clinical chorioamnionitis, because there was no uniformity and guideline on this issue.

Cerclages would be removed around 37 weeks of gestation or presenting the indication for earlier removal sutures such as active preterm labor, clinical evidence of chorioamnionitis, heavy vaginal bleeding, preterm premature rupture of membranes, or fetal compromise.

Data Collection

Maternal data included age, previous obstetrics history, prior cervical intervention, gestational weeks, ultrasound examination, size of cervical dilation, preoperative white blood cell count, C-reactive protein level, vaginal microbiotic smear, details of the operation, and perioperative management. Maternal and fetal outcomes included prolongation of pregnancy, gestational weeks at delivery, mode of delivery, complications, birth weight, perinatal death or survival, and placental pathologic examination.

Statistical Analysis

SPSS statistical software version 26.0 was used to analyze the data. Shapiro–Wilk was used to test the normality of continuous variables. According to the characteristics of the variables, data are presented as means ± standard deviations (SD) and median (interquartile range) for continuous variables and numbers (percentages) for categorical variables, respectively. The differences were compared between groups using Student's *t*-test (Gaussian distribution data) and Mann-Whitney *U* test (non-Gaussian distribution data). Chi-squared test or Fisher's exact test was used to analyze the categorical variables. *P* value of <0.05 was considered statistically significant. G*power 3 software [27] was used to perform the sample size calculation, and the effective size was calculated based on the present results with a significance level of 0.05 (one-tailed) and a power of 0.8.

RESULTS

During the study period, a total of 126 pregnant women who had short cervix or cervical dilation underwent ECC. Among 46 singleton pregnancies with cervical dilation and bulging membranes, 16 cases accepted ECC with amnioreduction and 30 cases that accepted ECC without amnioreduction were eligible for amnioreduction group and non-amnioreduction group, respectively (**Supplemental Table S1 and S2**). All 46 patients underwent successful ECC except one case with intraoperative membrane rupture in the non-amnioreduction group. The results of fetal chromosomal karyotyping and microarray analysis of amniotic fluid from patients with advanced maternal age or abnormal biochemical screening were normal.

Clinical Characteristics of Included Patients Before the Operation

The mean maternal age in amnioreduction group was older than that in the non-amnioreduction group (32.5 ± 4.4 vs. 29.4 ± 4.3 years, $P = 0.016$). The two groups were similar in the mean gestational age at cerclage, rates of primigravidity and nulliparous, rate of previous spontaneous miscarriage during the first and the second trimester, white blood cell count before the operation, and preoperative C-reactive protein value (**Table 1**). However, the preoperative size of cervical dilation

TABLE 1 | Baseline clinical characteristics of the included patients.

Variables	Amnioreduction group (*n* = 16)	Non-amnioreduction group (*n* = 30)	*P* value
Maternal age (years)	32.5 ± 4.4[e]	29.4 ± 4.3[e]	0.016[a]
Gestational age at cerclage (weeks)	22.9 ± 2.8[e]	22.9 ± 3.2[e]	0.993[a]
Primigravidity, *n* (%)	7 (43.8%)	9 (30.0%)	0.351[b]
Nulliparous, *n* (%)	12 (75.0%)	19 (63.3%)	0.421[b]
Previous spontaneous miscarriage during first trimester, *n* (%)	4 (25.0%)	7 (23.3%)	0.585[c]
Previous spontaneous miscarriage during second trimester, *n* (%)	1 (6.3%)	5 (16.7%)	0.307[c]
Cervical dilatation before operation (cm)	4.5 ± 2.2 4.0 (3.3)	2.2 ± 1.2 2.0 (2.0)	<0.001[d]
Cervical dilatation before operation ≥4 cm, *n* (%)	8 (50.0%)	3 (10.0%)	0.004[c]
White blood cell count before operation ($\times 10^9$/l)	14.6 ± 8.0[e] 11.7 (4.9)[f]	12.7 ± 3.0[e] 12.8 (3.3)[f]	0.960[d]
C-reactive protein value before operation (mg/l)	10.9 ± 5.3[e] 10.2 (9.0)[f]	11.6 ± 9.1[e] 8.0 (12.2)[f]	0.702[d]

[a]*Student's t-test*.
[b]*chi-squared test*.
[c]*Fisher's exact test*.
[d]*Mann Whitney U test*.
[e]*means ± standard deviations*.
[f]*median (interquartile range)*.

in the amnioreduction group was significantly larger than that in the non-amnioreduction group (4.5 ± 2.2 vs. 2.2 ± 1.2 cm, $P < 0.001$), and had more patients with cervical dilation ≥4 cm (50.0% vs. 10.0%, $P = 0.004$) (**Table 1**).

Outcomes After the Operation

The pregnancy outcomes were presented in **Table 2**, **Supplementary Table S1** and **Supplementary Table S2**. There were no significant differences when comparing the amnioreduction group and non-amnioreduction group in terms of operative time, prolongation of pregnancy, gestational age at delivery, rates of delivery ≥28 weeks, delivery ≥32 weeks, preterm premature rupture of membranes, clinical chorioamnionitis, and acute histologic chorioamnionitis. The neonatal outcomes were also statistically comparable in terms of birthweight (≥24 weeks), 1 min Apgar scores, 5 min Apgar scores, and the total survival rate between the amnioreduction group and non-amnioreduction group. There was no maternal morbidity related to ECC that occurred from operation to postdelivery.

TABLE 2 | Clinical outcomes after surgery between amnioreduction group and non- amnioreduction group.

Variables	Amnioreduction group ($n = 16$)	Non-amnioreduction group ($n = 30$)	*P* value
Operative time (minutes)	31.1 ± 9.2[e] 30.0 (15.3)[f]	27.9 ± 11.4[e] 26.5 (10.5)[f]	0.179[a]
Prolongation of pregnancy (days)	21.3 ± 21.5[e] 14.5 (21.8)[f]	38.7 ± 40.2[e] 26.5 (53.8)[f]	0.221[a]
Gestational age at delivery (weeks)	25.9 ± 4.5[e]	28.4 ± 6.1[e]	0.159[b]
Preterm premature rupture of membranes, *n* (%)	5 (31.3%)	11 (36.7%)	0.713[c]
Clinical chorioamnionitis, *n* (%)	2 (12.5%)	1 (3.3%)	0.274[d]
Acute histologic chorioamnionitis, *n* (%)	9/13 (69.2%)	13/22 (59.1%)	0.409[d]
Miscarriage or abortion < 24 weeks, *n* (%)	6 (37.5%)	7 (23.3%)	0.248[d]
Delivery 24-27^{+6} weeks, *n* (%)	6 (37.5%)	7 (23.3%)	0.248[d]
Delivery ≥28 weeks, *n* (%)	4 (20.0%)	16 (80.0%)	0.065[c]
Delivery ≥32 weeks, *n* (%)	2 (12.5%)	8 (26.7%)	0.236[d]
Neonatal birthweight (≥ 24 weeks, g)	1267 ± 503[e] 1135 (777.5)[f]	1683 ± 932[e] 1350 (1200)[f]	0.196[a]
Live birth, *n* (%)	9 (56.3%)	20 (66.7%)	0.486[c]
Neonatal birthweight (g)	1331 ± 487[e] 1150 (715)[f]	1843 ± 894[e] 1575 (1450)[f]	0.140[a]
1-min Apgar score	8.8 ± 1.9[e] 9.0 (1.5)[f]	9.2 ± 1.6[e] 10.0 (1.5)[f]	0.317[a]
5-min Apgar score	9.6 ± 0.5[e] 10.0 (1.0)[f]	10.0 ± 0.2[e] 10.0 (0.0)[f]	0.095[a]
Neonatal survival, *n* (%)	9 /9 (100.0%)	20/20 (100.0%)	/

[a]*Mann Whitney U test*.
[b]*Student's t-test*.
[c]*chi-squared test*.
[d]*Fisher's exact test*.
[e]*means ± standard deviations*.
[f]*median (interquartile range)*.

DISCUSSION

In this retrospective cohort study, we compared the clinical features and pregnancy outcomes from singleton patients who had cervical dilation and bulging membranes and underwent ECC with or without amnioreduction. The results showed that there were statistically comparable prolongation of pregnancy and perinatal outcomes among the two groups, even women with amnioreduction had larger cervical dilation, suggesting that amnioreduction may be a safe and feasible option to be applied before ECC, especially for those with advanced cervical dilation and bulging membranes.

As a salvage procedure, patients eligible for ECC all have cervical dilation with or without protruding membranes before the operation [3, 7, 10]. Therefore, the difficulty of performing ECC is higher than the standard procedure of cervical cerclage. When the cervical external os is open, the inferior amniotic sac would prolapse through the cervical canal or even protruding into the vagina. The membranes bulging outside the cervix will elevate the distension of prolapsed sac, and exposure to vaginal bacteria would increase the risk of infection [23, 28–30]. In addition, repeatedly pushing the membranes during surgery will further elevate the distension of the sac, thus increasing the risk of membranes rupture and uterine contraction. Therefore, successfully replacing the bulging membranes into the uterus is the key step for ECC. Some devices including moist gauze and inflated balloon (Foley catheter, cervical cook balloon, uniconcave balloon and balloon tamponade) have been used during ECC [11, 14, 31, 32]. However, for women with advanced cervical dilation or increased pressure of intra-amniotic sac, the above devices may not be effective due to limited contact area with membranes, limited supporting force or risk of rupture of membranes. In our series, the bulging membranes from eight cases with cervical dilation at 2–3 cm were hard to repositioned into the uterine cavity by moist gauze or inflated balloon due to the higher intra-amniotic pressure, resulting rupture of the membrane during the procedure in one case and turn to amnioreduction in seven cases.

Several studies demonstrated that patients with cervical dilation of more than 3–4 cm and bulging membranes had higher chance of failure of ECC, short prolongation time and more pregnancy complications [11, 14, 20, 33]. Some authors even concluded that ECC was not a rational option when patients had cervical dilation of more than 4 cm and protruding membranes [20]. However, a study by Pereira L. et al. demonstrated that if underwent expectantly management, women presenting with advanced cervical dilation of more than 4 cm would ultimately deliver within one week [34]. The main purpose of amnioreduction prior to ECC is to reduce intrauterine pressure. After amnioreduction,

it can be observed that the distension of the membranes was markedly reduced and makes it easier to expose dilated cervical edge, in turn reducing the surgical difficulty and improving outcomes [21, 23–26]. In our study, 11 cases with advanced cervical dilation at least 3 cm, including two cases near fully dilated before the operation, underwent successful ECC without procedure-related rupture of membrane, suggesting that the amnioreduction may be a feasible option before ECC in such conditions.

In view of the effectiveness of ECC, the prolongation of pregnancy and neonatal survival are both important points. Even with low and very low quality of evidence, the benefits of ECC have been confirmed by three comprehensive reviews [11, 12, 14], presenting the favorable prolongation of pregnancy from 4–5 weeks to 47 days, 2-fold reduction of preterm birth before 34 gestational weeks, later gestational age at delivery, and lower risks of fetal loss, very preterm birth and neonatal death. However, the pregnancy outcomes after ECC with amnioreduction have not been fully elucidated due to the lack of universal acceptance among clinicians and the rarity of valid control cases. Locatelli A. et al. have reported 16 patients with cervical dilation (2–5 cm) and prolapse of fetal membranes, including seven cases with ECC and nine cases with ECC and amnioreduction, and found that with the comparable prolongation of pregnancy, the amnioreduction before ECC is associated with a lower rate of delivery before 32 weeks and neonatal morbidity [23]. One recent study by Cakiroglu Y. et al. found that ECC yielded no different outcomes for prolongation of pregnancy and live birth rate after comparing between amnioreduction group and non-amnioreduction group [22]. Another compared study from Japan also showed similar pregnancy outcomes after ECC between eight patients with amnioreduction and nine cases without amnioreduction, even though the size of forewater detected by ultrasound was larger in amnioreduction group [24]. Furthermore, our study comprised relative more cases who underwent ECC with amnioreduction ($n = 16$) or no-amnioreduction ($n = 30$), and also found that there were no significant differences in prolongation of pregnancy, gestational weeks at delivery, live birth rate and neonatal survival between the two groups, nevertheless, the mean of cervical dilation in amnioreduction cases was significantly larger than that in non-amnioreduction cases, suggesting that amnioreduction may be a safe and feasible option before ECC.

The major limitation of our study was the lack of testing intra-amniotic infection or inflammation from the amniotic fluid withdrawn among cases with amnioreduction. The rates of intra-amniotic infection and inflammation determined by amniocentesis have been reported as high as 52% and 81%, respectively [28, 29]. However, a recent observational study found that antibiotics could effectively eradicate 75% of intra-amniotic inflammation and 60% of infection [30]. In our study, the broad-spectrum antibiotics were routinely administrated to all the cases during the perioperative period, and the rates of clinical and histologic chorioamnionitis after ECC were not significantly different between the two groups. Moreover, the benefits of excluding some cases of sub-clinical chorioamnionitis before ECC and increasing the risk of infection for exposure to bulging membranes to the vaginal bacteria when awaiting the results were hard to balance. Another major limitation was the retrospective and non-randomized control study with a relatively small sample size, which inevitably comprised unmatched baseline variables (such as maternal age and cervical dilation before operation) and also can lead a potential bias of selection and limit the statistical power. According to the sample size calculation (**Table 3**) based on the present results, the current sample size may not have statistical power to detect the difference in most parameters of pregnancy outcomes between two groups and this suggested that the definitive recommendation could not be drawn from the current data. Other limitations included different devices such as moist gauze and inflated balloon, or Foley catheter used during the procedure at the discretion of operators, no uniformity of perioperative tocolytic treatment strategies based on individual basis, and lack of long-term outcomes of infants. Therefore, further prospective studies with proper design and larger sample size to explore this issue are desirable.

TABLE 3 | Sample size calculation based on the present results.

Variables	Effective size	Alpha (one-tailed)	Power	Calculated sample size per group
Prolongation of pregnancy (days)	0.54	0.05	0.8	44
Preterm premature rupture of membranes	/	0.05	0.8	951
Miscarriage or abortion <24 weeks	/	0.05	0.8	129
Delivery 24-27^{+6} weeks	/	0.05	0.8	129
Delivery ≥28 weeks	/	0.05	0.8	10
Delivery ≥32 weeks	/	0.05	0.8	96
Live birth	/	0.05	0.8	270

In summary, although with larger cervical dilation, patients who underwent ECC with amnioreduction got the acceptable pregnancy outcomes when compared with cases who had relatively smaller cervical dilation without amnioreduction. Even definitive recommendations could not be drawn from this limited sample size, these findings suggested that amnioreduction may be a safe and feasible option to be applied before ECC, especially for those with advanced cervical dilation and bulging membranes with high pressure. Further prospective studies with larger sample to evaluate the benefits of amnioreduction before ECC will be needed to confirm our findings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review board of the Third Affiliated Hospital of Sun Yat-sen University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZYH, HYH and YZY conceptualized the study and was involved in study design; YZ and QQW collected the data; YZ and ZYH performed the data analysis; YZ and QQW drafted the manuscript and ZYH revised it critically. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.928322/full#supplementary-material.

REFERENCES

1. McNamee KM, Dawood F, Farquharson RG. Mid-trimester pregnancy loss. *Obstet Gynecol Clin North Am*. (2014) 41(1):87–102. doi: 10.1016/j.ogc.2013.10.007
2. Roman A, Suhag A, Berghella V. Overview of cervical insufficiency: diagnosis, etiologies, and risk factors. *Clin Obstet Gynecol*. (2016) 59 (2):237–40. doi: 10.1097/GRF.0000000000000184
3. ACOG Practice Bulletin No.142. Cerclage for the management of cervical insufficiency. *Obstet Gynecol*. (2014) 123(2 Pt 1):372–9. doi: 10.1097/01.AOG.0000443276.68274.cc
4. Slattery MM, Morrison JJ. Preterm delivery. *Lancet (London, England)*. (2002) 360(9344):1489–97. doi: 10.1016/S0140-6736(02)11476-0
5. Carmichael SL, Blumenfeld YJ, Mayo JA, Profit J, Shaw GM, Hintz SR, et al. Stillbirth and live birth at periviable gestational age: a comparison of prevalence and risk factors. *Am J Perinatol*. (2019) 36(5):537–44. doi: 10.1055/s-0038-1670633
6. Wood S, Tang S. Stillbirth and large for gestational age at birth. *J Matern Fetal Neonatal Med*. (2020) 33(12):1974–9. doi: 10.1080/14767058.2018.1534229
7. Brown R, Gagnon R, Delisle MF. Cervical insufficiency and cervical cerclage. *J Obstet Gynaecol Can*. (2013) 35(12):1115–27. doi: 10.1016/S1701-2163(15)30764-7
8. Alfirevic Z, Stampalija T, Medley N. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. *Cochrane Database Syst Rev*. (2017) 6(6). doi: 10.1002/14651858.CD008991.pub3
9. Suhag A, Berghella V. Cervical cerclage. *Clin Obstet Gynecol*. (2014) 57 (3):557–67. doi: 10.1097/GRF.0000000000000044
10. *Cervical Cerclage (Green-top Guideline No. 60), May 2011*. London: Royal College of Obstetricians and Gynaecologists (2011).
11. Wierzchowska-Opoka M, Kimber-Trojnar Ż, Leszczyńska-Gorzelak B. Emergency cervical cerclage. *J Clin Med*. (2021) 10(6):1270. doi: 10.3390/jcm10061270
12. Chatzakis C, Efthymiou A, Sotiriadis A, Makrydimas G. Emergency cerclage in singleton pregnancies with painless cervical dilatation: a meta-analysis. *Acta Obstet Gynecol Scand*. (2020) 99(11):1444–57. doi: 10.1111/aogs.13968
13. Ehsanipoor RM, Seligman NS, Saccone G, Szymanski LM, Wissinger C, Werner EF, et al. Physical examination-indicated cerclage: a systematic review and meta-analysis. *Obstet Gynecol*. (2015) 126(1):125–35. doi: 10.1097/AOG.0000000000000850
14. Hashim H A, Al-Inany H, Kilani Z. A review of the contemporary evidence on rescue cervical cerclage. *Int J Gynaecol Obstet*. (2014) 124(3):198–203. doi: 10.1016/j.ijgo.2013.08.021
15. Ito A, Maseki Y, Ikeda S, Tezuka A, Kuribayashi M, Furuhashi M. Factors associated with delivery at or after 28 weeks gestation in women with bulging fetal membranes before 26 weeks gestation. *J Matern Fetal Neonatal Med*. (2017) 30(17):2046–50. doi: 10.1080/14767058.2016.1236247
16. Chen R, Huang X, Li B. Pregnancy outcomes and factors affecting the clinical effects of cervical cerclage when used for different indications: a retrospective study of 326 cases. *Taiwan J Obstet Gynecol*. (2020) 59(1):28–33. doi: 10.1016/j.tjog.2019.11.004
17. Liddiard A, Bhattacharya S, Crichton L. Elective and emergency cervical cerclage and immediate pregnancy outcomes: a retrospective observational study. *JRSM Short Rep*. (2011) 2(11):91. doi: 10.1258/shorts.2011.011043
18. Namouz S, Porat S, Okun N, Windrim R, Farine D. Emergency cerclage: literature review. *Obstet Gynecol Surv*. (2013) 68(5):379–88. doi: 10.1097/OGX.0b013e31828737c7
19. Khan MJ, Ali G, Al Tajir G, Sulieman H. Evaluation of outcomes associated with placement of elective, urgent, and emergency cerclage. *J Obstet Gynaecol India*. (2012) 62(6):660–4. doi: 10.1007/s13224-012-0233-x
20. Uzun Cilingir I, Sayin C, Sutcu H, İnan C, Erzincan S, Yener C, et al. Does emergency cerclage really works in patients with advanced cervical dilatation? *J Gynecol Obstet Hum Reprod*. (2019) 48(6):387–90. doi: 10.1016/j.jogoh.2019.01.002
21. Goodlin RC. Cervical incompetence, hourglass membranes, and amniocentesis. *Obstet Gynecol*. (1979) 54(6):748–50.
22. Cakiroglu Y, Doger E, Yildirim Kopuk S, Gunlemez A, Oguz D, Caliskan E. Does amnioreduction increase success of emergency cervical cerclage in cases with advanced cervical dilatation and protruding membranes? *Clin Exp Obstet Gynecol*. (2016) 43(5):708–12. doi: 10.12891/ceog2120.2016
23. Locatelli A, Vergani P, Bellini P, Strobelt N, Arreghini A, Ghidini A. Amnioreduction in emergency cerclage with prolapsed membranes: comparison of two methods for reducing the membranes. *Am J Perinatol*. (1999) 16(2):73–7. doi: 10.1055/s-2007-993839
24. Makino Y, Makino I, Tsujioka H, Kawarabayashi T. Amnioreduction in patients with bulging prolapsed membranes out of the cervix and vaginal orifice in cervical cerclage. *J Perinat Med*. (2004) 32(2):140–8. doi: 10.1515/JPM.2004.026
25. Medjedovic E, Begic Z, Suljevic A, Muftic A, Dzihic E, Kurjak A. Amnioreduction in emergency rescue cervical cerclage with bulging membranes. *Med Arch (Sarajevo, Bosnia and Herzegovina)*. (2020) 74 (2):151–2. doi: 10.5455/medarh.2020.74.151-152
26. Zhang Y, Han Z, Gao Q, Bai X, Hou H. Amnioreduction in emergency cervical cerclage: a series of eight cases. *Int J Gynaecol Obstet*. (2020) 150 (3):416–7. doi: 10.1002/ijgo.13153
27. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. (2007) 39(2):175–91. doi: 10.3758/BF03193146
28. Romero R, Gonzalez R, Sepulveda W, Brandt F, Ramirez M, Sorokin Y, et al. Infection and labor. VIII. Microbial invasion of the amniotic cavity in patients with suspected cervical incompetence: prevalence and clinical significance. *Am J Obstet Gynecol*. (1992) 167(4 Pt 1):1086–91. doi: 10.1016/S0002-9378(12)80043-3

29. Lee SE, Romero R, Park CW, Jun JK, Yoon BH. The frequency and significance of intraamniotic inflammation in patients with cervical insufficiency. *Am J Obstet Gynecol.* (2008) 198(6):633.e631–638.
30. Oh KJ, Romero R, Park JY, Lee J, Conde-Agudelo A, Hong JS, et al. Evidence that antibiotic administration is effective in the treatment of a subset of patients with intra-amniotic infection/inflammation presenting with cervical insufficiency. *Am J Obstet Gynecol.* (2019) 221 (2):140.e141–140.e118. doi: 10.1016/j.ajog.2019.03.017
31. Lv M, Zhao B, Chen Y, Xi F, Zhan Q, Wang Y, et al. Balloon tamponade for successful emergency cervical cerclage. *J Obstet Gynaecol Res.* (2020) 46 (3):418–24. doi: 10.1111/jog.14186
32. Son GH, Chang KH, Song JE, Lee KY. Use of a uniconcave balloon in emergency cerclage. *Am J Obstet Gynecol.* (2015) 212(1):114.e111–114. doi: 10.1016/j.ajog.2014.07.022
33. Fuchs F, Senat MV, Fernandez H, Gervaise A, Frydman R, Bouyer J. Predictive score for early preterm birth in decisions about emergency cervical cerclage in singleton pregnancies. *Acta Obstet Gynecol Scand.* (2012) 91(6):744–9. doi: 10.1111/j.1600-0412.2012.01386.x
34. Pereira L, Cotter A, Gómez R, Berghella V, Prasertcharoensuk W, Rasanen J, et al. Expectant management compared with physical examination-indicated cerclage (EM-PEC) in selected women with a dilated cervix at 14(0/7)-25(6/7) weeks: results from the EM-PEC international cohort study. *Am J Obstet Gynecol.* (2007) 197(5):483.e481–488. doi: 10.1016/j.ajog.2007.05.041

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A new nomogram for predicting lung metastasis in newly diagnosed endometrial carcinoma patients: A study based on SEER

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Background: Lung metastasis (LM) is an independent risk factor for survival in patients with endometrial cancer (EC).
Methods: We reviewed data on patients diagnosed with EC between 2010 and 2015 from the Surveillance, Epidemiology, and End Results (SEER) database. The independent predictors of LM in patients with EC were identified using univariate and multivariate logistic regression analyses. A nomogram for predicting LM in patients with EC was developed, and the predictive model was evaluated using calibration and receiver operating characteristic (ROC) curves.
Results: Univariate and multivariate logistic regression analyses showed that high grade; specific histological type; high tumor and node stages; larger tumor size; and liver, brain, and bone metastases were positively associated with LM risk. A new nomogram was developed by combining these factors to predict LM in patients newly diagnosed with EC. Internal and external verification of the calibration charts showed that the nomogram was well calibrated. The areas under the ROC curves for the training and validation cohorts were 0.924 and 0.913, respectively.
Conclusion: We performed a retrospective analysis of 42,073 patients with EC using the SEER database, established a new nomogram for predicting LM based on eight independent risk factors, and visualized the model using a nomogram for the first time.

KEYWORDS

Endometrial carcinoma, lung metastases, nomogram, receiver operating characteristic curve, the surveillance, epidemiology, end results

Introduction

Endometrial cancer (EC) is one of the most serious epithelial malignancies that threatens women's health, ranked fourth in terms of incidence among malignancies affecting women (1). Although surgery and adjuvant radiation therapy have significantly improved disease-free and overall survival in patients with early EC (2),

the prognosis in patients with metastases is poor, with a 5-year survival rate of only 17% (1, 3), respectively. EC mainly spreads *via* intra-abdominal and lymph node metastases (4), while distant organ metastasis is rare. The most common distant metastatic sites of EC are the lungs, followed by the liver, bone, and brain (5). However, compared with other gynecological malignancies, such as cervical cancer and ovarian cancer, EC has the highest frequency of lung metastasis (LM), with a 20%–25% incidence in patients with relapse (6). Although distant metastasis is a rare event in EC (7), it has a significant impact on patient survival. The survival time of patients with EC with LM is only 11 months (8). Especially for early-stage patients, doctors' insufficient judgment on the risk of distant metastasis affects the formulation of treatment and follow-up plans, resulting in decreased patient survival time. Although analysis and modeling of risk factors affecting survival and distant metastasis in EC patients have been carried out, the visualization and evaluation of predictive models for metastasis risk factors are still lacking, which leads to inconvenience in clinical application. In this study, we aimed to evaluate patients with EC registered in the SEER database from 2010 to 2015, and to develop a validated LM nomogram with high accuracy for the first time. In this way, the prognosis can be accurately made and appropriate management strategies can be selected, making it more convenient for clinical management.

Materials and methods

Study population

Data were obtained from the Surveillance, Epidemiology, and End Results (SEER) database. SEER *Stat 8.3.5 software (https://seer.cancer.gov/data/) was used to access the database. As details of metastases were not recorded before 2010, patients with primary EC who were ≥18 years of age at diagnosis and between 2010 and 2015 were analyzed. The site code ICD-O-3 (International Classification of Diseases Oncology-3) is limited to C54.0–C54.9 and C55.9, and the exclusion criteria for patient selection were: unknown histological type classification, unknown American Joint Committee on Cancer (AJCC) tumor (T) and node (N) staging, unknown exact tumor size, and unknown metastatic information. The patient selection flowchart is shown in **Figure 1**. Histological types of ECs were classified according to ICD-0-3 site/histology (endometrioid: 8380–8383/3, 8140/3, 8210/3, 8211/3, 8560/ 3, 8260/3, 8262/3, 8263/3, 8570/3, 8261/3, 8480–8482/3; serous: 8441/3, 8460/3, 8461/3; carcinosarcoma: 8950/3, 8951/3, 8980/3, 8981/3; clear cells: 8310/3 and mixed epithelial cells: 8323/3, 8255/3).

Data on clinical and pathological characteristics, including age, ethnicity, marital status at diagnosis, histological type, grade, AJCC T and N stage, tumor size, and metastatic status, were collected from the SEER database. Based on the inclusion and exclusion criteria, 42,073 EC patients were enrolled in this study. We split all populations into training and validation cohorts in a 7/3 ratio. Because all personally identifiable information in the SEER database was withheld, informed consent was not required for the use of SEER data. This research project complied with the 1964 Declaration of Helsinki and its subsequent amendments or similar ethical standards.

Statistical analysis

Statistical analysis was performed using the SPSS 21 software. The Kolmogorov–Smirnov test was used to verify the normality of the variables. Categorical data are presented as frequency (%) and analyzed using the chi-square test. Normally distributed variables are expressed as mean ± standard deviation, whereas non-normally distributed variables are expressed as median (interquartile range). Univariate and multivariate logistic regression analyses were used to identify the risk factors. Simultaneously, 95% confidence intervals (CIs) and hazard ratios were calculated. Factors with p values <0.05 were included in the multivariate regression model.

The LM nomogram was also based on the results of a multivariate logistic analysis using the rms package in R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org). A receiver operating characteristic (ROC) curve was drawn, and the area under the ROC curve (AUC) was calculated to assess the discriminative ability of the nomogram. Finally, we evaluated the stability of the LM nomogram through internal validation of 1,000 bootstrap samples. A calibration plot was drawn to analyze the agreement between the observed and predicted probabilities.

Results

Characteristics of the study population

Based on the selection process, 42,073 patients were included in our study. Specifically, 29,451 patients were included in the training cohort, and the remaining 12,622 patients were included in the test cohort. The incidence of LM was 1.4% ($n = 603$). The baseline of 42,073 patients are shown in **Tables 1**, **2**. Among patients with and without LM, age ($p = 0.002$); tumor grade ($p < 0.001$), AJCC T stage ($p < 0.001$) and N stage ($p < 0.001$), and histological type ($p < 0.001$); race ($p < 0.001$); insurance status ($p = 0.001$);

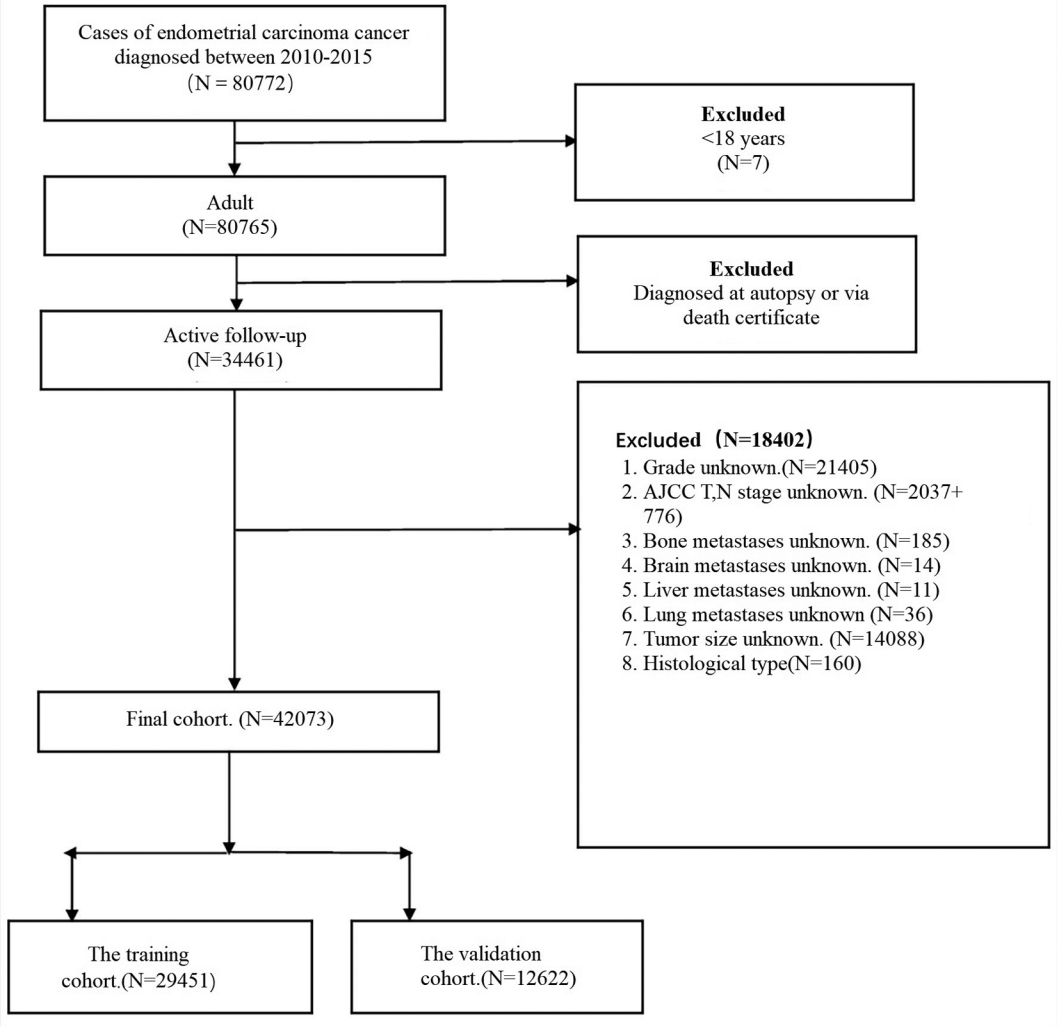

FIGURE 1
The flowchart of patient selection.

tumor size ($p < 0.001$); and the occurrence of bone ($p < 0.001$), brain ($p = 0.017$), and liver metastases ($p < 0.001$) were significantly different. There were no statistically significant differences in terms of the marital status ($p = 0.236$).

Risk factors for LM in patients with EC

Among the 42,073 patients, 603 (1.4%) had LM at the first visit, and 41,470 (98.6%) did not. Univariate logistic analysis was used to analyze 11 predictors to determine LM-related variables in patients with EC. The results showed that eight predictors were related to LM in patients with EC: tumor size ($p < 0.001$), grade ($p < 0.001$), histological type ($p < 0.001$), and AJCC T stage ($p < 0.001$) and N stage ($p < 0.001$); and bone ($p < 0.001$), liver ($p < 0.001$), and brain ($p < 0.001$) metastases (Table 3). Then, statistically significant factors of the univariate logistic analysis were included in the multivariate logistic regression analysis, and the results showed that higher grade ($p < 0.001$); larger tumor ($p < 0.001$); higher T stage ($p < 0.001$); higher N stage ($p < 0.001$); specific histological type ($p < 0.001$); and the occurrence of bone ($p < 0.001$), liver ($p < 0.001$), and brain metastases ($p < 0.001$) were risk factors for LM. These predictors were evaluated for newly diagnosed patients with EC (Table 3).

Development and verification of the LM diagnostic nomogram for newly diagnosed patients with EC

Based on the eight independent LM-related variables, a diagnostic nomogram was established for LM risk assessment in newly diagnosed patients with EC (Figure 2).

TABLE 1 Demographical and clinical characteristics between endometrial carcinoma patient with the lung metastases and without the lung metastases.

Variables	Total	Patients without lung metastases	Patients with lung metastases	*p*
	42,073 (100.0)	41,470 (98.6)	603 (1.4)	
Age (%)				0.014
<40	1,212 (2.9)	1,191 (2.9)	21 (3.5)	
40–49	3,650 (8.7)	3,583 (8.6)	67 (11.1)	
50–59	11,793 (28.0)	11,602 (28.0)	191 (31.7)	
60–69	14,762 (35.1)	14,577 (35.2)	185 (30.7)	
>70	10,656 (25.3)	10,517 (25.4)	139 (23.1)	
Race (%)				<0.001
White	33,660 (80.0)	33,241 (80.2)	419 (69.5)	
Black	4,018 (9.6)	3,900 (9.4)	118 (19.6)	
Other (American Indian/AK Native, Asian/Pacific Islander)	4,135 (9.8)	4,071 (9.8)	64 (10.6)	
Unknown	260 (0.6)	258 (0.6)	2 (0.3)	
Insurance status (%)				0.001
Insured	40,331 (95.9)	39,771 (95.9)	560 (92.9)	
Uninsured	1,257 (3.0)	1,226 (3.0)	31 (5.1)	
Unknown	485 (1.2)	473 (1.1)	12 (2.0)	
Marital status (%)				0.236
Married	21,472 (51.0)	21,187 (51.1)	285 (47.3)	
Unmarried	8,165 (19.4)	8,032 (19.4)	133 (22.1)	
Separated	10,472 (24.9)	10,315 (24.9)	157 (26.0)	
Unknown	1,964 (4.7)	1,936 (4.7)	28 (4.6)	
Histological type (%)				<0.001
Endometrioid histology	31,462 (74.8)	31,242 (75.3)	220 (36.5)	
Serous	3,078 (7.3)	3,026 (7.3)	52 (8.6)	
Carcinosarcoma	2,255 (5.4)	2,178 (5.3)	77 (12.8)	
Clear cell	531 (1.3)	523 (1.3)	8 (1.3)	
Mixed epithelial	2,850 (6.8)	2,813 (6.8)	37 (6.1)	
Others	1,897 (4.5)	1,688 (4.1)	209 (34.7)	
Grade (%)				<0.001
Well differentiated; Grade I	17,017 (40.4)	16,989 (41.0)	28 (4.6)	
Moderately differentiated; Grade II	11,531 (27.4)	11,462 (27.6)	69 (11.4)	
Poorly differentiated; Grade III	9,255 (22.0)	8,971 (21.6)	284 (47.1)	
Undifferentiated; anaplastic; Grade IV	4,270 (10.1)	4,048 (9.8)	222 (36.8)	
AJCC T stage (%)				<0.001
T1	33,664 (80.0)	33,482 (80.7)	182 (30.2)	
T2	3,168 (7.5)	3,069 (7.4)	99 (16.4)	
T3	4,631 (11.0)	4,373 (10.5)	258 (42.8)	
T4	610 (1.4)	546 (1.3)	64 (10.6)	
AJCC N stage (%)				<0.001
N0	37,320 (88.7)	36,949 (89.1)	371 (61.5)	
N1	2,850 (6.8)	2,710 (6.5)	140 (23.2)	
N2	1,903 (4.5)	1,811 (4.4)	92 (15.3)	
Tumor size (%)				<0.001
<2 cm	8,377 (19.9)	8,357 (20.2)	20 (3.3)	

(*continued*)

TABLE 1 | Continued

Variables	Total	Patients without lung metastases	Patients with lung metastases	*p*
2–5 cm	22,260 (52.9)	22,149 (53.4)	111 (18.4)	
>5 cm	11,436 (27.2)	10,964 (26.4)	472 (78.3)	
Brain metastasis (%)				<0.001
No	42,033 (99.9)	41,449 (99.9)	584 (96.8)	
Yes	40 (0.1)	21 (0.1)	19 (3.2)	
Liver metastasis (%)				<0.001
No	41,815 (99.4)	41,310 (99.6)	505 (83.7)	
Yes	258 (0.6)	160 (0.4)	98 (16.3)	
Bone metastasis (%)				<0.001
No	41,895 (99.6)	41,380 (99.8)	515 (85.4)	
Yes	178 (0.4)	90 (0.2)	88 (14.6)	

TABLE 2 Demographical and clinical characteristics between patient with the primary cohort and the validation cohort.

Variables	Total	The training cohort	The validation cohort	*p*
	42,073 (100)	29,451 (70.0)	12,622 (30.0)	
Age (%)				0.313
<40	1,212 (2.9)	874 (3.0)	338 (2.7)	
40–49	3,650 (8.7)	2,571 (8.7)	1,079 (8.5)	
50–59	11,793 (28.0)	8,257 (28.0)	3,536 (28.0)	
60–69	14,762 (35.1)	10,264 (34.9)	4,498 (35.6)	
>70	10,656 (25.3)	7,485 (25.4)	3,171 (25.1)	
Race (%)				0.186
White	33,660 (80.0)	23,565 (80.0)	10,095 (80.0)	
Black	4,018 (9.6)	2,767 (9.4)	1,251 (9.9)	
Other (American Indian/AK Native, Asian/Pacific Islander)	4,135 (9.8)	2,939 (10.0)	1,196 (9.5)	
Unknown	260 (0.6)	180 (0.6)	80 (0.6)	
Insurance status (%)				0.196
Insured	40,331 (95.9)	28,263 (96.0)	12,068 (95.6)	
Uninsured	1,257 (3.0)	863 (2.9)	394 (3.1)	
Unknown	485 (1.2)	325 (1.1)	160 (1.3)	
Marital status (%)				0.326
Married	21,472 (51.0)	15,069 (51.2)	6,403 (50.7)	
Unmarried	8,165 (19.4)	5,710 (19.4)	2,455 (19.5)	
Separated	10,472 (24.9)	7,333 (24.9)	3,139 (24.9)	
Unknown	1,964 (4.7)	1,339 (4.5)	625 (5.0)	
Histological type (%)				0.414
Endometrioid histology	31,462 (74.8)	22,063 (74.9)	9,399 (74.5)	
Serous	3,078 (7.3)	2,153 (7.3)	925 (7.3)	
Carcinosarcoma	2,255 (5.4)	1,552 (5.3)	703 (5.6)	
Clear cell	531 (1.3)	368 (1.2)	163 (1.3)	
Mixed epithelial,	2,850 (6.8)	1,963 (6.7)	887 (7.0)	
Others	1,897 (4.5)	1,352 (4.6)	545 (4.3)	
Grade (%)				0.265
Well differentiated; Grade I	17,017 (40.4)	11,865 (40.3)	5,152 (40.8)	

(*continued*)

TABLE 2 | Continued

Variables	Total	The training cohort	The validation cohort	*p*
Moderately differentiated; Grade II	11,531 (27.4)	8,153 (27.7)	3,378 (26.8)	
Poorly differentiated; Grade III	9,255 (22.0)	6,466 (22.0)	2,789 (22.1)	
Undifferentiated; anaplastic; Grade IV	4,270 (10.1)	2,967 (10.1)	1,303 (10.3)	
AJCC T stage (%)				0.488
T1	33,664 (80.0)	23,555 (80.0)	10,109 (80.1)	
T2	3,168 (7.5)	2,252 (7.6)	916 (7.3)	
T3	4,631 (11.0)	3,223 (10.9)	1,408 (11.2)	
T4	610 (1.4)	421 (1.4)	189 (1.5)	
AJCC N stage (%)				0.082
N0	37,320 (88.7)	26,185 (88.9)	11,135 (88.2)	
N1	2,850 (6.8)	1,972 (6.7)	878 (7.0)	
N2	1,903 (4.5)	1,294 (4.4)	609 (4.8)	
Tumor size (%)				0.119
<2 cm	8,377 (19.9)	5,899 (20.0)	2,478 (19.6)	
2–5 cm	22,260 (52.9)	15,632 (53.1)	6,628 (52.5)	
>5 cm	11,436 (27.2)	7,920 (26.9)	3,516 (27.9)	
Brain metastasis (%)				0.058
No	42,033 (99.9)	29,429 (99.9)	12,604 (99.9)	
Yes	40 (0.1)	22 (0.1)	18 (0.1)	
Liver metastasis (%)				0.796
No	41,815 (99.4)	29,268 (99.4)	12,547 (99.4)	
Yes	258 (0.6)	183 (0.6)	75 (0.6)	
Bone metastasis (%)				1
No	41,895 (99.6)	29,326 (99.6)	12,569 (99.6)	
Yes	178 (0.4)	125 (0.4)	53 (0.4)	
Lung metastasis (%)				0.452
No	41,470 (98.6)	29,020 (98.5)	12,450 (98.6)	
Yes	603 (1.4)	431 (1.5)	172 (1.4)	

TABLE 3 Univariable and multivariable logistic regression for analyzing the associated factors for developing liver metastases in endometrial carcinoma cancer patients.

Variables	Univariable			Multivariable		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age			0.163			
<40	References					
40–49	0.847	0.488–1.471	0.556			
50–59	0.767	0.466–1.261	0.295			
60–69	0.634	0.386–1.042	0.072			
>70	0.657	0.396–1.090	0.104			
Race			0.622			
White	References					
Black	2.530	1.983–3.228	<0.001			
Other	1.337	0.986–1.814	0.062			
Unknown	0.441	0.062–3.156	0.415			
Marital status			0.217			

(*continued*)

TABLE 3 | Continued

Variables	Univariable			Multivariable		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Married	References			References		
Unmarried	1.259	0.987–1.607	0.064			
Separated	1.069	0.844–1.354	0.581			
Unknown	1.330	0.868–2.038	0.190			
Insurance status			0.002			0.010
Insured	References			References		
Uninsured	1.912	1.249–2.927	0.003	1.525	0.950–2.448	0.080
Others/Unknown	1.989	1.018–3.886	0.044	2.550	1.238–5.256	0.011
Tumor size			**<0.001**			**<0.001**
<2 cm	References			References		
2–5 cm	1.575	0.941–2.637	0.084	0.999	0.583–1.712	0.997
>5 cm	14.565	9.055–23.429	<0.001	2.949	1.763–4.933	<0.001
Grade			**<0.001**		0.000	**<0.001**
Well differentiated; Grade I	References			References		
Moderately differentiated; Grade II	3.340	1.999–5.582	<0.001	2.046	1.206–3.471	0.008
Poorly differentiated; Grade III	18.374	11.713–28.822	<0.001	5.749	3.509–9.419	<0.001
Undifferentiated; anaplastic; Grade IV	31.724	20.085–50.107	<0.001	5.646	3.329–9.575	<0.001
AJCC T stage			**<0.001**			**<0.001**
T1	References			References		
T2	4.993	3.691–6.755	<0.001	1.761	1.250–2.481	0.001
T3	10.746	8.587–13.448	<0.001	3.103	2.361–4.079	<0.001
T4	20.762	14.596–29.535	<0.001	4.155	2.733–6.316	<0.001
AJCC N stage			**<0.001**			**<0.001**
N0	References			References		
N1	4.967	3.916–6.302	<0.001	1.542	1.160–2.050	0.003
N2	5.384	4.101–7.069	<0.001	1.735	1.256–2.397	0.001
Bone metastasis			**<0.001**			**<0.001**
No	References			References		
Yes	79.959	55.486–115.227	<0.001	15.099	9.769–23.338	<0.001
Brain metastasis			**<0.001**			**<0.001**
No	References			References		
Yes	47.587	20.232–111.930	<0.001	10.055	3.681–27.461	<0.001
Liver metastasis			**<0.001**	<0.001		**<0.001**
No	References			References		
Yes	54.979	40.199–75.195	<0.001	8.535	5.841–12.471	<0.001
Histological type			**<0.001**			**<0.001**
Endometrioid histology	References			References		
Serous	2.460	1.722–3.513	<0.001	0.623	0.415–0.933	0.022
Carcinosarcoma	4.935	3.609–6.747	<0.001	0.914	0.639–1.308	0.624
Clear cell	0.373	0.052–2.671	<0.001	0.098	0.013–0.711	0.022
Mixed epithelial	1.981	1.322–2.968	0.326	0.863	0.557–1.336	0.508
Others	17.083	13.571–21.505	0.001	4.430	3.262–6.015	<0.001

Simultaneously, the ROC curves of the training and validation cohorts were established. The AUC of the nomogram in the training cohort was 0.924, sensitivity was 0.903, and specificity was 0.792 (Figure 3A). The AUC of the nomogram in the validation cohort was 0.913, with a sensitivity of 0.892 and specificity of 0.779 (Figure 3B). In addition, to test the

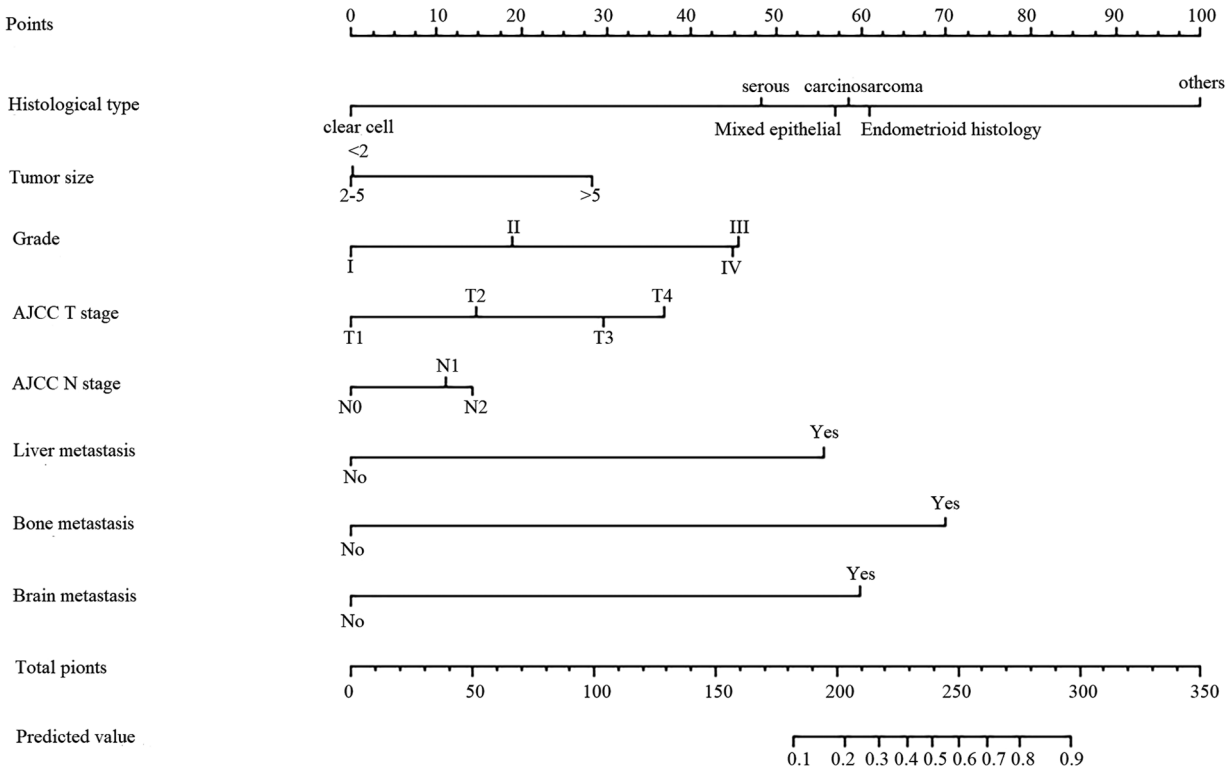

FIGURE 2
Nomogram predicting the probability of LM. The first line shows the point assignment of each variable. Lines 2–9 show the variables included in the model. When using a nomogram for a single patient, a point is assigned to each variable based on clinicopathological characteristics, and all points are added. Each score in the total score in row 9 will correspond to the probability of risk in the last row.

performance of the nomogram, 1,000 bootstrap resampling cycles were performed for internal verification. The calibration curves showed good agreement between the training and validation cohorts (**Figures 3C,D**).

Discussion

Approximately 15%–25% of patients with EC are already at an advanced stage at the time of diagnosis. Surgery, chemotherapy, and radiotherapy are the main treatments for patients with EC (9), which can improve the survival rate of patients. Studies have found that the early detection of metastases and surgery at the primary site play an important role in improving the survival rate of patients. The median cancer-specific survival time of patients with solitary LM undergoing surgery and those not undergoing surgery is 23 months and 9 months, respectively (10). LM-directed radiotherapy can control local tumors and improve the survival rate of patients (11). Therefore, the early detection of LM from EC and appropriate clinical measures are critical for patient survival. Regarding LM in EC, there are only studies on its risk factors (12), and no predictive model has been developed to depict the risk of LM more intuitively (8) so that it can be conveniently applied in clinical management. Therefore, a clinical model for predicting LM is urgently required to guide clinical strategies and improve the survival rate of patients with LM. This study was the first to develop a nomogram using the SEER database to predict concurrent LM in patients with EC. The total score can be calculated by obtaining data on several variables on the nomogram for each patient with EC. The risk of LM can then be easily identified using the nomogram, providing guidance for further clinical management.

Our study found that the incidence of LM was 1.4%, which is similar to that in previous studies (8). We found that a high tumor grade; large tumor size; higher T and N stages; specific histological type; and presence of bone, liver ($p < 0.001$), and brain metastases ($p < 0.001$) were risk factors for LM and were included in the prediction model. Adachi et al. also found that LM is associated with stage IV disease and deep muscle infiltration (13). Jiang et al. found that large tumor size and deep muscle invasion may be risk factors for LM in patients with stage I endometrioid EC (14). Mao's clinical case study on EC found that tissue type is a risk factor for LM, and carcinosarcoma is more prone to LM (8, 13). We also found that different histological types could affect the occurrence of LM. Compared with endometrioid histology, serous

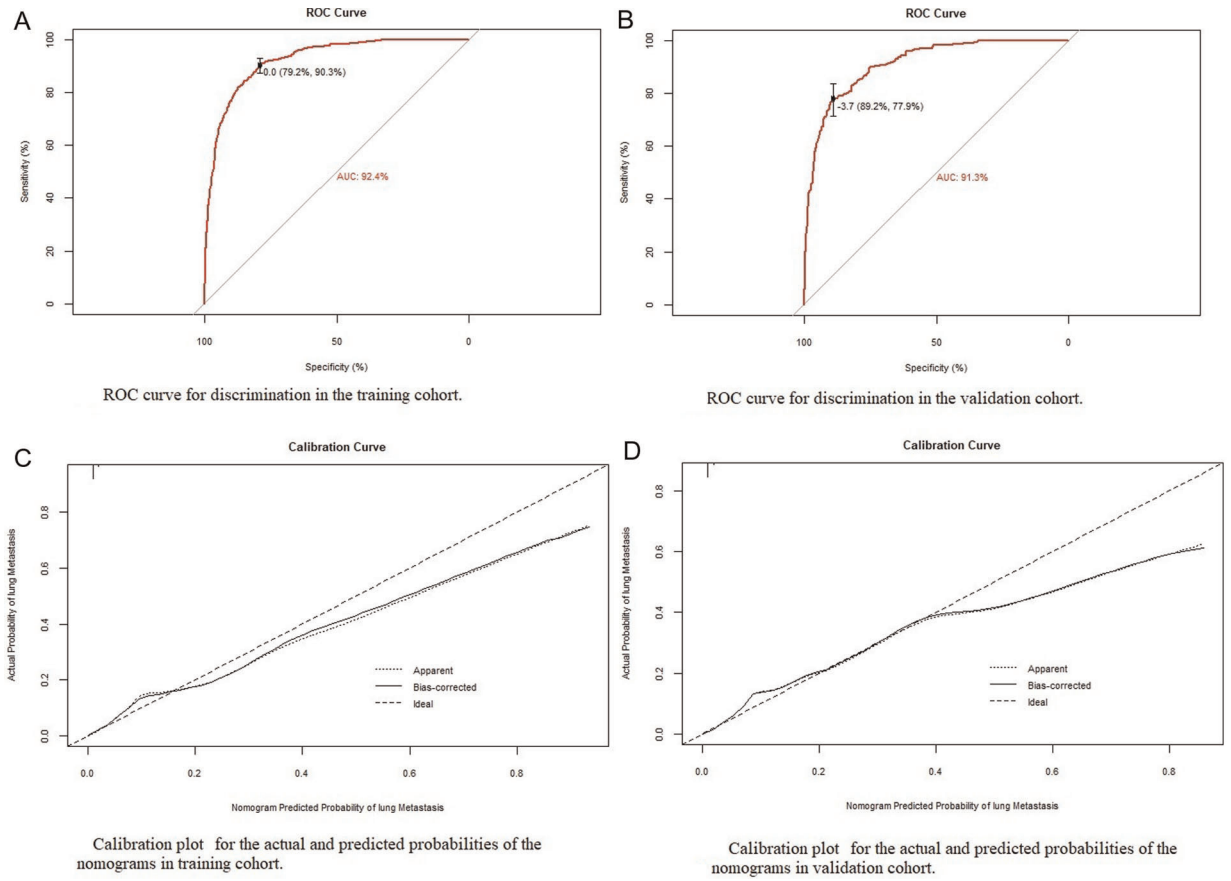

FIGURE 3
Identification and calibration of the nomogram in the training and validation cohorts. (A,B) ROC curve used to distinguish between training and validation cohorts. The area under the curve (AUC) is 0.924 and 0.913, indicating that the model has good performance. (C,D) Calibration curve of training cohort and validation cohort. The *x*-axis shows the predicted probability of the model, and the *y*-axis shows the actual probability.

and clear cells are less prone to LM, and carcinosarcoma is more prone to LM (15). In Guo's retrospective study of 730 patients, poor differentiation was an independent high-risk factor for extraperitoneal metastasis and has been widely accepted by clinicians as a feature of high-risk EC (10). Once distant metastasis occurs, it indicates that there has been extraperitoneal diffusion and cervical interstitial infiltration, therefore LM is also more likely to occur. We verified the nomogram internally and externally. There was consistency between the predicted results and those observed during verification. The ROC curve's AUC in the training cohort was 0.924 and the AUC of the line graph was 0.913 in the validation cohort. Through this predictive model, obstetricians and gynecologists will be able to estimate the likelihood of LM in patients with EC. For patients with a higher likelihood of LM, a closer follow-up should be performed. The nomogram can be used to evaluate patients with EC before chest computed tomography (CT) to determine whether the patient requires CT. If the patient's first CT evaluation cannot determine whether metastasis is present, CT follow-up should be encouraged for patients with a high risk of LM shown on the nomogram.

This study had some limitations. First, this was a retrospective study, and there are inherent biases associated with this type of study design. Additionally, only patients with LM at their first visit were analyzed. LMs occurring later in the disease were not analyzed because they may not have been recorded in the SEER database. Third, the nomograms in our study were only validated in the same population, and there may be biases in the validation of the model performance. Therefore, more clinical data should be collected for external validation of this model in the future.

Conclusion

In conclusion, this study performed a retrospective analysis of 42,073 patients with EC using the SEER database and established for the first time a new nomogram for predicting LM based on eight independent risk factors. The verification of the model proved that it has good performance. Although predictive models have certain limitations, nomograms can

reveal the relationship between clinicopathological features and LM risk in patients with EC. Through this predictive model, physicians will be able to estimate the likelihood of developing LM in patients with EC, providing guidance for further clinical management.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/data-software.

Author contributions

YY and RW contributed equally to this manuscript. (I) Conception and design: YY; (II) administrative support: JZ, YY; (III) provision of study materials or patients: RW; (IV) collection and assembly of data: YZ; (V) data analysis and interpretation: RW; (VI) manuscript writing: All authors; (VII) final approval of manuscript: All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin*. (2016) 66(1):7–30. doi: 10.3322/caac.21332

2. Elshaikh MA, Vance S, Suri JS, Mahan M, Munkarah A. Improved survival endpoints with adjuvant radiation treatment in patients with high-risk early-stage endometrial carcinoma. *Int J Radiat Oncol Biol Phys*. (2014) 88(2):351–6. doi: 10.1016/j.ijrobp.2013.11.003

3. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. *Lancet*. (2005) 366(9484):491–505. doi: 10.1016/S0140-6736(05)67063-8

4. Lewin SN. Revised FIGO staging system for endometrial cancer. *Clin Obstet Gynecol*. (2011) 54(2):215–8. doi: 10.1097/GRF.0b013e3182185baa

5. Liu Y, Chi S, Zhou X, Zhao R, Xiao C, Wang H. Prognostic value of distant metastatic sites in stage IV endometrial cancer: a SEER database study of 2948 women. *Int J Gynaecol Obstet*. (2020) 149(1):16–23. doi: 10.1002/ijgo.13084

6. Sohaib SA, Houghton SL, Meroni R, Rockall AG, Blake P, Reznek RH. Recurrent endometrial cancer: patterns of recurrent disease and assessment of prognosis. *Clin Radiol*. (2007) 62(1):28–34; discussion 5–6. doi: 10.1016/j.crad.2006.06.015

7. Mariani A, Webb MJ, Keeney GL, Podratz KC. Routes of lymphatic spread: a study of 112 consecutive patients with endometrial cancer. *Gynecol Oncol*. (2001) 81(1):100–4. doi: 10.1006/gyno.2000.6111

8. Mao W, Wei S, Yang H, Yu Q, Xu M, Guo J, et al. Clinicopathological study of organ metastasis in endometrial cancer. *Future Oncol*. (2020) 16(10):525–40. doi: 10.2217/fon-2020-0017

9. Brooks RA, Fleming GF, Lastra RR, Lee NK, Moroney JW, Son CH, et al. Current recommendations and recent progress in endometrial cancer. *CA Cancer J Clin*. (2019) 69(4):258–79. doi: 10.3322/caac.21561

10. Guo J, Cui X, Zhang X, Qian H, Duan H, Zhang Y. The clinical characteristics of endometrial cancer with extraperitoneal metastasis and the value of surgery in treatment. *Technol Cancer Res Treat*. (2020) 19, 1533033820945784. doi: 10.1177/1533033820945784

11. Baschnagel AM, Mangona VS, Robertson JM, Welsh RJ, Kestin LL, Grills IS. Lung metastases treated with image-guided stereotactic body radiation therapy. *Clin Oncol (R Coll Radiol)*. (2013) 25(4):236–41. doi: 10.1016/j.clon.2012.12.005

12. Zhu L, Sun X, Bai W. Nomograms for predicting cancer-specific and overall survival among patients with endometrial carcinoma: a SEER based study. *Front Oncol*. (2020) 10:269. doi: 10.3389/fonc.2020.00269

13. Adachi M, Mizuno M, Mitsui H, Kajiyama H, Suzuki S, Sekiya R, et al. The prognostic impact of pulmonary metastasectomy in recurrent gynecologic cancers: a retrospective single-institution study. *Nagoya J Med Sci*. (2015) 77(3):363–72. PMID: 26412882; PMCID: PMC4574323

14. Jiang W, Chen J, Tao X, Huang F, Zhu M, Wang C, et al. Possible risk factors of pulmonary metastases in patients with international federation of gynecology and obstetrics stage I endometrioid-type endometrial cancer. *Int J Gynecol Cancer*. (2017) 27(6):1206–15. doi: 10.1097/IGC.0000000000001002

15. Kurra V, Krajewski KM, Jagannathan J, Giardino A, Berlin S, Ramaiya N. Typical and atypical metastatic sites of recurrent endometrial carcinoma. *Cancer Imaging*. (2013) 13:113–22. doi: 10.1102/1470-7330.2013.0011

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CASE REPORT
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Pelvic Lymph Node Lymphangiomyomatosis Found During Surgery for Gynecological Fallopian Tube Cancer: A Case Report and Literature Review

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Background: Lymphangioleiomyomatosis (LAM) is a rare low-grade metastatic tumor with an unknown origin that spreads through lymphatic vessels. It is characterized by the proliferation of smooth muscle-like or epithelioid tumor cells in the lung and axial lymphatic system. Extrapulmonary LAM is a localized disease with a low incidence rate, and the location of the related lesions is atypical. It is difficult to diagnose. The LAM of pelvic lymph nodes is hidden. It is usually found through gynecological oncology surgery.

Case presentation: We report a 57-year-old postmenopausal woman with a pelvic mass and vaginal bleeding as the main symptoms. The patient had no history of pulmonary LAM, tuberous sclerosis complex (TSC), or renal angiomyolipoma and had not used exogenous hormones. We performed a total hysterectomy, bilateral adnexectomy, greater omentum resection, and pelvic lymphadenectomy under laparoscopy. The postoperative pathology confirmed high-grade serous carcinoma of the left fallopian tube, and four lymph nodes were found in the pelvic lymph nodes, suggesting lymphangiomyomatosis. Immunohistochemical results also showed that these cells could express markers of smooth muscle cells and melanoma cells. The patient was treated with chemotherapy after the operation. Chest CT did not suggest lung LAM during the postoperative follow-up, and there was no tumor recurrence.

Conclusion: The diagnosis of this disease is challenging. At the same time, due to insufficient clinical samples, it is still unknown whether there is a potential relationship between pelvic and peritoneal lymph node LAM found in the surgical staging of gynecological tumors and lung LAM and/or TSC. There is no evidence that pelvic and peritoneal lymph node LAM will increase the risk of pulmonary LAM. Therefore, additional clinical data are required to analyze and summarize the relationship between pelvic and peritoneal lymph node LAM, pulmonary LAM, and the source of LAM. We present a case of pelvic lymph node LAM and propose a hypothesis that the pathogenesis of endometriosis can be used for reference in the study of this disease.

Keywords: lymphangiomyomatosis, gynecological surgery, fallopian tube carcinoma, pelvic lymph nodes, case report

INTRODUCTION

Lymphangiomatosis, also known as lymphangioleiomyomatosis (LAM), is a tumor composed of lymphangiomyocytes proliferating around lymphatics, sometimes with lymphocyte aggregation. Focal lesions are called lymphangiomyomas, and those with or without the involvement of pulmonary parenchyma are called lymphangiomyomatosis. Von Stossel first reported it in 1937. It belongs to one of the lesion families collectively known as perivascular epithelial cell tumors (PEComa). It is a slow-moving, low-grade, metastatic systemic disease characterized by progressive cystic lung destruction, abdominal tumors, and chylous fluid accumulations, including angioleiomyoma and lymphangioleiomyoma (1, 2). This disease is rare and easily misdiagnosed. It occurs almost exclusively in women, mainly in those of childbearing age. According to statistics, approximately 3.4–7.8 people per million women suffer from LAM (3). LAM can be distributed or concurrent based on TSC. LAM is most common in the lung. LAM lesions found in pelvic and peritoneal lymph nodes are rare and hidden. At the same time, LAM lesions have been reported in the uterus (4). Whether lesions in the uterus are metastatic or the source of cancer has always been the focus of debates. Primary extrapulmonary LAM is extremely rare. According to the currently reported cases, pelvic lymph node LAM found in gynecological surgery is usually uterine body cancer, cervical cancer, ovarian cancer, hysteromyoma, endometriosis, adenomyosis, and other diseases. To the best of our knowledge, primary pelvic lymph node LAM found in primary fallopian tube cancer surgery is relatively rare. Here, we report a case of pelvic lymphangiomyomatosis in the staging operation of gynecological fallopian tube cancer, and there was no pulmonary LAM at the 12-month postoperative follow-up.

CASE PRESENTATION

A 57-year-old female patient was hospitalized for "one year of menopause, pelvic mass with irregular vaginal bleeding for 3 weeks." The patient had a history of well-controlled hypertension, denied a relevant family, and disease history. There is no history of lung disease, exogenous hormone use, TSC, or renal angiomyolipoma. 1-0-0-1, spontaneous labor. The patient was admitted to the hospital for an ultrasound examination, which showed that the intima was 7.3 mm, and the echo of the intima was uneven. There was a mixed echo on the left side of the pelvic cavity, with a size of 99 mm × 48 mm, which was mainly hypoechoic with a pipe-like structure. Preoperative PET-CT examination revealed an irregular cystic, solid mass on the left side of the pelvis, an abnormal increase in FDG metabolism in the solid part in front of the mass, the maximum value of SUV is 6.51, 7.02 after delay, the uptake range is 38 mm × 25 mm and possible large malignant lesions from the left appendix. Preoperative chest CT showed a small amount of pleural effusion on both sides, and no apparent abnormalities were found in the rest. The results of the preoperative pulmonary function examination were normal. We performed a laparoscopic total hysterectomy, bilateral adnexectomy, greater omentum resection, and pelvic lymphadenectomy. During the operation, the left fallopian tube was thickened and twisted, approximately 15 cm long, and brittle tumor tissue was seen at the fimbriae end. The uterus is slightly enlarged, and a small intramural myoma was seen in the posterior wall. There was no right fallopian tube abnormality and bilateral ovarian atrophy. The left pelvic wall adhered to the intestinal canal, and the greater omentum adhered to the abdominal wall. There was no evident lymphadenopathy. The postoperative pathology showed that the malignant epitheliogenic tumor of the left adnexa was consistent with high-grade serous carcinoma, and the possibility of fallopian tube origin was high. No definite vascular and nerve recidivism. No tumor metastasis was found in the bilateral parauterine and cervical margins. One of the eight lymph nodes in the left pelvic cavity showed lymphangiomyomatosis, 2 mm in diameter. Among the seven lymph nodes in the left obturator, two lymph nodes showed lymphangiomyomatosis, 5 mm in diameter. Among the five lymph nodes in the right obturator, one lymph node is seen, showing lymphangiomyomatosis, 5 mm in diameter. See in (**Figures 1A,B**) for the H&E staining results of the lymph node LAM pathological sections. Immunohistochemistry showed a-SMA positivity, Desmin positivity, HMB45 (scattered cells +), D2-40 (vessels +), β-catenin (cytoplasmic +), ER, and PR were negative (see **Figures 2A–G**).

According to the pathological report after the operation, the patient was diagnosed with high-grade serous carcinoma of the left fallopian tube (p-T1aN0M0 stage IA). We gave the patient a cycle of chemotherapy with paclitaxel and carboplatin. After chemotherapy, the patient had no discomfort or bone marrow suppression, so she was discharged from the hospital. The follow-up patient elected to stop treatment because of pronounced nausea and vomiting after chemotherapy. As of 7 April 2021, the patient was followed up in our hospital again. Nearly 8 months had passed since the operation and chemotherapy. A small amount of pleural effusion was still seen on chest CT, similar to before the operation. There were no apparent abnormalities in others, and there was no evident recurrence on upper abdominal enhanced CT and pelvic enhanced MRI. The patient was followed up for 12 months after the operation, and there were no related pulmonary symptoms.

DISCUSSION

Lymphangiomyomatosis (LAM) is a rare and slow-moving multisystem disease. The common manifestation is abnormal smooth muscle-like cells infiltrating the lung parenchyma, resulting in cystic destruction of the lung (1). LAM is most common in the lungs, and its extrapulmonary features are mainly angiomyolipoma and lymphatic abnormalities. Angiomyolipomas are benign mixed mesenchymal tumors most often found in the kidney. They can be found in approximately 30–40% of women with sporadic LAM and 88–96% of women with TSC-LAM (5, 6), and most of these tumors are small and asymptomatic (7). Lymphatic manifestations include the formation of lymphangioleiomyoma and chylous pleural and ascites, occasional chylous pericardial effusion, chylous hemoptysis, and chyluria (1).

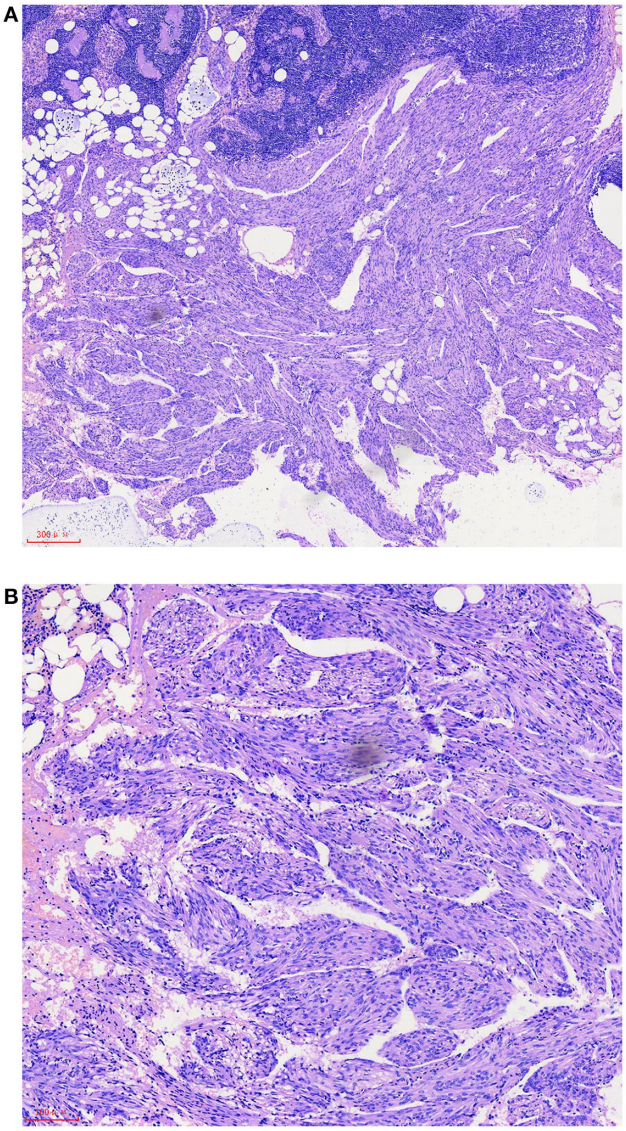

FIGURE 1 | After hematoxylin-eosin (HE) staining, it is found that there is a fascicular proliferative smooth muscle-like spindle cell area outside the pelvic lymph nodes, which has a clear boundary with the surrounding tissues **(A).** Smooth muscle-like spindle cell nuclei have no atypia and are mostly arranged around reticular or sinusoidal cavities lined with flat endothelium. Residual lymph nodes can be seen in local areas between proliferative spindle cells **(B).** The scale represents 300 μm **(A)** and 100 μm **(B)**.

The cell source of this disease is unknown and often complicated with TSC. TSC is a multisystem autosomal dominant disease caused by germline mutations of the TSC gene, TSC1, or TSC2. Gene mutation can lead to the constitutive activation of the rapamycin (mTOR) mechanical target pathway, the imbalance of LAM cell growth and proliferation, and the obstruction of lymphangiogenesis, resulting in a lung remodeling disorder (1). LAM cells have the appearance of "immature" smooth muscle-like cells. They can express smooth muscle-like specific proteins (α-smooth muscle actins, Desmin) and the melanoma cell marker gp100, in which gp100 can be recognized by the antibody HMB45 (human melanoma black 45) (8, 9). In this case, the immunohistochemical hints of LAM in the patient's lymph nodes α-SMA, Desmin, and HMB-45 were all positive (see **Figures 2A–C**), which was consistent with the characteristics of LAM cells.

In addition to the overactivation of the mTOR pathway, LAM may also have a metastasis mechanism. The study found that LAM recurrence occurred after single lung transplantation, indicating that the metastasis mechanism may be involved in the progression of LAM disease (10). Szpurek et al. reported a case of a 47-year-old female primary uterine LAM with ovarian and lung metastasis (11), indicating that although LAM is considered benign histologically, LAM has the biological tendency to transform into a malignant tumor. LAM cells have the ability to grow, migrate, and invade, enter the lungs through lymphatic circulation, and even destroy distant tissues (12). However, due to the long duration of the disease, patients can remain in good condition for several years.

LAM is difficult to diagnose. The diagnostic features include TSC, angiomyolipoma, chylous pleural effusions or ascites, and lymphangioleiomyomas (2). For patients whose chest CT shows LAM lesions but there is no other confirmed evidence, it is recommended to detect vascular endothelial growth factor D (VEGF-D) before lung biopsy (2). The guidelines (2) recommend that patients with LAM be treated with sirolimus, but the guidelines do not advocate hormone therapy, including progesterone, gonadotropin-releasing hormone agonist, selective estrogen receptor modulator, and oophorectomy, because most patients do not show beneficial results.

Extrapulmonary LAM is usually a benign lesion, and lymph node lymphomyomalosis is challenging to detect. It is occult. It is occasionally found in lymph nodes of gynecological tumors and surgical stages of urinary system malignant tumors, including (13–15) of the uterus, oviduct, ovarian cancer, or bladder cancer. The total incidence rate in gynecologic malignant tumor staging surgery is 1.3% (16). It has been found that most extrapulmonary LAM occurs in lymph nodes along the mediastinum or retroperitoneal lymphatics, with three main locations followed by the posterior mediastinum, the upper retroperitoneal region close to the abdominal aorta, and the pelvis (17). These three places are all candidate sites for primary LAM, but there is some evidence that LAM originates in the pelvis and moves along the lymphatic direction (18).

The origin of LAM is still under study. Hayashi et al. reported that 90% of patients with pulmonary LAM have uterine LAM, and all uterine LAM lesions are accompanied by LAM lesions of retroperitoneal or pelvic lymph nodes. Therefore, it is assumed that the uterus or the area near the retroperitoneal or pelvic cavity may be the primary site for LAM, and LAM cells can spread to the lung through lymphatic vessels (4). At the same time, Suzuki et al. found that LAM originated in uterine smooth muscle and then invaded retroperitoneal lymph nodes through lymphatic circulation (19), which is more consistent with what Hayashi et al. said. However, since LAM also occurs in men (20), there should be other potential sources.

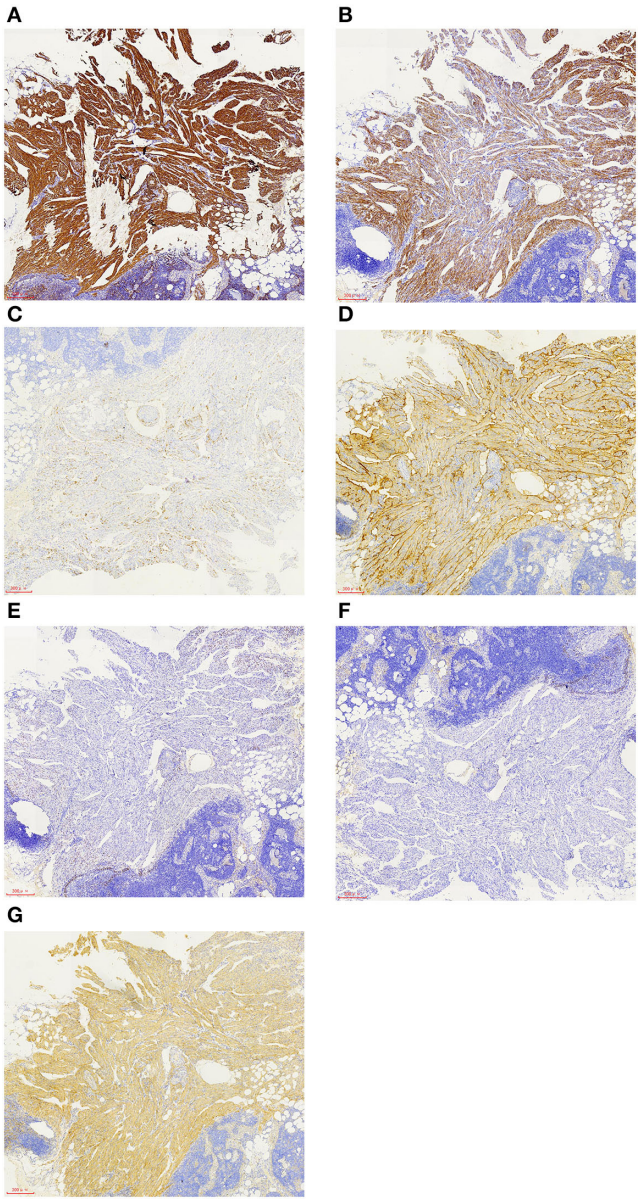

FIGURE 2 | Immunohistochemistry of LAM cells showed that the smooth muscle-like specific protein markers a-SMA **(A)** and desmin **(B)** were positive, the melanocyte marker HMB45 was focally positive **(C),** D2-40 was positive **(D),** ER and PR were negative **(E,F),** and β-catenin was positive **(G).** The scale represents 300 μm **(A–G)**.

In this case, only pelvic lymph node LAM was found, and no lesions were found in the uterus or lungs. Currently, pelvic lymph nodes are the primary site. Whether they can develop into pulmonary LAM remains to be further followed up. The relationship between lung LAM and lymph node LAM is not clear. Some scholars found that in patients without symptoms and signs of lung LAM, lymph node LAM may be a high-risk indicator for the development of lung LAM (17). Some scholars also believe that occult lymph node LAM found in the surgical staging of gynecological cancer has nothing to do with lung LAM and TSC. However, these two diseases still need to be evaluated in detail (13).

We summarized some cases of sporadic lymph node LAM during surgery. We found that only a tiny portion (2/61) developed pulmonary LAM, the vast majority did not develop pulmonary LAM, and the association with TSC was very low (2/61) (see **Table 1**) (13–15, 18–22). As reported in this case, we were followed up for 12 months, but there was no significant pulmonary LAM. However, due to the slow progression of the disease, there is also the possibility that the follow-up time is not long enough, and lung involvement does not appear. According to Matsui et al., it may take 1–2 years for lymph node LAM to develop into pulmonary LAM (17), and the size of lymph node lesions in patients with pulmonary LAM is at least 10 mm. Kuno et al. (21) reported that a woman with <10 mm of lymphadenopathy developed pulmonary LAM 7 years after the operation. Therefore, lymph node LAM may be a high-risk factor for the development of pulmonary LAM. However, for more than 1–2 years without developing pulmonary LAM, it may take longer and may be related to the size of lymph node lesions.

In addition, LAM mainly occurs in women of childbearing age and easily worsens during pregnancy. It is known that LAM cells express estrogen and progesterone receptors simultaneously, and a study found that the expression of PR is usually higher than that of ER (23), so female hormones play an essential role in the development and progression of the disease. However, many postmenopausal women also have LAM, and the course of disease of postmenopausal women with LAM is relatively stable (24). The patient, in this case, has been postmenopausal for 1 year. It is worth mentioning that the patient was confirmed to have high-grade serous carcinoma of the fallopian tube by postoperative pathology. Primary fallopian tube carcinoma (PFTC) is a rare malignant tumor in women, accounting for 0.14–1.8% of all female reproductive tract malignant tumors (25). Her ovaries are in a non-functional state, and we found that ER and PR were negative when staining pathological specimens (see **Figures 2E,F**). Therefore, hormone dependence may not be applicable in this case. It is speculated that the patient may have had pelvic lymph node LAM before menopause, but it has not been found. However, the condition is relatively stable after menopause, and there is no clinical manifestation of LAM. It is also possible that the patient developed pelvic lymph node LAM after menopause. However, pelvic and peritoneal lymph node LAM is also found in postmenopausal endometrial cancer (13–15). Most patients with endometrial cancer are in a state of relative excess estrogen, indicating that hormone levels still play an essential role in the occurrence and development of the disease.

Although LAM is hormone-dependent, it is interesting that LAM is not unique to women and, in rare cases, exists in men (20). Just as endometriosis is also a hormone-dependent disease common in women, it is now found to be not unique to women and sporadic in men (26). Combined with the metastatic characteristics of the disease, we believe that the disease has certain similarities with endometriosis in occurrence and development. They are hormone-dependent and have

TABLE 1 | Female cases of pelvic and peritoneal lymph node LAM found during the operation.

Case report	Number of patients involved	Age, median and range	Disease type	Immunohisto chemistry	TSC	Develop into lung LAM	Follow up time, median and range	Prognosis
Iwasa et al. (15)	*three cases*	*59 years old, (47-71 years old)*	*one case of cervical squamous cell carcinoma and two cases of endometrial adenocarcinoma*	*α-SMA, desmin, HMB45, ER, PR, D2-40 were positive*	*Nothing*	*No*	*27.3 months, (20–39 months)*	*All survived*
School meester et al. (14)	*19 cases*	*56.3 years old (35-71 years old)*	*five cases of ovarian cancer, nine cases of uterine body cancer, one case of adult ovarian granulosa cell tumor, one case of cervical squamous cell carcinoma, one case of high-grade serous carcinoma of the fallopian tube, one case of hysteromyoma and one case of sporadic LAM*	*HMB45, β-catenin were positive*	*Nothing*	*No*	*33.8 months, (3–123 months)*	*One case died of uterine serous carcinoma 23 months after the operation, one case of sporadic LAM persisted, and the rest survived.*
Kuno et al. (21)	*eight cases*	*56 years old (36-74 years old)*	*four cases of uterine body cancer, two cases of ovarian cancer and two cases of cervical cancer*	*α-SMA, HMB45 were positive*	*Nothing*	*one case*	*26 months, (4–167 months)*	*All survived*
Ando et al. (18)	*three cases*	*46.7 years old, (44-49 years old)*	*one case of endometrial carcinoma and two cases of hysteromyoma*	*α-SMA, HMB45, D2-40 was positive*	*Nothing*	*No*	*11.3 months (4–18 months)*	*All survived*
Remo et al. (22)	*one case*	*44 years old*	*Cervical mucinous adenocarcinoma*	*α-SMA,HMB45 were positive*	*Nothing*	*Yes*	*10 months*	*survived*
Suzuki et al. (19)	*one case*	*47 years old*	*Endometrial carcinoma is complicated by systemic lupus erythematosus.*	*α-SMA, caldesmon, Melan A, HMB45 and ER were positive*	*Nothing*	*No*	*Not specified*	*survived*
Rabban et al. (13)	*26 cases*	*56 years old (31-79 years old)*	*17 cases of uterine cancer, five cases of ovarian cancer, three cases of cervical cancer, one case of bladder cancer*	*α-SMA(23/23), HMB45(24/25), ER and D2-40 were positive*	*2 cases*	*No*	*18 months (3–156 months)*	*All survived; one case had a local recurrence of uterine body cancer.*

malignant biological behaviors such as migration and invasion. At the same time, most of the common and incidental parts of the two are similar, but the treatment methods of the two are different. Therefore, can the pathogenesis of endometriosis be used to explain the occurrence of the disease? As far as this case is concerned, this idea is difficult to realize and is not mature. We just put forward a new research idea, and more and broader clinical data are still needed for summary and analysis.

CONCLUSION

We report a case of sporadic pelvic lymph node LAM during staged surgery for primary fallopian tube cancer. At present, the source and pathogenesis of LAM cells are not clear. We propose that the disease is similar to endometriosis in hormone dependence and biological behavior. At the same time, the relationship between sporadic lymph node LAM and pulmonary LAM remains uncertain. It may be only a matter of time for sporadic lymph node LAM to develop into intrapulmonary LAM. It is also possible that the two are not related. At this stage, the long-term follow-up of internal medicine and gynecologists is essential for the correct diagnosis of LAM and cancer-related diseases.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The study was approved by the Institutional Review Board of the LongHua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine. Written informed consent was obtained from the patient for the publication of this case report

and for the publication of any potentially identifiable data or images.

AUTHOR CONTRIBUTIONS

SX and YC have made great contributions to the collation and analysis of case data, conception and design, and writing manuscripts. QT and LX participated in the clinical diagnosis, treatment, and follow-up of patients. LZ and ZW participated in the literature review and manuscript drafting. EY is the main surgery, which has made great contributions to the formulation of a patient's clinical diagnosis and treatment plan and the revision of manuscripts. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. McCarthy C, Gupta N, Johnson SR Yu JJ, McCormack FX. Lymphangioleiomyomatosis: pathogenesis, clinical features, diagnosis, and management. *Lancet Respir Med.* (2021) 9:1313–27. doi: 10.1016/S2213-2600(21)00228-9
2. McCormack FX, Gupta N, Finlay GR, Young LR, Taveira-DaSilva AM, Glasgow CG, et al. Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guidelines: lymphangioleiomyomatosis diagnosis and management. *Am J Respir Crit Care Med.* (2016) 194:748–61. doi: 10.1164/rccm.201607-1384ST
3. Harknett EC, Chang WY, Byrnes S, Johnson J, Lazor R, Cohen MM, et al. Use variability in national and regional data to estimate the prevalence of lymphangioleiomyomatosis. *QJM.* (2011) 104:971–9. doi: 10.1093/qjmed/hcr116
4. Hayashi T, Kumasaka T, Mitani K, Terao Y, Watanabe M, Oide T, et al. Prevalence of uterine and adnexal involvement in pulmonary lymphangioleiomyomatosis: a clinicopathologic study of 10 patients. *Am J Surg Pathol.* (2011) 35:1776–85. doi: 10.1097/PAS.0b013e318235edbd
5. Ryu JH, Moss J, Beck GJ, Lee JC, Brown KK, Chapman JT, et al. The NHLBI lymphangioleiomyomatosis registry: characteristics of 230 patients at enrollment. *Am J Respir Crit Care Med.* (2006) 173:105–11. doi: 10.1164/rccm.200409-1298OC
6. Taveira-DaSilva AM, Jones AM, Julien-Williams P, Yao J, Stylianou M, Moss J. Severity and outcome of cystic lung disease in women with tuberous sclerosis complex. *Eur Respir J.* (2015) 45:171–80. doi: 10.1183/09031936.00088314
7. Yeoh ZW, Navaratnam V, Bhatt R, McCafferty I, Hubbard RB, Johnson SR. Natural history of angiomyolipoma in lymphangioleiomyomatosis: implications for screening and surveillance. *Orphanet J Rare Dis.* (2014) 9:151. doi: 10.1186/s13023-014-0151-3
8. Zhe X, Schuger L. Combined smooth muscle and melanocytic differentiation in lymphangioleiomyomatosis. *J Histochem Cytochem.* (2004) 52:1537–42. doi: 10.1369/jhc.4A6438.2004
9. Krymskaya VP. Smooth muscle-like cells in pulmonary lymphangioleiomyomatosis. *Proc Am Thorac Soc.* (2008) 5:119–26. doi: 10.1513/pats.200705-061VS
10. Bittmann I, Rolf B, Amann G, Löhrs U. Recurrence of lymphangioleiomyomatosis after single lung transplantation: new insights into pathogenesis. *Hum Pathol.* (2003) 34:95–8. doi: 10.1053/hupa.2003.50
11. Szpurek D, Szubert S, Zielinski P, Frankowski A, Sajdak S, Moszynski R. Malignant presentation of uterine lymphangioleiomyomatosis. *Taiwan J Obstet Gynecol.* (2015) 54:603–7. doi: 10.1016/j.tjog.2015.08.015
12. Krymskaya VP, McCormack FX. Lymphangioleiomyomatosis: A Monogenic Model of Malignancy. *Annu Rev Med.* (2017) 68:69–83. doi: 10.1146/annurev-med-050715-104245
13. Rabban JT, Firetag B, Sangoi AR, Post MD, Zaloudek CJ. Incidental pelvic and para-aortic lymph node lymphangioleiomyomatosis detected during surgical staging of pelvic cancer in women without symptomatic pulmonary lymphangioleiomyomatosis or tuberous sclerosis complex. *Am J Surg Pathol.* (2015) 39:1015–25. doi: 10.1097/PAS.0000000000000416
14. Schoolmeester JK, Park KJ. Incidental nodal lymphangioleiomyomatosis is not a harbinger of pulmonary lymphangioleiomyomatosis: a study of 19 cases with evaluation of diagnostic immunohistochemistry. *Am J Surg Pathol.* (2015) 39:1404–10. doi: 10.1097/PAS.0000000000000470
15. Iwasa Y, Tachibana M, Ito H, Iwami S, Yagi H, Yamada S, et al. Extrapulmonary lymphangioleiomyomatosis in pelvic and paraaortic lymph nodes associated with uterine cancer: a report of 3 cases. *Int J Gynecol Pathol.* (2011) 30:470–5. doi: 10.1097/PGP.0b013e318212e1e6
16. Nagasaka T, Murakami Y, Sasaki E, Hosoda W, Nakanishi T, Yatabe Y. Minute perivascular epithelioid cell (PEC) nests in the abdominal lymph nodes–a putative precursor of PEComa. *Pathol Int.* (2015) 65:193–6. doi: 10.1111/pin.12262
17. Matsui K, Tatsuguchi A, Valencia J, Yu ZX, Bechtle J, Beasley MB, et al. Extrapulmonary lymphangioleiomyomatosis (LAM): clinicopathologic features in 22 cases. *Hum Pathol.* (2000) 31:1242–8. doi: 10.1053/hupa.2000.18500
18. Ando H, Ogawa M, Watanabe Y, Tsurunaga K, Nakamura C, Tamura H, et al. Lymphangioleiomyoma of the uterus and pelvic lymph nodes: a report of 3 cases, including the potentially earliest manifestation of extrapulmonary lymphangioleiomyomatosis. *int J Gynecol Pathol.* (2020) 39:227–32. doi: 10.1097/PGP.0000000000000589
19. Suzuki K, Nagasaka K, Oda K, Abe H, Maeda D, Matsumoto Y, et al. A case of lymphangioleiomyomatosis associated with endometrial cancer and severe systemic lupus erythematosus. *BMC Cancer.* (2016)16:390. doi: 10.1186/s12885-016-2413-z
20. Schiavina M, Di Scioscio V, Contini P, Cavazza A, Fabiani A, Barberis M, et al. Pulmonary lymphangioleiomyomatosis in a karyotypically normal man without tuberous sclerosis complex. *Am J Respir Crit Care Med.* (2007) 176:96–8. doi: 10.1164/rccm.200610-1408CR
21. Kuno I, Yoshida H, Shimizu H, Uehara T, Uno M, Ishikawa M, et al. Incidental lymphangioleiomyomatosis in the lymph nodes of gynecologic surgical specimens. *Eur J Obstet Gynecol Reprod Biol.* (2018) 231:93–7. doi: 10.1016/j.ejogrb.2018.10.027
22. Remo A, Zanella C, Parcesepe P, et al. Diagnostic management of occult nodal lymphangioleiomyomatosis detected during pelvic cancer staging. Localized finding or systemic disease? *Sarcoidosis Vasc Diffuse Lung Dis.* (2019) 36:33–8.
23. Gao L, Yue MM, Davis J, Hyjek E, Schuger L. In pulmonary lymphangioleiomyomatosis expression of progesterone receptor is

frequently higher than that of estrogen receptor. *Virchows Arch.* (2014) 464:495–503. doi: 10.1007/s00428-014-1559-9
24. Johnson SR, Tattersfield AE. Decline in lung function in lymphangioleiomyomatosis: relation to menopause and progesterone treatment. *Am J Respir Crit Care Med.* (1999) 160:628–33. doi: 10.1164/ajrccm.160.2.9901027
25. Pectasides D, Pectasides E, Economopoulos T. Fallopian tube carcinoma: a review. *Oncologist.* (2006) 11:902–12. doi: 10.1634/theoncologist.11-8-902
26. Al-Obaidy KI, Idrees MT. endometriosis with cystic degeneration: a rare disease of males. *Int J Surg Pathol.* (2019) 27:311–4. doi: 10.1177/1066896918797438

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Expression of CD44, Transforming Growth Factor-β, and Matrix Metalloproteinases in Women With Pelvic Organ Prolapse

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Background: Defects in the pelvic floor connective tissue may underlie the etiology of pelvic organ prolapse (POP). We hypothesized that the expression of proteins regulating extracellular matrix turnover is altered in the uterosacral ligament of women with POP. We compared the expression of CD44, transforming growth factor (TGF)-β, and matrix metalloproteinases (MMPs) 2/9 in women with and without POP.

Methods and Results: This matched case-control study included 30 postmenopausal women, with POP stage 2 and higher according to the POP quantification system, and 30 postmenopausal women without POP. Immunohistochemical analyses of the uterosacral ligament specimens obtained after hysterectomy were performed to determine CD44, TGF-β, MMP-2, and MMP-9 expression. The expression was quantified using ImageJ software, and the association between prolapse occurrence and risk factors was evaluated using Spearman's correlation analysis. CD44 expressions were significantly lower ($p < 0.05$), whereas MMP-2 and MMP-9 expression was higher ($p < 0.0001$ and $p < 0.05$, respectively), in the POP group than in the control group. The expression of TGF-β was similar in both groups. The occurrence of uterine prolapse was positively correlated with age, postmenopausal age, and MMP-2 and MMP-9 expression ($p < 0.01$) and negatively correlated with CD44 expression ($p < 0.05$).

Conclusion: CD44, MMP-2, and MMP-9 may play critical roles in the pathogenesis of POP and may be candidate biomarkers of POP progression.

Keywords: CD44, extracellular matrix, matrix metalloproteinase, pelvic organ prolapse, transforming growth factor-β

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INTRODUCTION

Pelvic organ prolapse (POP) is a birth-induced joint urinary/gynecological condition that affects one in four women of all ages and more than 50% of parous women over the age of 50 (1). POP is the most prevalent among women aged 60–69 years (2). The incidence of POP is 3%–6% based on symptoms, and can reach 50% based on vaginal examination; among patients with

symptoms, 6%–18% receive surgical treatment. The requirement for medical assistance to treat pelvic floor defects is growing twice as fast as the population (3). Therefore, the prevention of POP has become an important issue in obstetrics and gynecology.

Pelvic organs are supported by the pelvic floor muscle complex, main ligament, uterosacral ligament (USL), and pelvic fascia. The pelvic fascia is a connective tissue structure that covers the walls and floor of the pelvis. It consists mostly of collagen fibers interlaced with elastin, smooth muscle cells, and fibroblasts, is abundant in extracellular matrix (ECM) that envelops the USL-cardinal ligament, and is thought to provide a critical level of support. The USL is one of the major ligaments holding the uterus and, thus, is a very important component of the pelvic support system. The mechanisms underlying pelvic floor laxity are not clearly understood. Studies in humans and animals have suggested that USL repair defects are due to changes in the structure and organization of fibrous connective tissue (4), including the amount and composition of the ECM, which is a major factor affecting tissue stability (5).

Collagen and elastin are the primary constituents of the ECM that provide strength and flexibility to the USL. A decrease in collagen deposition or changes in the proportion of collagen types can affect tissue stiffness and increase the susceptibility to POP. Type I and type III collagens are responsible for the stiffness and elasticity of connective tissue, respectively (6). Collagen is degraded by enzymes of the matrix metalloproteinase (MMP) family, which have distinct activities and functions. Among the MMPs, MMP-2 and MMP-9 break down degenerated collagen and elastin peptides into smaller fragments and are important factors in ECM turnover (7).

Transforming growth factor (TGF)-β is a fibrogenic cytokine that plays a key role in ECM remodeling and regulation of tissue integrity. TGF-β activity can alter the balance between ECM synthesis and degradation and is implicated in the pathophysiology of many fibrotic disorders, including pulmonary fibrosis (8) and cardiac fibrosis associated with heart failure (9). Furthermore, some studies show that TGF-β expression is altered in fibroblasts and pubic fascia of women with POP (10, 11). However, some reports show that TGF-β is not associated with the prognosis for patients with POP. Thus, there is no consensus regarding the role of TGF-β in the pathogenesis of POP, and further investigation is required.

The transmembrane glycoprotein CD44 is a major cell surface receptor for hyaluronic acid and can also interact with other ECM components, such as collagen and laminin. CD44 is implicated in the regulation of numerous attachment-dependent processes, such as cell proliferation, migration, and differentiation (12). Furthermore, extensive evidence indicates that CD44 plays a role in fibroblast invasion and progressive fibrosis of the lung and heart, not only through the establishment of specific transmembrane complexes but also through its participation in key signal transduction cascades (13–16). These data suggest that CD44 may be incorporated into the biochemical pathways responsible for the pathogenic alterations in the ECM that may promote POP. However, the role of CD44 in POP has not been investigated and, to the best of our knowledge, there have been no studies on CD44 expression in the USL of women with POP.

The main objective of this study was to compare the expression levels of CD44, TGF-β, MMP-2, and MMP-9 in the USL of patients with and without POP. We hypothesized that CD44 would be lower in the tissues of prolapse patients compared with those of the control group. We believe that this is the first report to illustrate the difference in CD44 expression between POP and non-POP women, aa well as the correlation between these indicators and uterine prolapse.

MATERIALS AND METHODS

Clinical information, including follow-up data, was extracted from the Department of Gynecology database between 2020 and 2021. Ethical approval was obtained from the Clinical Research Ethics Committee of the First Affiliated Hospital of Zhejiang University School of Medicine, China (approval number: IIT20210069B-R1). All procedures were performed in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The case group ($n = 30$) included postmenopausal women who had prolapse of POP stage 2 or higher (according to the POP quantification system) and underwent planned vaginal hysterectomy because of POP-related symptoms. The control group ($n = 30$) consisted of women without prolapse who had undergone hysterectomy for other benign diseases. The patients had no oxidative stress-related disorders, including connective tissue disease or coronary heart disease. Patients who had taken estrogen in the past 3 months were excluded from the study. Informed consent was obtained from all individual participants included in the study.

Tissue Collection and Immunohistochemistry

USL specimens were obtained from tissues extracted by hysterectomy. Samples (approximately 5 mm^3 in size) were taken from the dorsal part of the cervix, 1 cm from the beginning of the cervix (at the left side), and verified by histological analysis.

Tissue samples were fixed in 10% neutral buffered formalin, embedded in paraffin, and treated with citric acid buffer (pH 6.0) in a microwave for antigen retrieval. Sections were then incubated in 3% hydrogen peroxide solution at room temperature in the dark for 25 min to inhibit endogenous peroxidases, then blocked in 3% bovine serum albumin at room temperature for 30 min. Reactions with primary antibodies against CD44 (dilution 1:100; GB13065), MMP-2 (dilution 1:500; GB11130), MMP-9 (dilution 1:500; GB11132-2), and TGF-β (dilution 1:100; GB13028) (all from Servicebio, Wuhan, China) were performed overnight at 4°C. After incubation with horseradish peroxidase-labeled secondary antibodies (Servicebio) at room temperature for 50 min, immune reactivity was detected with diaminobenzidine (K5007, DAKO, Wuhan, China); color development was

observed under a microscope. Nuclei were counterstained with Harris hematoxylin. The percentages of positively stained areas were quantified using ImageJ software (version 1.8.0, National Institutes of Health, Bethesda, MD, USA).

Statistical Analyses

Data of at least three independent experiments were expressed as mean ± standard deviation. Patient groups were compared using two-sample *t*-tests, Mann–Whitney test, and Fisher's exact test, separately for means and proportions. Spearman's test was used for the correlation analysis of non-normally distributed continuous variables. Statistical analyses were performed using SPSS (version 23.0; IBM, Armonk, NY, USA) and Prism Version 8.01 (GraphPad Software, La Jolla, CA, USA). Statistical significance was set at $p < 0.05$.

RESULTS

Clinical Characteristics of the Study Population

In total, 60 postmenopausal women who had undergone hysterectomy were analyzed: 30 with symptomatic POP (cases) and 30 without POP (controls); their clinical parameters are shown in **Table 1**. Women with POP were significantly older ($p < 0.001$), had a longer postmenopausal period ($p < 0.0001$), and showed a higher incidence of hypertension ($p = 0.038$) than women without POP. Women in the POP group had a vaginal hysterectomy as the standard surgical treatment for symptomatic POP. In the control group, hysterectomy was performed for uterine leiomyoma ($n = 20$), postmenopausal bleeding ($n = 2$), uterine adenomyosis ($n = 7$), and cervical intraepithelial neoplasia ($n = 3$).

Differential Expression of CD44, TGF-β, MMP-2, and MMP-9 in Women with and Without POP

Figure 1 shows representative images of USL sections from the POP and control groups after staining with antibodies against CD44, TGF-β, MMP-2, and MMP-9. Quantitative analyses revealed a significant decrease in CD44 expression and an increase in MMP-2 and MMP-9 expression in the POP group compared with those in the control group (**Figure. 2**). The percentages of USL-positive areas stained with anti-CD44 antibodies were 11.8% in patients with and 13.5% in those without POP ($p = 0.0263$). The CD44 expression levels in younger and older POP patients did not differ significantly from those in younger and older control subjects (11.6% vs. 11.9% and 14.5% vs. 13.1% stained areas in younger and older patients, respectively). The expression levels of MMP-2 and MMP-9 were similar in the POP group (13.2% and 13.7% stained areas, respectively) but significantly higher than those in the control group (9.92% and 11.4%; $p < 0.0001$ and $p = 0.0155$, respectively). However, there was no significant difference in the expression of TGF-β between the POP and control groups (9.34% vs. 10.2%; $p = 0.2213$).

TABLE 1 | Clinical characteristics of the study population.

Variable	Case ($n = 30$)	Control ($n = 30$)	*p*-value
Age, years (mean ± SD)	63.9 ± 6.30	55.0 ± 5.60	<0.0001*
Age at menopause, years (mean ± SD)	50.4 ± 2.97	50.0 ± 2.66	0.5536
Years from menopause (mean ± SD)	13.5 ± 7.73	5.03 ± 4.85	<0.0001*
BMI (mean ± SD)	24.1 ± 5.33	24.6 ± 2.98	0.6517
Parity (mean ± SD)	2.07 ± 0.98	1.90 ± 0.66	0.6796
Hypertension, *n* (%)	18 (60)	10 (33.3)	0.038*
Diabetes, *n* (%)	10 (33.3)	3 (10)	0.089

SD, standard deviation; BMI, body mass index.
**Statistically significant.*

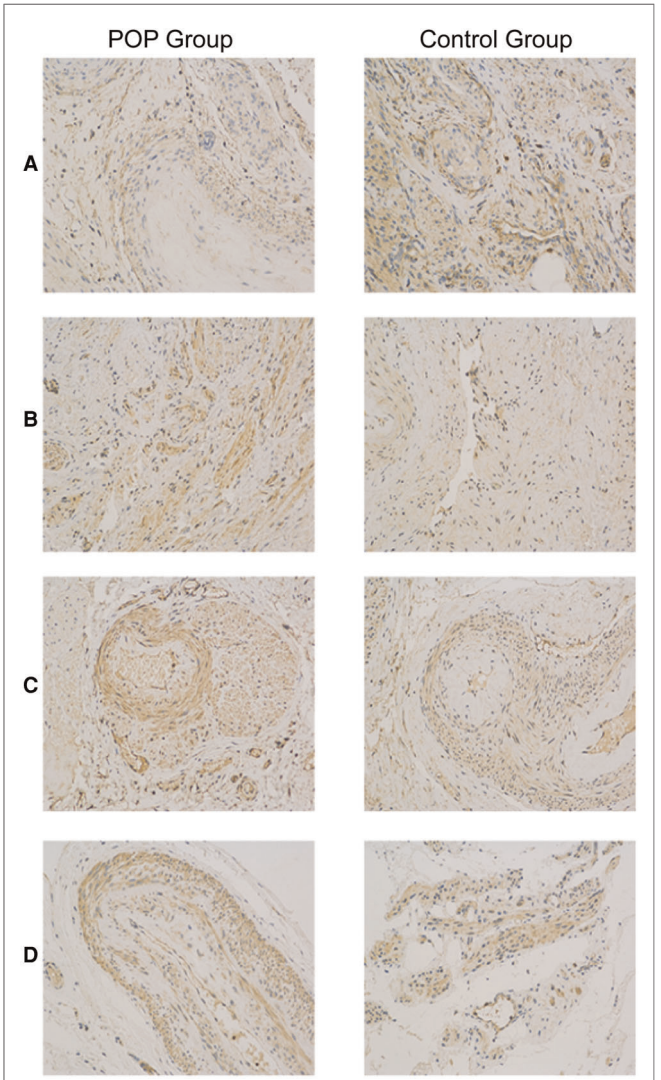

FIGURE 1 | Immunohistochemistry analysis of uterosacral ligaments from women with and without pelvic organ prolapse. Sections of uterosacral ligaments obtained from women who had undergone hysterectomy were stained with antibodies against CD44 (**A**), transforming growth factor-β (**B**), matrix metalloproteinase (MMP)-2 (**C**), and MMP-9 (**D**).

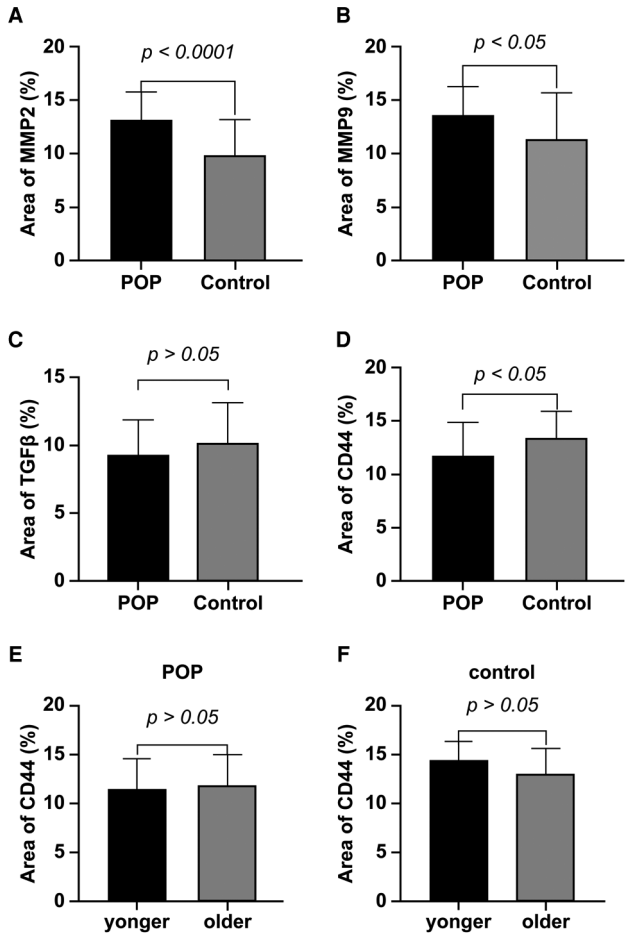

FIGURE 2 | Quantification of matrix metalloproteinase (MMP)-2 (**A**), MMP-9 (**B**), transforming growth factor (TGF)-β (**C**), and CD44 (**D**) expression in uterosacral ligaments. Sections of uterosacral ligaments were stained with antibodies against CD44, TGF-β, MMP-2, and MMP-9, and counterstained with Harris hematoxylin. The percentages of positively stained areas were quantified using ImageJ software and are expressed as means ± standard deviations. POP, pelvic organ prolapse.

TABLE 2 | Correlations between pelvic organ prolapse and risk factors.

Variables	Pelvic organ prolapse	
	Spearman's correlation	*p*-value
Age	0.582	<0.01*
Age at menopause	0.083	0.531
Years from menopause	0.618	<0.01*
BMI	0.074	0.575
Parity	0.015	0.911
CD44	−0.308	0.017*
MMP-2	0.467	<0.01*
MMP-9	0.346	<0.01*
TGF-β	0.132	0.317

BMI, body mass index.
**Statistically significant.*

Risk Factors of Uterine Prolapse

Spearman's correlation analyses were performed to determine the associations of various risk factors with POP. The results indicated that the occurrence of uterine prolapse was positively correlated with age, postmenopausal age, and MMP-2 and MMP-9 expression ($p < 0.01$), and negatively correlated with CD44 expression ($p < 0.05$) (**Table 2**).

DISCUSSION

In this study, we showed that postmenopausal women with symptomatic POP, and those without POP, differed in the expression of factors involved in the synthesis and turnover of the ECM. Specifically, the levels of CD44 were significantly lower, and those of MMP-2 and MMP-9 were higher in the USLs of the POP group than in the USLs of the control group. Furthermore, CD44 levels were negatively correlated and MMP-2/9 levels positively correlated with prolapse. However, there was no difference in the expression of TGF-β between women with and without POP. These results support our hypothesis that CD44 could be involved in the pathogenesis of POP and are consistent with roles for CD44, MMP-2, and MMP-9 in the mechanisms underlying the balance between the production and degradation of the ECM.

POP is commonly considered as a condition caused by the weakness of pelvic floor muscles and fascia due to childbirth, age, and abnormalities in connective tissue. The ECM is a key component of connective tissue that provides a framework for pelvic support; therefore, it may play a critical role in the occurrence of POP (17). The ECM is dynamically reshaped through quantitative and qualitative changes in cellular and non-cellular components, including enzymes such as collagenase and MMPs that regulate ECM turnover (18). MMPs are closely involved in ECM remodeling in normal and pathological conditions as they can cleave most ECM proteins (19). One of the major functions of MMP-2 is to degrade type IV collagen, elastin, and fibronectin. It is regulated by tissue inhibitor of MMP-2 (TIMP-2), which irreversibly inactivates the enzyme, preventing ECM degradation. MMP-9 is also involved in ECM protein degradation and is implicated in the development of several diseases (20). Previous studies revealed higher expression of MMPs, including MMP-2 and MMP-9, and lower expression of TIMP-2, in USL and vaginal wall biopsies from patients with POP (21, 22). These data, together with our results, suggest that the increased expression of MMP-2 and MMP-9 can accelerate ECM breakdown and promote POP.

TGF-β is considered a critical fibrogenic cytokine that plays a role in myofibroblast differentiation in different tissues (23). The TGF-β/Smad signaling pathway regulates the activity of MMPs and promotes stress-related urinary incontinence after natural birth in animal experiments, whereas TGF-β is downregulated after excessive mechanical strain or oxidative stress (17, 20). However, the role of TGF-β in POP is controversial. For example, a study reports that TGF-β1 expression in patients with POP is significantly reduced (22), whereas another study

did not detected any difference in TGF-β1 levels in the USL of women with and without POP (24). In our study, we also did not observe a significant difference in TGF-β expression between the POP and control groups. However, the TGF-β1 pathway is known as a signaling mechanism critical for the cellular response to mechanical stress (17) and, as such, may be related to the pathophysiology of uterine prolapse in postmenopausal women.

To the best of our knowledge, this is the first report on the expression of CD44 in the USL of women with POP. CD44, a cell surface glycoprotein, participates in cell proliferation, adhesion, and migration, as well as in hematopoiesis and lymphocyte activation (25), through binding to its ligands including hyaluronic acid, MMP-9, vascular endothelial growth factor, epidermal growth factor, fibronectin, type I collagen, and osteopontin (11, 26). It has also been shown that fibril-associated collagen XIV can directly interact with CD44 (27). However, the role of CD44 in ECM deposition and fibrogenesis is unclear. On the one hand, some reports indicate that CD44 may promote the synthesis of ECM constituents. For example, it has been reported that CD44-deficient mice show reduced fibroblast infiltration and collagen deposition but increased proliferative activity of fibroblasts (28), and that they also have decreased collagen breakdown and fibrous collagen deposition (29). However, CD44 knockout mice with acute lung injury do not show significant changes in the accumulation of lung interstitial collagen (14). An interesting novel role of CD44 was observed in an *in vitro* study showing that CD44 may be involved in the coordination of cell motility and proliferative responses to ECM stiffening (30). These data suggest that the effects of CD44 on ECM-related processes may depend on the specific environment. Our results, that CD44 expression was significantly associated with POP, may indicate the involvement of CD44 in the pathophysiology of prolapse.

The mechanism of uterine prolapse is complex and not well-understood. Our results implicate CD44, along with MMP-2 and MMP-9, in the development of POP. This is consistent with a previous report on the synergy between CD44, MMP-2, MMP-9, and TGF-β in the physiological mechanism of tissue remodeling (26). Our results can further improve our understanding of the molecular mechanisms underlying POP pathology and contribute to the establishment of novel therapeutic targets in POP.

Our study had some limitations. As it was a case-control investigation, it was not possible to determine the cause-and-effect relationship between POP and protein expression, and we can only refer to the correlation between the occurrence of prolapse and protein expression detected by immunohistochemistry. Furthermore, additional studies involving young patients are needed to establish the role of CD44 in the etiology of POP. Nevertheless, our results suggest an interesting link between CD44 expression and POP in postmenopausal women that has not been reported previously.

In summary, this study provides evidence that CD44 may be a risk factor for uterine prolapse and a novel candidate biomarker of POP. As the prevalence of POP is rapidly increasing with the increase in the aging population, the identification of new biomarkers offers a foundation for the development of improved therapeutic interventions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Clinical Research Ethics Committee of the First Affiliated Hospital of Zhejiang University School of Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by HZ, WWY, and YPH. The first draft of the manuscript was written by WWY and all authors commented on previous versions of the manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Dietz HP. Pelvic floor trauma in childbirth. *Aust N Z J Obstet Gynaecol*. (2013) 53(3):220–30. doi: 10.1111/ajo.12059
2. Barber MD, Maher C. Epidemiology and outcome assessment of pelvic organ prolapse. *Int Urogynecol J*. (2013) 24(11):1783–90. doi: 10.1007/s00192-013-2169-9
3. Wu JM, Vaughan CP, Goode PS, Redden DT, Burgio KL, Richter HE, et al. Prevalence and trends of symptomatic pelvic floor disorders in U.S. Women. *Obstet Gynecol*. (2014) 123(1):141–8. doi: 10.1097/AOG.0000000000000057
4. Kerkhof MH, Hendriks L, Brolmann HA. Changes in connective tissue in patients with pelvic organ prolapse–a review of the current literature. *Int Urogynecol J Pelvic Floor Dysfunct*. (2009) 20(4):461–74. doi: 10.1007/s00192-008-0737-1
5. Gong R, Xia Z. Collagen changes in pelvic support tissues in women with pelvic organ prolapse. *Eur J Obstet Gynecol Reprod Biol*. (2019) 234:185–9. doi: 10.1016/j.ejogrb.2019.01.012
6. Leegant A, Zuckerwise LC, Downing K, Brouwer-Visser J, Zhu C, Cossio MJ, et al. Transforming growth factor Beta1 and extracellular matrix protease expression in the uterosacral ligaments of patients with and without pelvic

organ prolapse. *Female Pelvic Med Reconstr Surg*. (2015) 21(1):53–8. doi: 10.1097/SPV.0000000000000130
7. Nagase H, Visse R, Murphy G. Structure and function of matrix metalloproteinases and timps. *Cardiovasc Res*. (2006) 69(3):562–73. doi: 10.1016/j.cardiores.2005.12.002
8. Li FZ, Cai PC, Song LJ, Zhou LL, Zhang Q, Rao SS, et al. Crosstalk between calpain activation and Tgf-Beta1 augments collagen-I synthesis in pulmonary fibrosis. *Biochim Biophys Acta*. (2015) 1852(9):1796–804. doi: 10.1016/j.bbadis.2015.06.008
9. Huang XR, Chung AC, Yang F, Yue W, Deng C, Lau CP, et al. Smad3 mediates cardiac inflammation and fibrosis in angiotensin II-induced hypertensive cardiac remodeling. *Hypertension*. (2010) 55(5):1165–71. doi: 10.1161/HYPERTENSIONAHA.109.147611
10. Li BS, Hong L, Min J, Wu DB, Hu M, Guo WJ. The expression of glutathione peroxidase-1 and the anabolism of collagen regulation pathway transforming growth factor-beta1-connective tissue growth factor in women with uterine prolapse and the clinic significance. *Clin Exp Obstet Gynecol*. (2013) 40 (4):586–90.
11. Midgley AC, Rogers M, Hallett MB, Clayton A, Bowen T, Phillips AO, et al. Transforming growth factor-beta1 (Tgf-beta1)-stimulated fibroblast to myofibroblast differentiation is mediated by hyaluronan (Ha)-facilitated epidermal growth factor receptor (Egfr) and Cd44 co-localization in lipid rafts. *J Biol Chem*. (2013) 288(21):14824–38. doi: 10.1074/jbc.M113.451336
12. Suleiman M, Abdulrahman N, Yalcin H, Mraiche F. The role of Cd44, hyaluronan and Nhe1 in cardiac remodeling. *Life Sci*. (2018) 209:197–201. doi: 10.1016/j.lfs.2018.08.009
13. Ponta H, Sherman L, Herrlich PA. Cd44: from adhesion molecules to signalling regulators. *Nat Rev Mol Cell Biol*. (2003) 4(1):33–45. doi: 10.1038/nrm1004
14. Chang SH, Yeh YH, Lee JL, Hsu YJ, Kuo CT, Chen WJ. Transforming growth factor-Beta-mediated Cd44/Stat3 signaling contributes to the development of atrial fibrosis and fibrillation. *Basic Res Cardiol*. (2017) 112(5):58. doi: 10.1007/s00395-017-0647-9
15. Li Y, Jiang D, Liang J, Meltzer EB, Gray A, Miura R, et al. Severe lung fibrosis requires an invasive fibroblast phenotype regulated by hyaluronan and Cd44. *J Exp Med*. (2011) 208(7):1459–71. doi: 10.1084/jem.20102510
16. Muller J, Gorressen S, Grandoch M, Feldmann K, Kretschmer I, Lehr S, et al. Interleukin-6-dependent phenotypic modulation of cardiac fibroblasts after acute myocardial infarction. *Basic Res Cardiol*. (2014) 109(6):440. doi: 10.1007/s00395-014-0440-y
17. Zhang Q, Liu C, Hong S, Min J, Yang Q, Hu M, et al. Excess mechanical stress and hydrogen peroxide remodel extracellular matrix of cultured human uterosacral ligament fibroblasts by disturbing the balance of mmps/timps via the regulation of Tgfbeta1 signaling pathway. *Mol Med Rep*. (2017) 15(1):423–30. doi: 10.3892/mmr.2016.5994
18. Manou D, Caon I, Bouris P, Triantaphyllidou IE, Giaroni C, Passi A, et al. The Complex interplay between extracellular matrix and cells in tissues. *Methods Mol Biol*. (2019) 1952:1–20. doi: 10.1007/978-1-4939-9133-4_1
19. Theocharis AD, Skandalis SS, Gialeli C, Karamanos NK. Extracellular matrix structure. *Adv Drug Deliv Rev*. (2016) 97:4–27. doi: 10.1016/j.addr.2015.11.001
20. Malemud CJ. Matrix metalloproteinases and synovial joint pathology. *Prog Mol Biol Transl Sci*. (2017) 148:305–25. doi: 10.1016/bs.pmbts.2017.03.003
21. Dviri M, Leron E, Dreiher J, Mazor M, Shaco-Levy R. Increased matrix metalloproteinases-1,-9 in the uterosacral ligaments and vaginal tissue from women with pelvic organ prolapse. *Eur J Obstet Gynecol Reprod Biol*. (2011) 156(1):113–7. doi: 10.1016/j.ejogrb.2010.12.043
22. Liu C, Wang Y, Li BS, Yang Q, Tang JM, Min J, et al. Role of transforming growth factor beta1 in the pathogenesis of pelvic organ prolapse: a potential therapeutic target. *Int J Mol Med*. (2017) 40(2):347–56. doi: 10.3892/ijmm.2017.3042
23. Sampson N, Berger P, Zenzmaier C. Redox signaling as a therapeutic target to inhibit myofibroblast activation in degenerative fibrotic disease. *Biomed Res Int*. (2014) 2014:131737. doi: 10.1155/2014/131737
24. Carlin GL, Bodner K, Kimberger O, Haslinger P, Schneeberger C, Horvat R, et al. The role of transforming growth factor-ss (Tgf-Ss1) in postmenopausal women with pelvic organ prolapse: an immunohistochemical study. *Eur J Obstet Gynecol Reprod Biol X*. (2020) 7:100111. doi: 10.1016/j.eurox.2020.100111
25. Jordan AR, Racine RR, Hennig MJ, Lokeshwar VB. The role of Cd44 in disease pathophysiology and targeted treatment. *Front Immunol*. (2015) 6:182. doi: 10.3389/fimmu.2015.00182
26. Yu Q, Stamenkovic I. Cell surface-localized matrix metalloproteinase-9 proteolytically activates tgf-beta and promotes tumor invasion and angiogenesis. *Genes Dev*. (2000) 14(2):163–76. doi: 10.1101/gad.14.2.163
27. Ehnis T, Dieterich W, Bauer M, Lampe B, Schuppan D. A chondroitin/dermatan sulfate form of Cd44 is a receptor for collagen Xiv (Undulin). *Exp Cell Res*. (1996) 229(2):388–97. doi: 10.1006/excr.1996.0384
28. Huebener P, Abou-Khamis T, Zymek P, Bujak M, Ying X, Chatila K, et al. Cd44 is critically involved in infarct healing by regulating the inflammatory and fibrotic response. *J Immunol*. (2008) 180(4):2625–33. doi: 10.4049/jimmunol.180.4.2625
29. Govindaraju P, Todd L, Shetye S, Monslow J, Pure E. Cd44-dependent inflammation, fibrogenesis, and collagenolysis regulates extracellular matrix remodeling and tensile strength during cutaneous wound healing. *Matrix Biol*. (2019) 75-76:314–30. doi: 10.1016/j.matbio.2018.06.004
30. Razinia Z, Castagnino P, Xu T, Vazquez-Salgado A, Pure E, Assoian RK. Stiffness-dependent motility and proliferation uncoupled by deletion of Cd44. *Sci Rep*. (2017) 7(1):16499. doi: 10.1038/s41598-017-16486-z

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Single-port laparoscopic sacrospinous ligament suspension *via* the natural vaginal cavity (SvNOTES) for pelvic prolapse: The first feasibility study

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Objective: This study aims to investigate the feasibility and short-term efficacy of single-port laparoscopic-assisted transvaginal natural cavity endoscopic sacrospinous ligament suspensions (SvNOTES).

Methods: A total of 30 patients diagnosed with anterior or/and middle pelvic organ prolapse Stages III and IV underwent natural vaginal cavity (SvNOTES), and 30 patients who underwent conventional sacrospinous ligament (SSLF) were used as a control group. The operation time, blood loss, postoperative POP-Q score, length of hospital stay, and complications were compared between the two groups.

Results: The operation time for SvNOTE was (60 ± 13) min, which was longer than (30 ± 15) min for SSLF ($P = 0.04$). However, the bleeding amount in SvNOTE was 29.44 ± 2.56, significantly lower than that in the SSLF group (80 ± 10; $P = 0.02$), and the postoperative hospital stay in the SvNOTE group was (4 ± 2) days, longer than (3 ± 1) days in SSLF ($P = 0.02$). However, there were no intraoperative complications in the SvNOTE group, whereas one ureteral injury occurred in the SSLF group; in addition, the postoperative POP-Q score was significantly better in the SvNOTE group than that in the SSLF group with increasing time ($P < 0.001$).

Conclusion: Compared with SSLF, single-port laparoscopic sacrospinous ligament suspension *via* the natural vaginal cavity is visualized, greatly improving the success rate of sacrospinous ligament fixation, with less blood loss and fewer complications, arguably a safer and minimally invasive surgical approach.

KEYWORDS

pelvic floor dysfunction (PFD), sacrospinal ligament fixation, surgery, single-port laparoscopic, natural vaginal cavity

Introduction

Pelvic floor dysfunction (PFD) is a series of functional disorders caused by the development of defects, weakness, degradation, damage, and dysfunction of the pelvic floor support structure, which leads to pelvic organ displacement and comprises the social activity of patients (1, 2). As the aging started to increase in China, the incidence rate of PFD has increased significantly. As a result, it has become a common disease that seriously affects the quality of life of middle-aged and older women.

In recent decades, novel minimally invasive surgery technologies have been developed. Due to the lower level of postoperative pain, short hospitalization time, rapid recovery, and a good cosmetic effect, natural orifice transluminal endoscopic surgery (NOTES), a novel minimally invasive surgical method, has gained preference, and a large number of reports have been published on this technique (3). In this surgical method, the abdominal cavity is entered through natural orifices, such as the mouth, urethra, and anus, without any abdominal incisions being made (4, 5). Compared with laparoscopic surgery, NOTES has the advantages of being minimally invasive, eliminating the need for any abdominal incisions and reducing postoperative abdominal pain, incision infection, hernia formation, and adhesion (6).

Most NOTES operations can be performed *via* the vagina or oral cavity. Since the vagina can be easily decontaminated and provides direct access, safety, and easy closure, transvaginal NOTES has been widely used for cholecystectomy, nephrectomy, and various gynecological diseases (7–9). In addition, NOTES has been commonly used in several surgical procedures not only by gynecologists (10) but also by general surgeons and has been proven safe and easy to close (11, 12).

The management of pelvic organ prolapse includes sacrocolpopexy, high uterosacral ligament suspension, and sacral spinal ligament fixation (SSLF). Publications have demonstrated that conventional or robotic NOTES sacrocolpopexy and high uterosacral ligament suspension are feasible and safe. However, there have been only a few reports published on the *sacrospinous ligament suspension* treatment of pelvic organ prolapse *via* NOTES.

Therefore, the purpose of this study was to compare the feasibility, safety, efficacy, and cosmetic effect of transvaginal endoscopy and conventional treatment for pelvic organ prolapse.

Methods

General Information

A total of 60 patients with Grade III or above anterior or middle pelvic prolapse admitted to the Department of Obstetrics and Gynecology of the First Affiliated Hospital of Wannan Medical University from January 2020 to 2021 were selected. All patients were postmenopausal women who presented to our obstetrics and gynecology department for symptomatic vaginal vault prolapse or uterine prolapse. Patients who had a diagnosis of gynecologic tumor or malignancy requiring open surgery or laparoscopy, who had an untreated vaginal infection, or who could not be followed up for 2 years at the beginning of the trial were excluded. Patients included in the trial underwent detailed urogynecological and medical history investigations before surgery. We assessed patients' urological, bowel symptoms, and sexual life by means of relevant questionnaires using the Pelvic Floor Impact Questionnaire-Short Form 7 (PFIQ-7) and the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12). The main questions included symptoms related to prolapse, such as sensation of the vaginal bulge, pelvic pressure, difficulties in voiding the bladder or bowel, urinary incontinence, coital frequency, dyspareunia, and possible effect of prolapse and surgery postoperatively on sexual function (13).

Patients were randomly assigned to one of two groups. The first group received fixation of the vaginal vault with the sacrospinous ligament, and the second group received single-port laparoscopic sacrospinous ligament suspension *via* the natural vaginal cavity. A computer-generated randomization list was developed by a statistician. Preoperative randomization was performed by an independent nurse who removed the card from one patient, blinded. The nurse removed a card from an opaque envelope.

Preoperative preparation

After admission, cervical cytology was performed to rule out cervical disease and ultrasound was performed to rule out uterine and bilateral adnexal disease (e.g., uterine fibroids, adnexal masses, etc.). A potassium permanganate sitz bath was given 3 days before surgery. One day before surgery, an oral magnesium sulfate retardant was given to prevent infection induced by leakage of intestinal contents due to intestinal injury during surgery.

Surgical methods

Vaginal sacrospinous ligament fixation

All patients underwent combined spinal and epidural anesthesia in the lithotomy position with the patient's legs kept buckled to prevent abduction. Then, 50 ml of normal saline was injected into the posterior vaginal mucosa and

the rectal space to create a water cushion to separate the pelvic tissue from the right sciatic spine and the right sacral spine ligament. The right sacral spine ligament was exposed. The cervical tissue attached to the sacral ligament was suspended at the midpoint of the right sacral spine ligament using a no. 7 silk suture, and the vaginal mucosa was sutured using a 2/0 absorbable vicryl suture.

Transvaginal natural orifice transluminal endoscopic surgery

The position of the posterior vaginal fornix was determined. Next, 50 ml of saline was injected into the rectovaginal space using the needle in the posterior vaginal fornix to form a water dissection and cushion. An electric knife was used to cut the whole layer out of the rear wall of the vagina, which was about 3 cm long, and a single-hole port (need to put port company's name here) was inserted and secured. CO_2 was insufflated at 10 mmHg to maintain sufficient pneumovagina. An ultrasonic blade was used to separate each layer of the vaginal wall to approach the sacral spine ligament. During the operation, nearby blood vessels and nerves were avoided, and the sacral spine ligament was found to be 2 cm long, according to the sciatic spine. Then, a 1-0 absorbable suture needle was placed under direct visualization through the ipsilateral sacral spine ligament and fixed on the cervical main sacral ligament or vaginal stump (**Figure 1**).

If the patient had vaginal anterior and posterior wall bulging, vaginal anterior and posterior wall repair was performed accordingly. If a preoperative diagnosis of stress urinary incontinence was provided, intraoperative transobturator tension-free vaginal tape was applied. The same experienced surgeon performed all operations.

Statistical methods

SPSS 21.0 software was used for all statistical analyses. Measurement data were expressed as mean ± standard deviation ($\chi \pm S$), and variance analysis was used to compare data between groups. The enumeration data were expressed as percentages, and the χ^2 test was performed on data between groups. A $P < 0.05$ was considered statistically significant.

Results

Basic situation of patients

As shown in **Table 1**, there were no significant differences in age, body mass index, parity, and uterine prolapse between the two groups ($P > 0.05$). The POP-Q at each indicator point (Aa, Ba, C, Ap, and Bp, as shown in **Table 1**) was recorded.

Intraoperative situation

In the SvNOTES group, the blood pressure of one patient decreased to 50/20 mmHg and blood oxygen saturation decreased to 30% after the formation of elevated air pressure during the operation. The procedure was immediately stopped, and conventional surgery was performed instead. In the SSLF group, one patient had a ureteral injury. There were no bladder and rectum injuries or complications such as large blood vessel and nerve injury in either of the two groups. The operation time in the SSLF group was 30 ± 15 min, while that in the SvNOTES group was 60 ± 13 min ($P = 0.04$), with a significant statistical difference between the two groups. Intraoperative blood loss in the SSLF group was 80 ± 10 ml, while that in the SvNOTES group was 20 ± 14 ml ($P = 0.02$), with statistical significance (**Table 2**).

Short-term postoperative complications

The residual urine level was 110 ± 12 ml in the SSLF group and 90 ± 10 ml ($P = 0.01$) in the SvNOTES group.

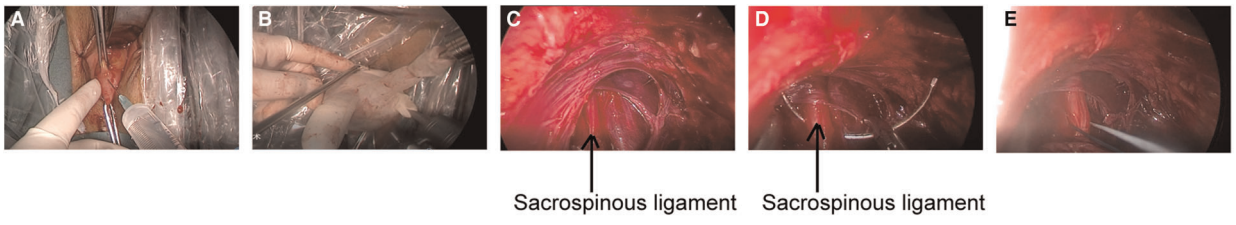

FIGURE 1
(A) Make a single incision after separating the gap. (B) Placement of homemade single-hole port. (C) Find and isolate the sacrospinous ligament. (D,E) Suture of the sacrospinous ligament.

TABLE 1 Characteristics of the study patients ($n = 101$).[a]

Characteristics	SSLF ($n = 30$)	SvNOTES ($n = 30$)	*P*-value
Age (years)	68 ± 5.2	68 ± 4.8	0.08
BMI	25 ± 4.3	29 ± 5.1	0.04
Delivery times	3 ± 1	2.5 ± 1.5	0.52
Preoperative POP-Q scores			
Aa	0.23 ± 1.0	0.31 ± 1.2	0.13
Ba	0.3 ± 1.1	0.4 ± 1.3	0.21
Ap	−0.6 ± 1.2	−0.4 ± 1.5	0.14
Bp	−0.5 ± 2.0	−0.4 ± 1.8	0.19
C	2.0 ± 1.7	2.6 ± 1.8	0.02
TVL	4.9 ± 0.3	6.1 ± 1.9	0.25
POP stage before the operation			
II	15	9	0.22
III	10	15	0.17
IV	5	6	0.30

[a]*Values are given as mean ± SD, number, number (percentage), or median (range), unless indicated otherwise.*

TABLE 2 Perioperative outcomes by the surgical group.[a]

Outcome	SSLF ($n = 30$)	SvNOTES ($n = 30$)	*P*-value
Decrease in oxygen saturation	0	1	–
Conversion to surgery	0	1	–
Blood loss (ml)	80 ± 10	20 ± 14	**0.02**
Operative time (minutes)	30 ± 15	60 ± 13	**0.04**
Postoperative stay (days)	3 ± 1	4 ± 2	**0.02**
Injury	1	0	–
Postoperative fever	1	0	**0.004**
Pain	3	7	**0.003**
Delayed hemorrhage	0	0	–
Infection	0	0	–
Abscessus	0	0	–

[a]*Values are given as mean ± SD or number (percentage) unless indicated otherwise.*
Bold value indicated p value was meaningful.

Patients with a residual urine level of more than 100 ml continued to retain catheterization, and electrical stimulation physiotherapy was performed. One week later, the catheter was removed again. The indwelling catheterization time was 7 ± 2 days in the SSLF group and 4 ± 1 days in the SvNOTES group ($P = 0.003$). There were no significant differences (Table 3) in postoperative normal activity time and postoperative body temperature stability time.

TABLE 3 Postoperative complications.[a]

	SSLF ($n = 30$)	SvNOTES ($n = 30$)	*P*-value
Stress urinary incontinence (SUI)			
Before surgery	15	18	0.45
After surgery	–	–	–
Improved	10	16	**0.02**
Persistent or worsened	2	0	–
Indwelling time of the catheter (days)	7 ± 2	4 ± 1	**0.003**
Residual urine (ml)	110 ± 12	90 ± 10	**0.01**
Relapse of prolapse	4	1	

[a]*Values are given as number (percentage) or number unless indicated otherwise.*
Bold value indicated p value was meaningful.

TABLE 4 Postoperative objective observation indexes.[a]

POP-Q	SSLF ($n = 30$)	SvNOTES ($n = 30$)	*P*-value
6 months			
Aa	−2.6 ± 0.4	−3.0 ± 0.2	0.63
Ba	−2.5 ± 0.3	−2.8 ± 0.3	0.53
Ap	– 2.5 ± 0.2	−2.9 ± 0.3	0.36
Bp	−2.7 ± 0.1	−2.7 ± 0.2	0.28
C	−7.0 ± 0.5	−8.0 ± 0.5	**<0.001**
TVL	7.2 ± 0.7	8.1 ± 0.4	**<0.001**
12 months			
Aa	−2.3 ± 0.3	−2.6 ± 0.5	0.32
Ba	−2.2 ± 0.3	−2.5 ± 0.3	0.23
Ap	−2.2 ± 0.2	−2.4 ± 0.4	0.55
Bp	−2.5 ± 0.2	−2.4 ± 0.1	0.44
C	−6.9 ± 0.3	−7.7 ± 0.2	**<0.001**
TVL	6.9 ± 0.5	7.8 ± 0.1	**<0.001**
24 months			
Aa	−2.2 ± 0.8	−2.3 ± 0.3	0.06
Ba	−2.0 ± 0.6	−2.2 ± 0.3	0.13
Ap	−2.0 ± 0.7	−2.2 ± 0.3	0.71
Bp	−2.1 ± 0.5	−2.2 ± 0.8	0.54
C	−6.7 ± 0.4	−7.5 ± 0.4	**<0.001**
TVL	6.7 ± 0.5	7.4 ± 0.2	**<0.001**

[a]*Values are given as mean ± SD unless indicated otherwise.*
Bold value indicated p value was meaningful.

Postoperative objective observation indexes and subjective symptom scores

After 24 months of follow-up, the Aa, Ba, C, Ba, and Bp were recorded (Table 4). The pelvic dysfunction scale (PFDI-20) was used to evaluate pelvic function. We found that the difference in postoperative PFDI-20 scores between the two groups was statistically significant ($P < 0.05$). The pelvic organ

prolapse disorder scale (POPDI-6), defecation dysfunction scale (CRADI-8), Pelvic Floor Impact Questionnaire-7 (PFIQ-7), and urinary dysfunction scale (UDI-6) were also collected. In addition, the sexual function scale (FSFI) was used to evaluate the quality of sexual life (the higher the score, the higher the quality of sexual energy). In this study, the pelvic function of the SvNOTE group was significantly better than that of the SSLF group (Table 5).

Postoperative complications

The recurrence of pelvic prolapse refers to Degree II or above prolapse after 6 weeks of operation. In the SSLF group, the recurrence rate was 13.3% (4/30) (there were three cases with Stage I and one case with Stage II pelvic organ prolapse). In the SvNOTES group, only one case of recurrence of pelvic organ prolapse was reported. After investigation, both operations were confirmed as recurrence of anterior pelvic prolapse (Table 3). The symptoms of the 10 patients with urinary incontinence in the SSLF group improved significantly, while that of two cases did not improve. V-NOTE combined with urinary incontinence was ultimately improved, with no new cases of urinary incontinence (Table 3).

TABLE 5 Subjective symptom score at the 2-year follow-up.[a]

Outcome	SSLF ($n = 30$)	SvNOTES ($n = 30$)	*P*-value
PFDI-20 score			
Preoperative	16.21 ± 3.92	16.41 ± 4.31	0.31
2-year follow-up	13.83 ± 0.35	11.02 ± 0.31	0.02
P-value	**0.006**	**<0.001**	–
PFIQ-7 score			
Preoperative	193.61 ± 46.09	194.68 ± 45.21	0.59
2-year follow-up	90.6 ± 10.5	70.7 ± 10.2	0.01
P-value	**<0.001**	**<0.001**	–
POPDI-6 score			
Preoperative	35.8 ± 9.8	37.8 ± 10.5	0.56
2-year follow-up	9.9 ± 1.8	6.8 ± 1.7	0.02
P-value	**<0.001**	**<0.001**	–
UDI-6 score			
Preoperative	29.4 ± 2.5	30.9 ± 2.8	0.66
2-year follow-up	9.8 ± 1.5	6.5 ± 1.5	0.01
P-value	**<0.001**	**<0.001**	–
CRADI			
Preoperative	25.51 ± 3.1	25.89 ± 3.4	0.08
2-year follow-up	12.2 ± 2.1	8.1 ± 2.7	0.03
P-value	**<0.001**	**<0.001**	–
FSFI score			
Preoperative	5 ± 2	4 ± 3	0.45
2-year follow-up	20 ± 3	30 ± 2	0.03
P-value	**0.03**	**0.02**	–

[a]*Values are given as mean ± SD unless indicated otherwise.*
Bold value indicated p value was meaningful.

Discussion

In clinical practice, transvaginal surgery was difficult for some obese patients or patients with vaginal stenosis, transvaginal NOTES is particularly suitable for those patients. The first clinical transvaginal NOTES transvaginal endoscopic cholecystectomy was performed by Zorrón et al. (14) at the University Hospital of Teresopolis, Brazil. Thereafter, Bessler et al. (15) performed the same at Columbia University Medical Center, New York, USA, and Marescaux et al. (16) performed the same at University Louis Pasteur, Paris, France, using similar procedures. Currently, the use of NOTES for gynecologic surgery, including transvaginal hydrolaparoscopy, transgastric adnexectomy, and tubal ligation (6, 17), has steadily advanced. However, there have very few reports on pelvic floor disorders, especially the sacrospinous ligament. To our knowledge, this is the first case series in which the sacrospinous ligament was fixed using SvNOTES. The successful completion of the procedure demonstrates the feasibility of a transnatural cavity with single-port laparoscopy to effectively improve the symptoms of pelvic organ prolapse in women.

Compared with conventional transvaginal surgery, the surgical field of SvNOTES can be clearly visualized using an endoscopic camera; any pathology beyond the reach of the operator can be easily managed with the assistance of laparoscopic instruments (18, 19). More importantly, it has the advantage of the absence of abdominal scarring (20).

As we all know, SSLF is a classic surgical procedure used for the treatment of pelvic prolapse (21), but the location of the sacral spine ligament is profound and its anatomy is complex (22, 23). This involves many nerves, internal pudendal arteries, sacral plexus vessels, and ureter, and the rectum is located near the sacral spinous ligament (24). Therefore, blind dissection and suturing may cause vascular nerve ureteral injury (25). In addition, the SSLF procedure is more difficult in patients who are infertile, obese, or have vaginal stenosis; one case in which the suture needle was broken and lost during the operation, resulting in reoperation due to postoperative pain, has been previously reported (26). In our research group, it was found that compared with SSLF, abdominal sacrospinal ligament suspension has the disadvantages of a longer operation time, significant trauma, slower recovery, and higher cost. Therefore, we designed SvNOTE based on operations that are currently performed. In our study, we found that this surgical method leads to a lower recurrence rate and fewer complications. Due to better visualization of vital anatomy during SvNOTES, the incidence

of ureteral injury decreased significantly (no ureteral injuries were reported in this study). In addition, the location of the intraoperative suture needle was constantly monitored, which significantly decreased the probability of suture needle loss.

In addition, the operation space available during SSLS is narrow, and the whole operation is wholly sutured or punctured based on the operator's experience. This may result in differences or errors in the anchoring position, which will lead to an increased postoperative recurrence rate. After SvNOTE surgery was implanted into the single-port laparoscopic PORT through the natural cavity, the sacrospinal ligament was exposed under direct visualization. Therefore, the blood vessels, nerves, and urethra surrounding the sacrospinal ligament were safely dissected. In addition, the intraoperative pneumoperitoneum can push the rectum away from the surgical field, which further helps in avoiding essential organs and blood vessels. In addition, when a small amount of bleeding is found during the operation, we can stop the bleeding in time, resulting in minimal intraoperative bleeding. Finally, since we sutured the exposed sacrospinal ligament to the top of the vagina, we could accurately anchor it in a specific position and strengthen it for the future. Our study demonstrated that the intraoperative bleeding of patients was significantly less in the SvNOTE group than that in the control group. The postoperative recurrence rate decreased significantly, and the postoperative recovery time of patients was not longer than that of the control group. Therefore, our surgical technique is safer and produces a lower recurrence rate than SSLS.

However, after port implantation, air pressure was used to expand the field of vision. The increase in air pressure may lead to the possibility of gas embolism. During our operation, the blood pressure of one of the patients dropped sharply after inflation. After immediate blood gas analysis, gas embolism was considered. After the data were analyzed, it was found that the intraoperative air pressure was slightly higher (13 mmHg). Therefore, the air pressure was controlled at 8–10 mmHg during the rest of the SvNOTE operations (27), and the blood oxygen saturation was closely monitored during the procedure by actively cooperating with anesthetists to ensure the safety of the operation. Since this is a single-hole process, the surgeon should not only be familiar with the pelvic floor structure but should also master the single-hole technology to avoid the chopstick effect. As this was a single-hole operation that required the bilateral sacral spine ligament to be clearly exposed, the operation time was longer than that of the conventional group. In addition, intraoperative attention should not be paid to arbitrary electrocoagulation or cutting, and membrane anatomy should be preserved as much as possible. Otherwise, adjacent organs may be damaged due to an unclear level of vision caused by bleeding.

SvNOTES are especially beneficial for patients considered as relative contraindications in conventional transvaginal surgery due to the restricted downward traction of pelvic organs for surgical manipulation and hemostasis (28). SvNOTES allow for scar lessness and exert a lesser degree of triangulation loss and instrument crowding due to vaginal elasticity. A surgeon who wishes to perform SvNOTES should be confident in PFD. Experience in PFD will certainly lower the learning curve and shorten the operative time.

However, our procedure has several drawbacks similar to those of conventional sacrospinous ligament suspension surgery, such as the vaginal axial bias to the side of suspension and posteriority, which increases the risk of anterior pelvic prolapse. However, our procedure can be performed through a natural channel using a single-hole laparoscope, which makes it minimally invasive or even noninvasive. In addition, we can precisely expose the sacrospinous ligament under direct vision and perform sacrospinous ligament fixation. This makes the anchoring position highly accurate, which greatly reduces the postoperative recurrence rate. Furthermore, intraoperative pneumoperitoneum pressure is used to push open the rectum, and the use of the laparoscope results in important blood vessels and nerves being avoided, which significantly reduces the incidence of surgical complications. In addition, since a mesh was not used during surgery, there is no risk of mesh erosion.

In conclusion, single-port laparoscopic sacrospinous ligament suspension *via* the natural vaginal cavity for pelvic prolapse is an original adding something new to the literature in the field of minimally invasive surgery for pelvic organ prolapse surgery. Our surgical approach improved surgical precision, significantly reduced the recurrence rate, and led to a significant decrease in intraoperative complications. The limitations of our study are the small sample size and the high operator requirements (proficiency in operating single-port laparoscopic surgery and great familiarity with pelvic floor anatomical findings). However, with the comparison group, we can validate the safety and efficacy of this procedure.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Wannan Medical College. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YYL was responsible for writing the article, HFD, JD and YHL were responsible for collecting data, XMG and GN was responsible for designing the procedure an dsurgery. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Wallace SL, Miller LD, Mishra K. Pelvic floor physical therapy in the treatment of pelvic floor dysfunction in women. *Curr Opin Obstet Gynecol.* (2019) 31(6):485–93. doi: 10.1097/GCO.0000000000000584

2. Lawson S, Sacks A. Pelvic floor physical therapy and women's health promotion. *J Midwifery Women's Health.* (2018) 63(4):410–17. doi: 10.1111/jmwh.12736

3. Atallah S, Martin-Perez B, Keller D, Burke J, Hunter L. Natural-orifice transluminal endoscopic surgery. *Br J Surg.* (2015) 102(2):e73–92. doi: 10.1002/bjs.9710

4. Autorino R, Yakoubi R, White WM, Gettman M, De Sio M, Quattrone C, et al. Natural orifice transluminal endoscopic surgery (NOTES): where are we going? A bibliometric assessment. *BJU Int.* (2013) 111(1):11–16. doi: 10.1111/j.1464-410X.2012.11494.x

5. Liu L, Chiu PW, Reddy N, Ho KY, Kitano S, Seo DW, et al. Natural orifice transluminal endoscopic surgery (NOTES) for clinical management of intra-abdominal diseases. *Dig Endosc.* (2013) 25(6):565–77. doi: 10.1111/den.12154

6. Jallad K, Walters MD. Natural orifice transluminal endoscopic surgery (NOTES) in gynecology. *Clin Obstet Gynecol.* (2017) 60(2):324–9. doi: 10.1097/GRF.0000000000000280

7. Peng C, Ling Y, Ma C, Ma X, Fan W, Niu W, et al. Safety outcomes of NOTES cholecystectomy vs. laparoscopic cholecystectomy: a systematic review and meta-analysis. *Surg Laparosc Endosc Percutan Tech.* (2016) 26(5):347–53. doi: 10.1097/SLE.0000000000000284

8. Swain P. Nephrectomy and natural orifice translumenal endoscopy (NOTES): transvaginal, transgastric, transrectal, and transvesical approaches. *J Endourol.* (2008) 22(4):811–18. doi: 10.1089/end.2007.9831

9. Evangelisti G, Barra F, Centurioni MG, D'Alessandro G, Alessandri F, Ferrero S. Vaginal natural orifice transluminal endoscopic surgery (NOTES) for treating benign adnexal diseases: past results and future developments. *J Invest Surg.* (2020) 35(2):409–10. doi: 10.1080/08941939.2020.1843205

10. Li CB, Hua KQ. Transvaginal natural orifice transluminal endoscopic surgery (vNOTES) in gynecologic surgeries: a systematic review. *Asian J Surg.* (2020) 43(1):44–51. doi: 10.1016/j.asjsur.2019.07.014

11. Kähler G. NOTES in visceral surgery: current status. *Chirurg.* (2017) 88(8):664–8. doi: 10.1007/s00104-017-0435-y

12. Sharif S, Afsar A. Learning curve and minimally invasive spine surgery. *World Neurosurg.* (2018) 119:472–8. doi: 10.1016/j.wneu.2018.06.094

13. Heinonen PK, Nieminen K. Combined anterior vaginal wall mesh with sacrospinous ligament fixation or with posterior intravaginal slingplasty for uterovaginal or vaginal vault prolapse. *Eur J Obstet Gynecol Reprod Biol.* (2011) 157(2):230–3. doi: 10.1016/j.ejogrb.2011.03.031

14. Zorrón R, Filgueiras M, Maggioni LC, Pombo L, Lopes Carvalho G, Lacerda Oliveira A. NOTES transvaginal cholecystectomy: report of the first case. *Surg Innov.* (2007) 14(4):279–83. doi: 10.1177/1553350607311090

15. Bessler M, Stevens PD, Milone L, Parikh M, Fowler D. Transvaginal laparoscopically assisted endoscopic cholecystectomy: a hybrid approach to natural orifice surgery. *Gastrointest Endosc.* (2007) 66(6):1243–5. doi: 10.1016/j.gie.2007.08.017

16. Marescaux J, Dallemagne B, Perretta S, Wattiez A, Mutter D, Coumaros D. Surgery without scars: report of transluminal cholecystectomy in a human being. *Arch Surg.* (2007) 142(9):823–6. discussion 826–827. doi: 10.1001/archsurg.142.9.823

17. Einarsson JI, Cohen SL, Puntambekar S. Orifice-assisted small-incision surgery: case series in benign and oncologic gynecology. *J Minim Invasive Gynecol.* (2012) 19(3):365–8. doi: 10.1016/j.jmig.2011.12.017

18. Lee CL, Wu KY, Huang CY, Yen CF. Comparison of LigaSure™ tissue fusion system and a conventional bipolar device in hysterectomy via natural orifice transluminal endoscopic surgery (NOTES): a randomized controlled trial. *Taiwan J Obstet Gynecol.* (2019) 58(1):128–32. doi: 10.1016/j.tjog.2018.11.024

19. Mat E, Kale A, Gundogdu EC, Basol G, Yildiz G, Usta T. Transvaginal natural orifice endoscopic surgery for extremely obese patients with early-stage endometrial cancer. *J Obstet Gynaecol Res.* (2021) 47(1):262–9. doi: 10.1111/jog.14509

20. Basol G, Cora AO, Gundogdu EC, Mat E, Yildiz G, Kuru B, et al. Hysterectomy via transvaginal natural orifice transluminal endoscopic surgery versus single-port laparoscopy: comparison of early outcomes. *J Obstet Gynaecol Res.* (2021) 47(9):3288–96. doi: 10.1111/jog.14874

21. Chou YM, Chuang FC, Kung FT, Yang TH, Wu LY, Huang KH. Sacrospinous ligament fixation with uterine preservation reduces the risk of anatomical recurrence in pelvic organ prolapse. *Low Urin Tract Symptoms.* (2021) 13(2):249–56. doi: 10.1111/luts.12361

22. Doğanay M, Aksakal O. Minimally invasive sacrospinous ligament suspension: perioperative morbidity and review of the literature. *Arch Gynecol Obstet.* (2013) 287(6):1167–72. doi: 10.1007/s00404-012-2687-6

23. Ng SC, Tsui KP, Huang L, Chen GD. Effects of uterine preservation on long-term subjective outcomes of sacrospinous ligament fixation for the treatment of pelvic organ prolapse. *Eur J Obstet Gynecol Reprod Biol.* (2019) 240:167–71. doi: 10.1016/j.ejogrb.2019.07.006

24. Paz-Levy D, Yohay D, Neymeyer J, Hizkiyahu R, Weintraub AY. Native tissue repair for central compartment prolapse: a narrative review. *Int Urogynecol J.* (2017) 28(2):181–9. doi: 10.1007/s00192-016-3032-6

25. Homola P, Hensel G, Košťál M. Sacrospinous hysteropexy—an alternative in primary surgical treatment of apical compartment prolapse. *Ces Gynekol.* (2021) 86(3):200–4. doi: 10.48095/cccg2021200

26. Hao Z, Yang S. Neovaginal prolapse treated with sacrospinous ligament suspension: a case report and review of the literature. *J Pediatr Adolesc Gynecol.* (2017) 30(4):505–7. doi: 10.1016/j.jpag.2016.12.005

27. He G, Liu L, Liu X, Guo H, Chen L, Li R. Comparison of clinical efficacy and safety of transvaginal natural endoscopic surgery and transumbilical single port laparoscopy surgery for endometrial cancer. *Am J Transl Res.* (2022) 14(4):2647–54. PMID: 35559407

28. Gitas G, Hanker L, Rody A, Ackermann J, Alkatout I. Robotic surgery in gynecology: is the future already here? *Minim Invasive Ther Allied Technol.* (2022) 6:1–10. doi: 10.1080/13645706.2021.2010763

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A preliminary clinical report of transvaginal natural orifice transluminal endoscopic Sacrospinous Ligament Fixation in the treatment of moderate and severe pelvic organ prolapse

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Objective: To study the efficacy and safety of transvaginal natural orifice transluminal endoscopic Sacrospinous Ligament Fixation in the treatment of moderate and severe pelvic organ prolapse.
Design: Patients were selected into this study on a voluntary basis to evaluate the short-term efficacy of this surgery by comparing the OP-Q scores before the operation, three months after the operation, and six months after the operation.
Setting and Patients: Evaluate the clinical efficacy and safety by a retrospective analysis of the clinical data of the 18 patients with POP-Q grade III–IV pelvic organ prolapse treated by the Department of Gynecology of Nanjing Medical University Affiliated Changzhou No.2 People's Hospital from April 2020 to November 2020, and their post-operation follow-ups.
Interventions: Patients with postoperative follow-ups found no obvious relapse without intervention measures.
Measurements and Main Results: The transvaginal natural orifice transluminal endoscopic Sacrospinous Ligament Fixation was performed successfully, and the anterior and posterior walls of vagina and/or trans-vaginal hysterectomy were repaired as appropriate. Except the total vaginal length (TVL), the *P* values of numerical analysis for all points before, three months after, and six months after the operation were all <0.05, being statistically significant.
Conclusion: This method is effective in the treatment of moderate and severe pelvic organ prolapse with few complications, but more cases and longer-term follow-up data are needed to determine the long-term effect of this procedure. For the selection of puncture sites, more anatomical data are needed to get more accurate result.

KEYWORDS

pelvic organ prolapse (POP), transvaginal single-port laparoscopy, sacrospinous ligament suspension, V-NOTES, surgical research

Introduction

With the age increases, the incidence of pelvic organ prolapse increases significantly among women, especially for those who have delivered many times. Studies have shown that about 4.1% of pelvic prolapse patients aged 80 and above have clinical symptoms, which affect their quality of life (1–4). Research has indicated that about 11% of women below 80 underwent operation because of pelvic organ prolapse or stress urinary incontinence (5). While China is facing the challenge of an aging society, many other countries in the world, such as Japan and the United States, have already faced or are about to experience the arrival of an aging society (6, 7). At present, there are a variety of treatment methods for pelvic organ prolapse. For patients with clinical symptoms after failure of non-operative treatment, and who are unwilling to accept non-surgical intervention, surgical intervention has become the main option. The principle of treatment is to restore the normal anatomical structure of the pelvic floor. Since the sacrospinous ligament suspension was invented by Sederl in the 1950s, the operation has received constant improvements. Some studies have shown that the five-year failure rate of sacral ligament suspension is as high as 70.3% (8), but this is quite different from the about 37% failure rate reported by most studies (9–12). The author believes that the difference of postoperative recurrence rate may be caused by some factors, such as poor visual field of vaginal surgery, poor visual field of puncture during Sacrospinous Ligament Fixation, and different level of surgeons. Transvaginal natural orifice transluminal endoscopic (V-Notes) surgery has a history of years. The security and feasibility of these two methods have been proved. Therefore, the author believes that under the premise of good surgical skills and meticulous operation, the surgical method may be safe, feasible, and appropriate. V-Notes has gradually replaced some vaginal surgery because of its advantages of being minimally invasive, beautiful, and visualized. To this end, the author team has designed the transvaginal natural orifice transluminal endoscopic Sacrospinous Ligament Fixation. The good clinical results are reported as follows:

Data and methods

General data

18 patients with pelvic organ prolapse were selected from April 2020 to November 2020 in the Nanjing Medical University Affiliated Changzhou No. 2 People's Hospital. All patients were diagnosed according to the definition set forth in the ACOG guidelines, namely pelvic organ prolapse refers to the decline of one or more aspects of the vagina and uterus: the anterior wall of the vagina, the posterior wall of the vagina, the uterus (cervix), or the top of the vagina (vaginal vault or cuff scar after hysterectomy) (13). The average age of the patients was 62.61 ± 10.26 years old, and the average number of parturition was 2.00 ± 0.77. Each patient was scored and recorded by POP-Q after admission (14). Among them, 12 cases were Grade III and 6 cases were Grade IV. (Details are shown in **Table 1**.)

Case selection criteria

(1) Patients rated Grade III or above by POP-Q staging; (2) Patients who require surgical treatment after receiving non-operative treatment (Pessary, pelvic floor muscle training, etc.); (3) Patients who voluntarily accept this procedure and sign the informed consent form for the operation.; (4) Patients with good postoperative compliance and who can be followed up on time.

Case exclusion criteria

(1) Patients with severe medical complications who cannot tolerate surgery and anesthesia; (2) Patients with related surgical contraindications (such as acute reproductive tract infection, vaginal injury, and genital tract deformities such as vaginal stricture); (3) Patients with malignant tumors of pelvic and abdominal organs.

Methods

Preoperative preparation

Explain the risks related to the procedure before operation, sign the informed consent form, prepare patients for the routine gynecological laparoscopy before operation, change them to fluid diet, and carry out vaginal disinfection three days before the procedure to reduce the probability of postoperative infection. Patients with atrophy of vaginal mucosa were treated with estrogen ointment to improve the vaginal environment before the procedure. Prepare vaginal surgical instruments and transvaginal single-hole laparoscopic instruments before operation.

Establishment of surgical approach platform

After the surgical area and vagina were disinfected, towels and indwelling catheterization were disinfected. The No. 1 silk thread was sutured on both sides to fix the bilateral labia minora to the root of the bilateral thighs to expose the surgical field. After the speculum is slowly inserted, the posterior lip of the cervix was clamped with cervical forceps and pulled upward to expose the posterior wall of the vagina. The wall was cut longitudinally in the middle and lower part, and the connective tissue in the vaginal rectal space was

TABLE 1 Basic information of 18 patients.

Number	BMI (kg/m^2)	Age (years)	Admission blood pressure (mmHg)	Reproductive history	Time for symptoms of prolapse
1	25.10	50	166/111	2-0-1-2	5 months
2	24.03	68	111/68	3-0-1-3	10 years
3	22.58	64	128/64	1-0-2-1	4 months
4	22.64	73	144/81	2-0-0-2	6 years
5	23.94	58	142/88	2-0-1-2	5 years
6	23.24	54	144/97	3-0-0-3	6 months
7	19.63	48	112/81	2-0-2-2	3 years
8	22.03	72	154/68	2-0-1-2	1 years
9	23.71	53	131/87	1-0-2-1	4 months
10	24.02	65	108/86	1-0-1-1	5 months
11	22.67	75	132/74	3-0-0-3	6 months
12	22.43	74	145/83	2-0-2-2	1 years
13	23.52	68	133/68	1-0-2-1	2 years
14	27.11	56	138/90	1-0-0-1	2 months
15	21.23	59	138/80	3-0-0-3	5 years
16	26.83	43	125/91	1-0-2-1	8 years
17	23.05	75	149/75	3-0-2-3	5 years
18	24.97	72	147/85	2-0-0-2	10 years

separated step by step, exposing the pelvic floor muscle and the adjacent tissue, so as to create the space for the operation and insert the special port for the single hole of the vagina.

Surgical instruments and materials

Stryker complete digital laparoscopic system, transvaginal single-hole protective cover and special port (Beijing Aerospace Cadi Company), one pair of conventional laparoscopic scissors, one needle holder, one ultrasonic knife, one attractor, one bipolar electrocoagulation forceps, two surgical separation forceps, one 30° conventional laparoscopic lens, one light source system and pneumoperitoneum system, one set of conventional surgical instruments, two Ethibond Excel W6937 non-absorbable sutures, and other absorbable sutures, silk thread, and so on.

Anesthesia and posture

Tracheal intubation general anesthesia was used in this operation. Before anesthesia, itinerant nurses assisted patients with the bladder lithotomy position (keeping head low, foot high ≥30°, legs abduction <90°). The posterior was about one punch beyond the operating table to provide space, and braces were placed on both shoulders to prevent slippage injury.

Surgical procedure

For patients with anterior and posterior vaginal wall prolapse, anterior and posterior vaginal wall repair was feasible, followed by transvaginal single-hole laparoscopic Sacrospinous Ligament Fixation, and vaginal hysterectomy could be performed first for patients requiring hysterectomy. For patients with prolapse of the anterior vaginal wall, the anterior vaginal wall could be cut longitudinally to trim off part of the excess anterior wall tissue, and for patients with stress urinary incontinence, the bladder could be wrapped inside the anterior wall during purse suture after pruning to increase perineal pressure. Method of transvaginal single-hole laparoscopy: After exposing the surgical field, take the middle and lower part of the posterior wall of the vagina, longitudinally cut open the wall about 2.0–3.0 cm, separate a small airtight cavity with blunt fingers, and at the same time push the rectum to the left of the patient as far as possible to avoid intraoperative complications. Suture the skin flap around the incision, so as to prevent air leakage when tightening the purse after placing the protective sleeve of the incision. The incision protective sleeve is placed in the purse to open the incision and the closed space to make room for operation. Connect the incision protective sleeve to the specialized port of V-Notes to connect the pneumoperitoneum platform. Form the pneumoperitoneum by filling CO_2 gas until the pressure reached 11 mmHg (1 mmHg = 0.133 kPa). Place a 30° laparoscopic lens into the operating hole to observe the visual field. Block the intestinal tube with a separation forceps to avoid injury, and then carefully separate the surrounding connective tissue with an ultrasonic knife to further enlarge the cavity. For beginners, the anatomical structure can be gradually separated to dissect the sacrum and the surrounding blood vessels and nerves, so

as to avoid injuring blood vessels and nerves. After they get skilled, it is not necessary to expose too much tissue to locate the sacrospinous ligament. During the separation to enlarge the cavity, gauze can be used to stop the bleeding. The sacrospinous ligament can be located and the suture site of the sacrospinous ligament can be exposed through the landmark anatomical structures of the pelvic floor, such as sacrum, coccygeus, ischial spine, inferior gluteal blood vessel, and sciatic nerve. During the procedure, the ischial spine and sacrospinous ligament can be located by anal examination, and the suture site can be marked by bipolar after the position is determined. Two Ethibond Excel W6937 non-absorbable sutures can be used to suture the sacrospinous ligament with two stitches, with the depth being about 1/2 the thickness of the ligaments, and the distance between the two stitches being around 1 cm. After the needle is inserted, judge the tension by pulling the suture with the separation forceps without knotting. Then remove the port and tie the other end of the non-absorbable line with the suture at the top of the vaginal fornix of the hysterectomy patient, or tie it with the suture about 3 cm from the cervical orifice of the inferior wall of the cervix (that is, the uterine-sacral ligament close to the cervix) of the patient whose uterus was not removed after the repair of the anterior and posterior wall of the vagina. After tying the knot, lift the cervix with cervical forceps to detect whether it was fixed at the level of sacrospinous ligament. Suture the incision of the posterior wall of the vagina to end the operation. After vaginal disinfection, place a piece of iodophor gauze at the site and remove it the next day. (For detailed steps, see **Figures 1A–1H**.)

Postoperative management and follow-up

All the 18 patients returned to the ward safely after operation and underwent ECG monitoring within 24 h, with close attention paid to the postoperative vital signs and continuous low-flow oxygen inhalation. They received vagina disinfection on a daily basis during the three days after operation. After operation, the patients were immobilized in bed for 4 to 6 h. (The purpose was to prevent them from falling due to the residual effect of anesthesia. When patients were awake enough to get out of bed and walk around, we encouraged them to get out of bed as soon as possible to avoid the formation of venous thrombosis of the lower extremities.) They were given antibiotics to prevent infection and, if necessary, analgesics and sedatives. The outpatients were followed up in the 3rd, 6th, and 12th months, and their POP-Q scores were measured and recorded. Among the 18 patients, one who underwent operation on May 12, 2020, reported dull pain in both lower limbs two months after surgery, and another patient who underwent operation on November 9, 2020, reported lumbosacral distension sensation on November 30. Both of them have recovered. During the postoperative follow-up in the 6th month, one patient reported slight distension of the anterior vaginal wall. Only the data of the 3rd and 6th month follow-ups were analyzed because some of the patients underwent operation less than 12 months ago. (Details are shown in **Table 2**.)

Statistical analysis

The data of this study were statistically analyzed by SPSS21.0 statistical software. The measurement data were expressed by (mean ± standard deviation). The POP-Q scores of preoperative and postoperative follow-ups were tested by paired sample t-test, and the difference was considered to be statistically significant when P is <0.05.

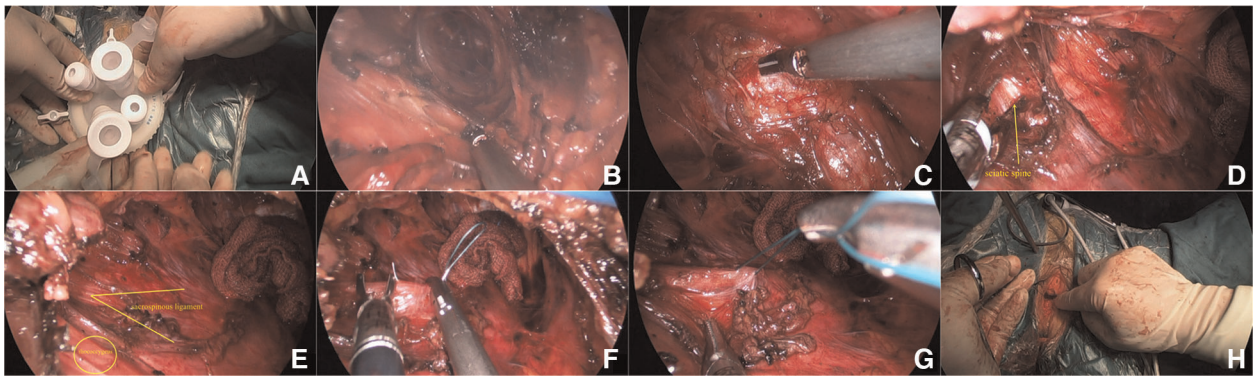

FIGURE 1
Surgical procedures. (A) Installing a specialized port for transvaginal single hole; (B) Separate tissue; (C) Expose the sacrospinous ligament at the sacrococcygeal attachment; (D) Expose the sciatic spine; (E) Expose the sacrospinous ligament and iliococcygeus; (F) Ethibond Excel W6937 non-absorbable suture to suture the sacral spine ligament; (G) Pull the suture to judge the tension; (H) Tie a knot with the suture.

TABLE 2 Information related to patients' surgery.

Number	operation time (min)	Intraoperative bleeding volume (ml)	HGB before operation (g/l)	HGB after operation (g/l)	Postoperative hospital stay (days)	VAS pain score (Before operation)	VAS pain score (Three months after operation)
1	275	100	125	96	10	5	1
2	205	80	140	141	6	4	1
3	125	100	122	116	5	5	1
4	175	100	139	118	6	5	1
5	175	80	126	116	6	5	1
6	200	100	138	116	9	5	2
7	160	150	124	89	5	4	1
8	170	500	94	104	13	5	2
9	145	50	132	125	9	5	0
10	200	300	141	92	12	4	1
11	180	100	120	106	7	5	1
12	250	200	108	100	7	5	1
13	190	100	131	107	9	5	1
14	215	80	142	126	8	5	1
15	145	80	129	118	7	5	1
16	225	50	136	116	5	5	0
17	195	50	142	117	11	5	1
18	240	200	134	106	8	5	1

TABLE 3 POP-Q scores before and 3 months after operation.

Group	Number	Aa	Ba	Ap	Bp	C	TVL
Before operation	18	1.00 ± 1.00	2.31 ± 1.19	0.86 ± 0.97	1.64 ± 1.08	5.19 ± 2.18	8.72 ± 0.46
3 month after operation	18	−2.25 ± 0.24	−2.68 ± 0.15	−2.34 ± 0.16	−2.68 ± 0.13	−7 ± 0.42	7.31 ± 0.57
t		13.41	17.67	13.87	16.82	23.27	8.18
p		0.014	0.001	0.005	0.001	0.001	0.559

TABLE 4 POP-Q scores before and 6 months after operation.

Group	Number	Aa	Ba	Ap	Bp	C	TVL
Before operation	18	1.00 ± 1.00	2.31 ± 1.19	0.86 ± 0.97	1.64 ± 1.08	5.19 ± 2.18	8.72 ± 0.46
6 month after operation	18	−2.17 ± 0.45	−2.52 ± 0.17	−2.32 ± 0.20	−2.55 ± 0.23	−7 ± 0.41	7.31 ± 0.57
t		12.25	17.03	13.67	16.07	23.27	8.18
p		0.037	0.001	0.007	0.001	0.001	0.559

Results

All the 18 patients completed the operation successfully and underwent transvaginal single-hole laparoscopic Sacrospinous Ligament Fixation. As per the individual conditions and wishes, anterior vaginal wall repair, posterior vaginal wall repair, transvaginal hysterectomy, or V-Notes adnexectomy was carried out. A total of 2 patients underwent Mann's operation at the same time, and 14 received vaginal hysterectomy at the same time. The adjacent pelvic organs were not injured during the operation, and the patients were able to urinate on their own after the catheter was removed after operation. The operation duration was (192.78 ± 38.81) min, and the amount of blood loss was (134.44 ± 111.21) ml. Except for the total vaginal length (TVL), the *P* values of numerical analysis for all points before, three months after, and six months after the operation were all <0.05, being statistically significant. (Details are shown in Tables 3 and 4.)

Discussion

POP has a variety of risk factors, such as age, hysterectomy, obesity (BMI > 30 kg/m^2), smoking, long-term chronic Valsalva (cough, fatigue and weightlifting) stimulation, history of multiple births and vaginal delivery, and genetic defects in pelvic floor support (13, 15). The average age of 18 patients in this study was 62.61 ± 10.26 years, the average number of parturition was 2.00 ± 0.77, the average BMI was 23.49 ± 1.81 kg/m^2, and no patient had BMI > 30 kg/m^2. In POP, when the organ is still above the hymen, the most obvious symptom is the sensation of swelling and pressure in the vagina, followed by the influence of urination and defecation function. It has been reported that the incidence of POP with symptoms is between 3% and 12% (1). According to statistics, with the POP staging method, 40% of the patients were diagnosed Grade II or above, but only 10% - 20% of the patients went to the hospital (16). Since 1992, with DeLancey's three levels of vaginal support theory, namely the Level I apical vaginal support, Level II midvaginal support, and Level III distal vaginal support (17), gynaecologists have had more theoretical support for the treatment of POP. However, there is no uniform standard for the treatment, and nor is there any guide or expert consensus to clearly indicate which regimen is the gold standard for the treatment of POP. Pelvicfloormuscletraining (PFMT) is recommended for the prevention and treatment of POP (18), especially for patients with mild prolapse where PEMT can significantly improve the POP symptoms. Meanwhile, PEMT has been proposed to enhance the surgical effect of POP patients (19), but there is also literature concluding that PFMT cannot improve the results of surgical treatment (20–22). As a non-operative method for the treatment of symptomatic POP, Pessary is suitable for patients with surgical contraindications (23–26), but patients should find a suitable uterine support (27). Meanwhile, regular follow-ups should be conducted to monitor the contraindications of uterine support, such as vaginal atrophy, vaginal mucosal ulcer, erosion, and active vaginal vulvar infection. Mesh has also been one of the important methods for the treatment of pelvic organ prolapse, but now it is still a controversial topic whether to use mesh implantation to treat pelvic prolapse. Sacrocolpopexy (SC) is a surgical method for repairing horizontal defects at Level I. SC uses the anterior sacral ligament as the posterior anchor point to repair the vaginal axis. It is generally believed that suspending the vagina to the sacral promontory can avoid the formation of intestinal prolapse in the posterior pit. Abdominal sacrocolpopexy (ASC), Laparoscopic sacrocolpopexy (LSC) and Robotic-assisted Abdominal Sacrocolpopexy all have good therapeutic effects (28–36). Transvaginal single-hole laparoscopy can also be used in mesh-related surgery (37–39). But what cannot be ignored is the incidence of postoperative complications, especially the incidence of mesh erosion (40–42).

Repairing the three levels of support is the basic idea of more surgical treatment of POP. It has been reported that if only the anterior and posterior vaginal wall repair is completed, but the apical support is insufficient, there is still a possibility that POP repair fails (43, 44). Therefore, apical support repair is the most basic and important for the repair of pelvic organ prolapse. The use of patient's own tissue suspension can reduce the cost of surgery while reducing mesh complications (45–47). Here are four types of surgery to improve the apical support repair of patients' own tissue, which are widely used. (1) Modified McCall culdoplasty: Absorbable suture was used to suture one side of the hysterosacral ligament to the Douglas fossa and vaginal stump, and then suture the contralateral uterine sacral ligament. (2) Uterosacral ligament suspension (ULS): The rectovaginal fascia and pubic cervical fascia are suspended on the strong part of the uterosacral ligament. The part of the uterine-sacral ligament suspended from or above the ischial spine usually provides sufficient vaginal length and support. Shull suspension: Three stitches were sutured on each side of uterosacral ligament with 0 delayed absorbable suture, and the lowest suture was at the level of ischial spine. Three stitches were made upward at an interval of 1 cm, totaling fix sutures on both sides (48, 49). (3) Iliococcygeus fixation (ICF) is to fix the top of the vagina to the iliococcyx muscle and its fascia, usually suspended bilaterally. (4) Sacrospinous Ligament Fixation (SSLF): The sacrospinous ligament is used as the anchor point to suspend the vaginal fornix, and the right sacral ligament suspension is often performed, especially for patients with fornix prolapse. Through long-term follow-ups and comparison of the four surgical methods, some scholars believe that there is no significant difference in recurrence rate between Shull suspension and modified McCall culdoplasty (50, 51). There was no significant difference in success rate and recurrence rate between ICF and SSLF in a prospective non-randomized case-control study (52). An OPTIMAL randomized trial result showed that there was no significant difference in anatomical and functional results between USL and SSLF (21). According to a multicentre randomized trial, there was no significant statistical difference in SSLF versus vaginal hysterectomy with ULS within five years after operation among female patients with uterine prolapse Stage 2 or higher (53). Some similar studies suggested that the main determinant of recurrence rate was preoperative POP-Q stage, the recurrence rate increased with the increase of POP stage, and there was no significant difference in postoperative recurrence rate between USLS and SSLF (54).

There is currently no unified regulation on the surgical methods for the treatment of pelvic prolapse, and there are

about 100 surgical methods for the treatment of pelvic prolapse and related diseases. At this stage, the surgical methods for pelvic prolapse are highly individualized (55). However, it should be noted that each technique has its shortcomings. A retrospective study with a nine-year follow-up period found that there was no significant difference between modified McCall culdoplasty and SSLF recurrence rate of 15% (11). However, there is a risk of ureteral obstruction or injury in the modified McCall culdoplasty operation, and it is recommended to check the ureter during the operation. A prospective non-randomized controlled trial compared the efficacy and safety of ICF and ASC in patients with vaginal fornix prolapse with similar objective and subjective success rates. In the ICF group, the operation time was shortened, but the average blood loss was higher (56). As early as 1997, some scholars thought that the possibility of recurrence after SSLF was as high as 29%, requiring secondary intervention (57). A Danish national cohort study of Ipsilateral uterosacral ligament suspension (IUSLS) and SSLF found that the probability of recurrence after SSLF was higher than that after IUSLS (58). It has been reported that the incidence of postoperative anterior vaginal wall prolapse is high (59). This OPTIMAL randomized trial also found 13.7% recurrence of anterior wall prolapse exceeding hymen in SSLF group (21). Some scholars have proposed that the patients with wide genital hiatus have a higher recurrence rate after SSLF (60). The author believes that the recurrence rate of genital hiatus, SSLF is closely related to the exposure of the operative field, the accuracy of the puncture position of the suspended suture, and the operative experience. Excluding the surgical experience, the success rate of SSLF can be improved by improving the exposure of the surgical field and the accuracy of the puncture site.

In addition to the minimally invasive laparoscopic technology, another advantage is that it can greatly improve the surgical field and use high-definition lens and light source, so that surgical technique has seen rapid advancement. With the introduction of the Natural Orifice Transluminal Endoscopic Surgery (NOTES), this technique has quickly fueled the clinical exploration of this kind of surgery, and has become a hot topic in the field of minimally invasive surgery (61, 62). Some scholars confirmed that there were no surgical complications in the perioperative period, the standard one-month follow-up period, or the subsequent follow-up period (up to 14 months), concluding that V-Notes would not increase the risk of surgical infection (63). Based on this, the author team combines V-NOTES and SSLF and their respective advantages. The use of tough and non-extensible Sacrospinous Ligament can avoid the prolongation of traction caused by daily life, reduce the recurrence rate, and have little effect on the vaginal axis (64).

No matter what kind of operation is chosen, it is closely related to clinical anatomy. The proposal of the accurate medical treatment concept also echoes with the minimally invasive clinical surgery. How to more accurately complete the suspension of the sacral spine ligament, determine the length of the suspension position from the ischial spine and other anatomical structures and the depth of the needle, and how to avoid damage to the surrounding nerve plexus, blood vessels, rectum and so on, all require anatomic concepts for support. Most of the disadvantages of traditional postoperative complications such as postoperative pain and recurrent prolapse of transvaginal sacral ligament are caused by the inaccurate puncture site during the operation, the injury of the peripheral nerve plexus, or a too shallow or too deep suspension puncture site. If peripheral blood vessels are injured during operation, it is estimated that up to 1.9% of patients need blood transfusion treatment (65). This is a material departure from the minimally invasive concept, so we can see the importance of anatomy to precision medicine. The pelvic surface of Sacrospinous Ligament fits the coccygeus, but the Sacrospinous Ligament is thinner and tougher. The main nerves around it are lumbosacral trunk nerve, Posterior femoral cutaneous nerve, pudendal nerve, and small branches, with blood vessels such as arteriae glutaea inferior and arteriae pudenda interna. How to avoid the damage to these tissues is one of the keys to a successful operation. The average length of Sacrospinous Ligament is about 5.1–5.2 cm, and the thickness is about 0.2 cm. Because the upper and lower edges of coccygeus are beyond the range of Sacrospinous Ligament, the two are closely linked. If Sacrospinous Ligament is forcibly stripped, it will cause serious damage to coccygeus. Maldonado et al. put forward the concept of coccygeus sarospinous ligament (CSSL) (66). Because Sacrospinous Ligament is closely connected with coccygeus and anadesma, Hayashi et al. think that Sacrospinous Ligament is formed by the growth and development of coccygeus (67), and some scholars think that the suspension tissue selected by SSLF is very likely to be coccygeus of CSSL (68). However, the author believes that if the suture is too shallow, only coccygeus and its anadesma will be suspended, because its texture and extensibility may lead to a suspension failure, so the needle depth, angle, needle distance, and puncture site need to be well selected. Most of the Pudendal canal composed of pudendal artery, Pussy vein, and pudendal nerve were located on the dorsal side of the Sacrospinous Ligament. Because the rectum is located on the left, the right Sacrospinous Ligament is generally selected for SSLF to avoid rectal injury. Chinese reports suggest that the anatomical distance between the right Pudendal canal and the ischial spine is mostly about 1.51 cm, and the anatomical distance between the ischial spine and the ischial spine is about 2.1–2.5 cm. The data outside China is higher, about 2.1–2.5 cm or even 2.75 cm (63, 69, 70). The difference in value may be related to the

race of the population, measurement errors, and individual differences of cadavers. According to the current data, SSLF in China should be at least 1.51 cm away from sciatic spine to reduce the probability of damage to the pudendal tube. From the anatomical data, it can also be concluded that the probability of damage to Sacrospinous Ligament can be reduced by selecting the 1/2 depth of the shallow layer of the Sacrospinous Ligament 2.5 cm away from sciatic spine (71). S3, S4 and pudendal nerve are mostly on the upper edge of Sacrospinous Ligament (72). Therefore, choosing the place near the inferior edge as the puncture point can reduce the probability of injury to these nerves. The distance between nervi ischiadicus and Sacrospinous Ligament is about 2 cm, and the probability of nervi ischiadicus injury during operation is small. However, the sciatica of some patients reported in the literature may be caused by traction of Sacrospinous Ligament during suspension, most of which can be relieved by themselves. It has long been confirmed that musculi levator ani is controlled not only by internal anal sphincter nerves but also by pudendal nerve branches (73). Therefore, the clinical manifestation of puncture injury after internal anal sphincter nerves is not obvious. To sum up, the best puncture position on the right side of Sacrospinous Ligament selected by SSLF is at least 2.5 cm from the ischial spine, close to the inferior edge of 2.5 cm, and the depth is about 1 mm, where it can avoid damage to the surrounding blood vessels and nerves as much as possible while providing enough strength for suspension.

In this study, the data was derived from 18 patients, as shown in **Tables 1**, **2**. The average operation duration was 192.78 ± 38.81 min, which was longer than the reported 92.3 ± 31.5 min of 453 patients with SSLF (74), longer than the 122.8 ± 36.1 min of 57 SSLF patients (75), and longer than the 86.04 ± 28.70 min of 50 patients with H-SSLF (76). This outcome may be related to the increased difficulty of transvaginal single-port laparoscopic surgery. The intraoperative blood loss of this study was 134.44 ± 111.21 ml, which was higher than the 92.3 ± 91.4 ml of 453 SSLF patients (74) and 86.80 ± 91.44 of 50 H-SSLF patients (76). This outcome may be related to factors such as increased surgical difficulty, small sample size, and initial surgery. The mean preoperative hemoglobin in this study was 129.06 ± 12.64 g/L, the mean postoperative hemoglobin was 111.61 ± 12.96 g/L, and the mean decrease in preoperative and postoperative hemoglobin was about 17 g/L, similar to the reported Preoperative Hb: 12.3 ± 1.06 (g/dl), Postoperative Hb:10.4 ± 1.07 g/dl decrease (75). The mean post-operative hospital stay in this study was 7.94 ± 2.41d. According to the data in **Tables 3**, **4**, the treatment efficacy for the 18 patients lasted till three and six months after the operation, without obvious recurrence. One patient received the operation on May 12, 2020, and was reported dull pain in February. Another patient received the operation on November 9, 2020, and was reported lumbosacral swelling in 2020. Both patients have improved themselves, considering that the symptoms of the two patients may be caused by small nerve injury from suture suspension.

The advantages of this method are as follows: (1) Laparoscopic operation under direct vision can reduce unnecessary injury. If there is accidental injury during operation, the laparoscopic mode is easier to deal with the issue. (2) For some patients who are difficult to complete SSLF, especially those with deep position of sacral ligament making the site locating in the vaginal mode difficult to complete, this scheme can better expose and distinguish the pelvic tissues such as sacral spine ligament and ischial spine, and locate the suspension puncture site more accurately to complete the suspension of sacral spine ligament. (3) Through the laparoscopic mode, it is easier for doctors to recognize the sacral ligament and to teach and inherit SSLF. The disadvantage lies in that (1) Because of the single-hole laparoscopic model, the operation cost may be higher than that of SSLF. It is believed that with the development of single-hole laparoscopic model and the reduction of port and other consumables costs, the gap between the surgical costs will also be narrowed. (2) The operator needs to adapt to the operation mode of V-NOTES, after which SSLF may become easier to locate the sacrospinous ligament under the laparoscopic mode.

As mentioned above, this study preliminarily concluded that this operation has good short-term effect and few complications in the treatment of moderate and severe pelvic organ prolapse, but the sample size of this study is small, and the follow-up period is less than 5 years. Therefore, more cases and longer-term follow-up data are needed to determine the long-term effect of this procedure. For the selection of puncture sites, more anatomical data are needed to get more accurate results.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

ZQ: Writing - Original Draft; ZD: Validation; HT: Software; SZ: Investigation; HW: Resources; MB: Data Curation; WW: Methodology; RS: Visualization; JC: Conceptualization and Funding acquisition; BX: Supervision and Project administration. All authors contributed to the article and approved the submitted version.

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Irb approval or exemption

This study has been approved by the Ethics Committee of Nanjing Medical University Affiliated Changzhou No. 2 People's Hospital, Jiangsu Province, China.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Nygaard I, Barber MD, Burgio KL, Kenton K, Meikle S, Schaffer J, et al. Prevalence of symptomatic pelvic floor disorders in US women. *JAMA*. (2008) 300(11):1311–6. doi: 10.1001/jama.300.11.1311

2. Mant J, Painter R, Vessey M. Epidemiology of genital prolapse: observations from the Oxford Family Planning Association Study. *Br J Obstet Gynaecol*. (1997) 104(5):579–85. doi: 10.1111/j.1471-0528.1997.tb11536.x

3. Hendrix SL, Clark A, Nygaard I, Aragaki A, Barnabei V, McTiernan A. Pelvic organ prolapse in the Women's Health Initiative: gravity and gravidity. *Am J Obstet Gynecol*. (2002) 186(6):1160–6. doi: 10.1067/mob.2002.123819

4. Leijonhufvud Å, Lundholm C, Cnattingius S, Granath F, Andolf E, Altman D. Risk of surgically managed pelvic floor dysfunction in relation to age at first delivery. *Am J Obstet Gynecol*. (2012) 207(4):303.e1-7. doi: 10.1016/j.ajog.2012.08.019

5. Fialkow MF, Newton KM, Lentz GM, Weiss NS. Lifetime risk of surgical management for pelvic organ prolapse or urinary incontinence. *Int Urogynecol J Pelvic Floor Dysfunct*. (2008) 19(3):437–40. doi: 10.1007/s00192-007-0459-9

6. Chen R, Xu P, Song P, Wang M, He J. China Has faster pace than Japan in population aging in next 25 years. *Biosci Trends*. (2019) 13(4):287–91. doi: 10.5582/bst.2019.01213

7. Kanasi E, Ayilavarapu S, Jones J. The aging population: demographics and the biology of aging. *Periodontol 2000*. (2016) 72(1):13–8. doi: 10.1111/prd.12126

8. Jelovsek JE, Barber MD, Brubaker L, Norton P, Gantz M, Richter HE, et al. Effect of uterosacral ligament suspension vs sacrospinous ligament fixation with or without perioperative behavioral therapy for pelvic organ vaginal prolapse on surgical outcomes and prolapse symptoms at 5 years in the OPTIMAL randomized clinical trial. *JAMA*. (2018) 319(15):1554–65. doi: 10.1001/jama.2018.2827

9. Nager CW, Visco AG, Richter HE, Rardin CR, Komesu Y, Harvie HS, et al. Effect of sacrospinous hysteropexy with graft vs vaginal hysterectomy with uterosacral ligament suspension on treatment failure in women with uterovaginal prolapse: 5-year results of a randomized clinical trial. *Am J Obstet Gynecol*. (2021) 225(2):153.e1–e31. doi: 10.1016/j.ajog.2021.03.012.

10. Paraiso MF, Ballard LA, Walters MD, Lee JC, Mitchinson AR. Pelvic support defects and visceral and sexual function in women treated with sacrospinous ligament suspension and pelvic reconstruction. *Am J Obstet Gynecol*. (1996) 175(6):1423–30; discussion 1430–1. doi: 10.1016/s0002-9378(96)70085-6

11. Colombo M, Milani R. Sacrospinous ligament fixation and modified McCall culdoplasty during vaginal hysterectomy for advanced uterovaginal prolapse. *Am J Obstet Gynecol*. (1998) 179(1):13–20. doi: 10.1016/s0002-9378(98)70245-5

12. Al-Badr A, Perveen K, Al-Shaikh G. Evaluation of sacrospinous hysteropexy vs. uterosacral suspension for the treatment of uterine prolapse: a retrospective assessment. *Low Urin Tract Symptoms*. (2017) 9(1):33–7. doi: 10.1111/luts.12104

13. American College of Obstetricians and Gynecologists and the American Urogynecologic Society; INTERIM UPDATE: This Practice Bulletin is updated as highlighted to reflect the US Food and Drug Administration order to stop the sale of transvaginal synthetic mesh products for the repair of pelvic organ prolapse. Pelvic organ prolapse. *Female Pelvic Med Reconstr Surg*. (2019) 25(6):397–408. doi: 10.1097/SPV.0000000000000794

14. Bump RC, Mattiasson A, Bø K, Brubaker LP, DeLancey JO, Klarskov P, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obstet Gynecol*. (1996) 175(1):10–7. doi: 10.1016/s0002-9378(96)70243-0

15. Jelovsek JE, Maher C, Barber MD. Pelvic organ prolapse. *Lancet*. (2007) 369(9566):1027–38. doi: 10.1016/S0140-6736(07)60462-0

16. Rodríguez-Mias NL, Martínez-Franco E, Aguado J, Sánchez E, Amat-Tardiu L. Pelvic organ prolapse and stress urinary incontinence, do they share the same risk factors? *Eur J Obstet Gynecol Reprod Biol*. (2015) 190:52–7. doi: 10.1016/j.ejogrb.2015.04.015

17. DeLancey JO. Anatomic aspects of vaginal eversion after hysterectomy. *Am J Obstet Gynecol*. (1992) 166(6 Pt 1):1717–24; discussion 1724–8. doi: 10.1016/0002-9378(92)91562-o

18. Piya-Anant M, Therasakvichya S, Leelaphatanadit C, Techatrisak K. Integrated health research program for the Thai elderly: prevalence of genital prolapse and effectiveness of pelvic floor exercise to prevent worsening of genital prolapse in elderly women. *J Med Assoc Thai*. (2003) 86(6):509–15

19. Zhang FW, Wei F, Wang HL, Pan YQ, Zhen JY, Zhang JX, et al. Does pelvic floor muscle training augment the effect of surgery in women with pelvic organ prolapse? A systematic review of randomized controlled trials. *Neurourol Urodyn*. (2016) 35(6):666–74. doi: 10.1002/nau.22784.Lakeman MM, Koops SE, Berghmans BC, Roovers JP. Peri-operative physiotherapy to prevent recurrent symptoms and treatment following prolapse surgery: supported by evidence or not? Int Urogynecol J (2013); 24(3): 371–5. doi: 10.1007/s00192-012-1973-y.

20. Frawley HC, Phillips BA, Bø K, Galea MP. Physiotherapy as an adjunct to prolapse surgery: an assessor-blinded randomized controlled trial. *Neurourol Urodyn*. (2010) 29(5):719–25. doi: 10.1002/nau.20828

21. Barber MD, Brubaker L, Burgio KL, Richter HE, Nygaard I, Weidner AC, et al. Comparison of 2 transvaginal surgical approaches and perioperative behavioral therapy for apical vaginal prolapse: the OPTIMAL randomized trial. *JAMA*. (2014) 311(10):1023–34. doi: 10.1001/jama.2014.1719. Erratum in: JAMA. 2015; 313(22): 2287

22. Pauls RN, Crisp CC, Novicki K, Fellner AN, Kleeman SD. Pelvic floor physical therapy: impact on quality of life 6 months after vaginal reconstructive surgery. *Female Pelvic Med Reconstr Surg*. (2014) 20(6):334–41. doi: 10.1097/SPV.0000000000000090

23. Fernando RJ, Thakar R, Sultan AH, Shah SM, Jones PW. Effect of vaginal pessaries on symptoms associated with pelvic organ prolapse. *Obstet Gynecol*. (2006) 108(1):93–9. doi: 10.1097/01.AOG.0000222903.38684.cc

24. Barber MD, Walters MD, Cundiff GW. Responsiveness of the pelvic floor distress inventory (PFDI) and pelvic floor impact questionnaire (PFIQ) in women undergoing vaginal surgery and pessary treatment for pelvic organ

prolapse. *Am J Obstet Gynecol*. (2006) 194(5):1492–8. doi: 10.1016/j.ajog.2006.01.076

25. Komesu YM, Rogers RG, Rode MA, Craig EC, Gallegos KA, Montoya AR, et al. Pelvic floor symptom changes in pessary users. *Am J Obstet Gynecol*. (2007) 197(6):620.e1-6. doi: 10.1016/j.ajog.2007.08.013

26. Rusavy Z, Bombieri L, Freeman RM. Procidentia in pregnancy: a systematic review and recommendations for practice. *Int Urogynecol J*. (2015) 26(8):1103–9. doi: 10.1007/s00192-014-2595-3

27. Geoffrion R, Zhang T, Lee T, Cundiff GW. Clinical characteristics associated with unsuccessful pessary fitting outcomes. *Female Pelvic Med Reconstr Surg*. (2013) 19(6):339–45. doi: 10.1097/SPV.0b013e3182a26174

28. Serati M, Bogani G, Sorice P, Braga A, Torella M, Salvatore S, et al. Robot-assisted sacrocolpopexy for pelvic organ prolapse: a systematic review and meta-analysis of comparative studies. *Eur Urol*. (2014) 66(2):303–18. doi: 10.1016/j.eururo.2014.02.053

29. Pan K, Zhang Y, Wang Y, Wang Y, Xu H. A systematic review and meta-analysis of conventional laparoscopic sacrocolpopexy versus robot-assisted laparoscopic sacrocolpopexy. *Int J Gynaecol Obstet*. (2016) 132(3):284–91. doi: 10.1016/j.ijgo.2015.08.008

30. Ploumidis A, Spinoit AF, De Naeyer G, Schatteman P, Gan M, Ficarra V, et al. Robot-assisted sacrocolpopexy for pelvic organ prolapse: surgical technique and outcomes at a single high-volume institution. *Eur Urol*. (2014) 65(1):138–45. doi: 10.1016/j.eururo.2013.05.054

31. Merseburger AS, Herrmann TR, Shariat SF, Kyriazis I, Nagele U, Traxer O, et al. EAU guidelines on robotic and single-site surgery in urology. *Eur Urol*. (2013) 64(2):277–91. doi: 10.1016/j.eururo.2013.05.034

32. Costantini E, Brubaker L, Cervigni M, Matthews CA, O'Reilly BA, Rizk D, et al. Sacrocolpopexy for pelvic organ prolapse: evidence-based review and recommendations. *Eur J Obstet Gynecol Reprod Biol*. (2016) 205:60–5. doi: 10.1016/j.ejogrb.2016.07.503

33. Lee RK, Mottrie A, Payne CK, Waltregny D. A review of the current status of laparoscopic and robot-assisted sacrocolpopexy for pelvic organ prolapse. *Eur Urol*. (2014) 65(6):1128–37. doi: 10.1016/j.eururo.2013.12.064

34. Clifton MM, Pizarro-Berdichevsky J, Goldman HB. Robotic female pelvic floor reconstruction: a review. *Urology*. (2016) 91:33–40. doi: 10.1016/j.urology.2015.12.006

35. Maher CF, Qatawneh AM, Dwyer PL, Carey MP, Cornish A, Schluter PJ. Abdominal sacral colpopexy or vaginal sacrospinous colpopexy for vaginal vault prolapse: a prospective randomized study. *Am J Obstet Gynecol*. (2004) 190(1):20–6. doi: 10.1016/j.ajog.2003.08.031

36. Brubaker L, Nygaard I, Richter HE, Visco A, Weber AM, Cundiff GW, et al. Two-year outcomes after sacrocolpopexy with and without burch to prevent stress urinary incontinence. *Obstet Gynecol*. (2008) 112(1):49–55. doi: 10.1097/AOG.0b013e3181778d2a. Erratum in: Obstet Gynecol. 2016; 127(5): 968–9

37. Mohr S, Siegenthaler F, Imboden S, Kuhn A, Mueller MD. Transvaginal excision of an eroded sacrocolpopexy mesh by using single-incision laparoscopic surgery equipment. *J Minim Invasive Gynecol*. (2017) 24(7):1079–80. doi: 10.1016/j.jmig.2017.04.001

38. Liu J, Kohn J, Fu H, Guan Z, Guan X. Transvaginal natural orifice transluminal endoscopic surgery for sacrocolpopexy: a pilot study of 26 cases. *J Minim Invasive Gynecol*. (2019) 26(4):748–53. doi: 10.1016/j.jmig.2018.08.009

39. Chen Y, Li J, Zhang Y, Hua K. Transvaginal single-port laparoscopy sacrocolpopexy. *J Minim Invasive Gynecol*. (2018) 25(4):585–8. doi: 10.1016/j.jmig.2017.10.017

40. Nygaard I, Brubaker L, Zyczynski HM, Cundiff G, Richter H, Gantz M, et al. Long-term outcomes following abdominal sacrocolpopexy for pelvic organ prolapse. *JAMA*. (2013) 309(19):2016–24. doi: 10.1001/jama.2013.4919. Erratum in: JAMA. (2013); 310(10): 1076

41. Nygaard IE, McCreery R, Brubaker L, Connolly A, Cundiff G, Weber AM, et al. Abdominal sacrocolpopexy: a comprehensive review. *Obstet Gynecol*. (2004) 104(4):805–23. doi: 10.1097/01.AOG.0000139514.90897.07

42. De Gouveia De Sa M, Claydon LS, Whitlow B, Dolcet Artahona MA. Robotic versus laparoscopic sacrocolpopexy for treatment of prolapse of the apical segment of the vagina: a systematic review and meta-analysis. *Int Urogynecol J*. (2016) 27(3):355–66. doi: 10.1007/s00192-015-2763-0

43. Summers A, Winkel LA, Hussain HK, DeLancey JO. The relationship between anterior and apical compartment support. *Am J Obstet Gynecol*. (2006) 194(5):1438–43. doi: 10.1016/j.ajog.2006.01.057

44. Rooney K, Kenton K, Mueller ER, FitzGerald MP, Brubaker L. Advanced anterior vaginal wall prolapse is highly correlated with apical prolapse. *Am J Obstet Gynecol*. (2006) 195(6):1837–40. doi: 10.1016/j.ajog.2006.06.065

45. Milani R, Frigerio M, Cola A, Beretta C, Spelzini F, Manodoro S. Outcomes of transvaginal high uterosacral ligaments suspension: over 500-patient single-center study. *Female Pelvic Med Reconstr Surg*. (2018) 24(1):39–42. doi: 10.1097/SPV.0000000000000403

46. Cheon C, Maher C. Economics of pelvic organ prolapse surgery. *Int Urogynecol J*. (2013) 24(11):1873–6. doi: 10.1007/s00192-013-2178-8

47. Kearney R, DeLancey JO. Selecting suspension points and excising the vagina during Michigan four-wall sacrospinous suspension. *Obstet Gynecol*. (2003) 101(2):325–30. doi: 10.1016/s0029-7844(02)02464-x

48. Shull BL, Bachofen C, Coates KW, Kuehl TJ. A transvaginal approach to repair of apical and other associated sites of pelvic organ prolapse with uterosacral ligaments. *Am J Obstet Gynecol*. (2000) 183(6):1365–73; discussion 1373–4. doi: 10.1067/mob.2000.110910

49. Restaino S, Ronsini C, Finelli A, Santarelli A, Scambia G, Fanfani F. Laparoscopic approach for shull repair of pelvic floor defects. *J Minim Invasive Gynecol*. (2018) 25(6):954. doi: 10.1016/j.jmig.2017.12.016

50. Spelzini F, Frigerio M, Manodoro S, Interdonato ML, Cesana MC, Verri D, et al. Modified McCall culdoplasty versus Shull suspension in pelvic prolapse primary repair: a retrospective study. *Int Urogynecol J*. (2017) 28(1):65–71. doi: 10.1007/s00192-016-3016-6

51. Novara L, Sgro LG, Pecchio S, Ottino L, Tomatis V, Biglia N. Transvaginal high uterosacral ligament suspension: an alternative to McCall culdoplasty in the treatment of pelvic organ prolapse. *Eur J Obstet Gynecol Reprod Biol*. (2019) 240:278–81. doi: 10.1016/j.ejogrb.2019.07.007

52. Maher CF, Murray CJ, Carey MP, Dwyer PL, Ugoni AM. Iliococcygeus or sacrospinous fixation for vaginal vault prolapse. *Obstet Gynecol*. (2001) 98(1):40–4. doi: 10.1016/s0029-7844(01)01378-3

53. Schulten SFM, Detollenaere RJ, Stekelenburg J, IntHout J, Kluivers KB, van Eijndhoven HWF. Sacrospinous hysteropexy vaginal hysterectomy with uterosacral ligament suspension in women with uterine prolapse stage 2 or higher: observational follow-up of a multicentre randomised trial. *Br Med J*. (2019) 366:l5149. doi: 10.1136/bmj.l5149

54. Topdagi Yilmaz EP, Yapca OE, Topdagi YE, Atakan Al R, Kumtepe Y. Comparison of two natural tissue repair-based surgical techniques; sacrospinous fixation and uterosacral ligament suspension for pelvic organ prolapse treatment. *J Gynecol Obstet Hum Reprod*. (2021) 50(4):101905. doi: 10.1016/j.jogoh.2020.101905

55. Barber MD, Maher C. Apical prolapse. *Int Urogynecol J*. (2013) 24(11):1815–33. doi: 10.1007/s00192-013-2172-1

56. Milani R, Cesana MC, Spelzini F, Sicuri M, Manodoro S, Fruscio R. Iliococcygeus fixation or abdominal sacral colpopexy for the treatment of vaginal vault prolapse: a retrospective cohort study. *Int Urogynecol J*. (2014) 25(2):279–84. doi: 10.1007/s00192-013-2216-6

57. Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. *Obstet Gynecol*. (1997) 89(4):501–6. doi: 10.1016/S0029-7844(97)00058-6

58. Husby KR, Larsen MD, Lose G, Klarskov N. Surgical repair of vaginal vault prolapse; a comparison between ipsilateral uterosacral ligament suspension and sacrospinous ligament fixation-a nationwide cohort study. *Int Urogynecol J*. (2021) 32(6):1441–9. doi: 10.1007/s00192-020-04515-x

59. Morgan DM, Rogers MA, Huebner M, Wei JT, Delancey JO. Heterogeneity in anatomic outcome of sacrospinous ligament fixation for prolapse: a systematic review. *Obstet Gynecol*. (2007) 109(6):1424–33. doi: 10.1097/01.AOG.0000264066.89094.21

60. Garcia AN, Ulker A, Aserlind A, Timmons D, Medina CA. Enlargement of the genital hiatus is associated with prolapse recurrence in patients undergoing sacrospinous ligament fixation. *Int J Gynaecol Obstet*. (2022) 157(1):96–101. doi: 10.1002/ijgo.13828

61. Lee GC, Sylla P. Shifting paradigms in minimally invasive surgery: applications of transanal natural orifice transluminal endoscopic surgery in colorectal surgery. *Clin Colon Rectal Surg*. (2015) 28(3):181–93. doi: 10.1055/s-0035-1555009

62. Dhillon KS, Awasthi D, Dhillon AS. Natural orifice transluminal endoscopic surgery (hybrid) cholecystectomy: the Dhillon technique. *J Minim Access Surg*. (2017) 13(3):176–81. doi: 10.4103/0972-9941.207838

63. Li J, Hu C, Wang X, Hua K, Chen Y. Transvaginal single-port laparoscopic pelvic reconstruction with Y-shaped mesh: experiences of 93 cases. *Int Urogynecol J*. (2021) 32(4):905–11. doi: 10.1007/s00192-020-04418-x

64. Cruikshank SH, Muniz M. Outcomes study: a comparison of cure rates in 695 patients undergoing sacrospinous ligament fixation alone and with other site-specific procedures–a 16-year study. *Am J Obstet Gynecol*. (2003) 188(6):1509–12; discussion 1512–5. doi: 10.1067/mob.2003.474

65. Leone Roberti Maggiore U, Venturini PL, Ferrero S. Operative time required to perform sacrospinous ligament suspension. *Arch Gynecol Obstet*. (2014) 289 (2):233–4. doi: 10.1007/s00404-013-2996-4

66. Maldonado PA, Chin K, Garcia AA, Corton MM. Anatomic variations of pudendal nerve within pelvis and pudendal canal: clinical applications. *Am J Obstet Gynecol*. (2015) 213(5):727.e1-6. doi: 10.1016/j.ajog.2015.06.009

67. Hayashi S, Kim JH, Rodriguez-Vazquez JF, Murakami G, Fukuzawa Y, Asamoto K, et al. Influence of developing ligaments on the muscles in contact with them: a study of the annular ligament of the radius and the sacrospinous ligament in mid-term human fetuses. *Anat Cell Biol*. (2013) 46(2):149–56. doi: 10.5115/acb.2013.46.2.149

68. Kong MK, Bai SW. Surgical treatments for vaginal apical prolapse. *Obstet Gynecol Sci*. (2016) 59(4):253–60. doi: 10.5468/ogs.2016.59.4.253

69. Katrikh AZ, Ettarh R, Kahn MA. Cadaveric nerve and artery proximity to sacrospinous ligament fixation sutures placed by a suture-capturing device. *Obstet Gynecol*. (2017) 130(5):1033–8. doi: 10.1097/AOG.0000000000002324

70. Qing-xia Z, Jing-he L, Lan Z, Nai-li W, Wen-ting L, Yin-hua K. A study on clinically oriented anatomy of the sacropinous ligament region in women. *J Reporductive Med*. (2009) 18(4):349–53. doi: 10.3969/j.issn.1004-3845.2009.04.006

71. Thompson JR, Gibb JS, Genadry R, Burrows L, Lambrou N, Buller JL. Anatomy of pelvic arteries adjacent to the sacrospinous ligament: importance of the coccygeal branch of the inferior gluteal artery. *Obstet Gynecol*. (1999) 94 (6):973–7. doi: 10.1016/s0029-7844(99)00418-4

72. Roshanravan SM, Wieslander CK, Schaffer JI, Corton MM. Neurovascular anatomy of the sacrospinous ligament region in female cadavers: implications in sacrospinous ligament fixation. *Am J Obstet Gynecol*. (2007) 197(6):660.e1-6. doi: 10.1016/j.ajog.2007.08.061

73. Stelzner S, Böttner M, Kupsch J, Kneist W, Quirke P, West NP, et al. Internal anal sphincter nerves - a macroanatomical and microscopic description of the extrinsic autonomic nerve supply of the internal anal sphincter. *Colorectal Dis*. (2018) 20(1):O7–O16. doi: 10.1111/codi.13942

74. Wu CJ, Chang WC, Huang KJ, Hsieh YC, Wei LH, Sheu BC. Long-term follow-up of 453 patients with pelvic organ prolapse who underwent transvaginal sacrospinous colpopexy with Veronikis ligature carrier. *Sci Rep*. (2020) 10(1):4997. doi: 10.1038/s41598-020-61995-z

75. Biler A, Ertaş İE, Tosun G, Hortu İ, Demir A, Taner CE, et al. Perioperative complications and short-term outcomes of abdominal sacrocolpopexy, laparoscopic sacrocolpopexy, sacrospinous ligament fixation, and iliococcygeus fixation procedures. *Turk J Med Sci*. (2018) 48(3):602–10. doi: 10.3906/sag-1712-203

76. Wang P, Li M, Sun H, Ni L, Cai H, Fan W, et al. Function, quality-of-life and complications after sacrospinous ligament fixation using an antegrade reusable suturing device (ARSD-Ney) at 6 and 12 months: a retrospective cohort study. *Ann Transl Med*. (2022) 10(10):582. doi: 10.21037/atm-22-2150

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Application of a new protocol for providing obstetric care in an outpatient service during the COVID-19 pandemic in a public hospital in Madrid, Spain

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Objective: To evaluate the clinical implementation of a preventive COVID-19 protocol regarding re-organization of appointments and documented infections among health workers in an obstetric outpatient service.

Methods: Descriptive analysis of the antenatal care at our obstetric outpatient service and infection rates among health care providers from March 19th to May 22nd, 2020. Appointments were divided into telephone calls or face-to-face examinations. A pre-consultation triage was implemented to identify suspected SARS-CoV2 infected women to reschedule them 14 days later or, if the consultation was non-delayable, to use complete Personal Protective Equipment (PPE). Firstly, the number of face-to-face appointments, telephone appointments, and COVID-19 diagnoses in pregnant women were analyzed. Secondly, the number of obstetricians and nurses diagnosed with SARS-CoV2 infection and their serologic status during universal screening in May 2020 were recorded.

Results: One thousand eight hundred forty-two obstetric appointments were scheduled during this period, including 432 (23.5%) telephone appointments (96.53% according to clinical protocol, 1.62% symptomatic patients advised to stay at home, and 1.85% COVID-19 confirmed cases), and 1,410 (76.5%) face-to-face appointments (9.7% did not attend due to fear of getting the infection, 3.1% were lost-to-follow-up, 0.5% were rescheduled due to COVID-19 symptoms and 86.7% who did attend). Of the 1,223 women attending their hospital appointment, 3.6% screened positive at the triage (72.7% rescheduled and 27.3% seen with PPE). 43 rRT-PCR-SARS-CoV2 tests were performed, and two tested positive. No COVID-19 symptoms were reported among health workers at the outpatient obstetric service, and only one nurse presented immunoglobulin (Ig)G anti-SARS-CoV2.

Conclusion: A prompt implementation of a preventive protocol in a hospital obstetric outpatient service, including triage, hygienic and preventive

measurements, and rescheduling pregnancy appointments, reduces the percentage of health workers affected by SARS-CoV2.

KEYWORDS

pregnancy, protocol, COVID-19 pandemic, obstetric care, SARS-CoV2, outpatient care

Introduction

On December 31st, 2019, the Authorities of the People's Republic of China reported several pneumonia cases of unknown etiology to the WHO in Wuhan, a city located in the Chinese province of Hubei (1). A week later, they confirmed that it was a new coronavirus named SARS-CoV2, and the disease it causes was named COVID-19 (1). The disease was transmitted similarly to influenza, SARS, or MERS virus, a person-to-person transmission through respiratory drops produced by coughing, sneezing, or speech in close contact. It was also reported that transmission could occur by touching a contaminated surface or any contaminated mucosa (2, 3). Although the contagion mainly occurred through symptomatic people, presymptomatic or very slightly symptomatic patients were also reported infectious (4, 5).

The first case in Spanish territory appeared on January 31st, but it was not until February 24th when the infection with transmission among the population was verified. The first case of local transmission was detected at Hospital Universitario de Torrejón in Madrid, a patient who had been admitted for pneumonia of unknown origin. From that moment, the city of Torrejón de Ardoz, where the hospital is located, became one of the hotspots for spreading infection in the Madrid area. For this reason and to assess the number of people that had been infected during the first peak of the pandemic, the city hall conducted a universal antibody screening undertaken by 75% of the city population (from 1 year old onwards) from May 29th to June 5th, 2020 (6). It was reported that 20.2% of the people presented anti-SARS-CoV2 immunoglobulin (Ig)G (20.3% in women), and 5.1% showed anti-SARS-CoV2 IgM. In contrast, in the subgroup of women of fertile age (15–44 years old), these percentages were 17.1 and 4.5%, respectively.

Since the onset of the disease, one of the major concerns has been the severe risk faced by health care providers, and many different strategies have been implemented to avoid their massive infection. Obstetric outpatient service were high-risk places for exposure since long periods of close contact with the patients are usually required to perform antenatal scans and examinations. Therefore, obstetricians and midwives constituted a particular risk group.

This study aimed to describe the clinical implementation of a preventive protocol in terms of first, re-organization of appointments and hospital visits, and second, the infection rate among health care workers in a hospital obstetric outpatient service during the first peak of the COVID-19 pandemic.

Materials and methods

Study design and population

This is a descriptive analysis of the antenatal care provided in the obstetric outpatient service at Hospital Universitario de Torrejón, from March 19th to May 22nd, 2020, during the peak of the first wave of the pandemic in Madrid, Spain. The number of face-to-face appointments, telephone appointments, and COVID-19 diagnoses in pregnant women during that period were analyzed.

Additionally, a universal screening by serological analysis of anti-SARS-CoV2 IgM and IgG was performed on all hospital health workers at the end of May 2020. The number of obstetricians and nurses attending pregnant women at the outpatient service who were diagnosed by rRT-PCR-SARS-CoV2 or presented IgG or IgM anti-SARS-CoV2 at the end of May was recorded.

Intervention

When the first patient was diagnosed with COVID-19 infection at the hospital on February 24th, 2020, obstetricians assisting pregnant women began to develop a preventive protocol to ensure safety among health care workers and patients. The first protocol version was implemented on March 7th, and the only change applied was related to contact measures. All personnel attending pregnant women in consultations were requested to wear a surgical mask during the entire examination and to take special care in hand hygiene before and after examining each pregnant woman. In addition, it was recommended that a pregnant woman with respiratory symptoms should wear a surgical mask. Since March 14th, the professionals' face mask was changed to an FFP2 (filtering face pieces type 2) if available, and a double pre-consultation triage was implemented. In addition, the government made strict confinement of the population mandatory, so an entire new prenatal care protocol was established to minimize hospital visits and ensure

TABLE 1 Triage questionnaire.

- Have you had or have a fever or feverish sensation in the last week?
- Have you had or have a persistent cough in the last week?
- Have you had or have muscle pain in the last week?
- Have you had or have general discomfort in the last week?
- Does food taste nothing or have you lost the smell?
- Are you or have you been positive for COVID-19? If the answer is yes:
  - Have been passed >5 weeks since the diagnosis?
- Do you live or are you in close contact with a patient with COVID-19?

pregnancy care on March 19th. The description of the protocol was as follows:

Accompaniment

No companion was allowed in the examination room. The access to the hospital was only limited to the strict necessarily.

Triage from the admission department

All pregnant women who required an appointment at the unit received a telephone text message 2–4 days before the visit confirming whether the consultation was face-to-face or by telephone. They were also advised to contact the hospital if they had any symptoms related to the COVID-19 disease. Furthermore, all pregnant women scheduled for a face-to-face appointment were contacted 24 h before their visit to conduct a 7-questions interview concerning COVID-19 (Table 1). If any question was answered positively, the pregnant woman was asked to stay home and wait for the health professional to call her the next day.

Triage upon arrival at consultations

Before entering the outpatient service, a receptionist was performing the same questionnaire (Table 1) again. If all the items in the survey were negative, she was allowed to enter the examination room. The patient was provided with a surgical mask, hand washing facilities, and latex gloves, and she was instructed to keep the security distance (2 empty chairs) in the waiting area.

If any item was positive, she was considered a possible SARS-CoV2 case, and the obstetrician was informed. The procedure was then as follows:

- If the symptoms were severe (fever higher than 37.5 degrees, dyspnea, severe cough, general malaise), the obstetrician referred the patient to the emergency department for clinical assessment without further evaluation, and subsequent management was assessed later.
- If the symptoms were mild, the patient was either rescheduled or assessed with complete PPE if that was a non-delayable appointment (Table 2).

TABLE 2 Rescheduling algorithm for patients screening or testing positive for COVID-19.

Appointment missed	Action
First-trimester appointment	Rescheduled for US scan 5 weeks later. - Normal ultrasound: cell-free DNA test for aneuploidy screening. - Abnormal* ultrasound: invasive testing.
20–22 weeks anomaly scan	- Fetal anatomy examination by US performed in the first trimester: rescheduled 14 days later. - No fetal anatomy examination by US in the first trimester: anomaly scan rescheduled before 22^{+3} weeks (with PPE).
35–37 growth scan or any other clinically guided scan	Rescheduled 3 weeks later.
Fetal monitoring at 40–41 weeks	- rRT-PCR-SARS-CoV-2 test. - Telephone appointment: ○ General well-being, fetal movements, and presence of eventualities inquiry. ○ Delivery plan. - Labor induction will be scheduled with all the security measures established if positive rRT-PCR-SARS-COV2.
Invasive test	- Suspected cases: delay the procedure 3 weeks. - Confirmed cases: delay 4 weeks after acute illness. - The procedure cannot be delayed: ○ Isolated room ○ Health workers with PPE ○ The minimum needed personnel The risk-benefit was individually assessed.

*Abnormal ultrasound refers to major fetal defects such as holoprosencephaly, omphalocele, megacystis, etc.
US, ultrasound; PPE, personal protection equipment.

Follow-up of non-complicated pregnancies

Appointments at the hospital were limited to the strictly necessary. All the appointments were divided into face-to-face and telephone consultations. Those appointments where complementary tests were not required (ultrasound, physical examination, etc.) were carried out by telephone (Table 3). Complementary tests were always performed simultaneously (ultrasound scans, blood tests), and telephone calls were arranged for results if needed.

TABLE 3 Pregnancy monitoring scheme*.

Face-to-face	Telephone
- Symptoms derived ultrasounds. - First-trimester scan and aneuploidy screening (including blood sampling). - 20–22 weeks anomaly scan. - Second-trimester blood sampling (+/- anti-D immunoglobulin administration). - Routine growth scan at 35–37 weeks, Streptococcus B-Agalactiae screening, and blood sampling. - Fetal cardiotocography monitoring at postdates.	- Results from blood analyses or other prenatal tests (including aneuploidy screening). - 30–32 weeks midwife appointment. - 38–39 weeks midwife appointment.

*High-risk cases were managed individually.

TABLE 4 Preparation and cleaning of obstetrics room.

Deep cleaning

Ultrasound rooms should be cleaned thoroughly (double cleaning) each morning before the arrival of the patients and each evening at the end of the session using CDC-approved cleaners. This cleaning includes:

- Computer, keyboard and mouse, printer, door handles, stretcher, chairs, armchairs, ultrasound machines, light switches.
- Tensiometer and weight scale.
- Fetal monitors.

Ultrasound transducers

- The use of ultrasound transducers was limited to only multi-frequency transabdominal ones (one per machine).
  - If other transducers were needed (i.e., transvaginal probe): double cleaning should be carried out before storing again.
- The transducers in use will be covered with a protector (cover, glove) and will be cleaned with CDC-approved cleaners between patients.

Intermediate cleaning (before the next patient was called into the room)

- Hand wash with soap and warm water or with an antimicrobial cleaner for at least 20 s.
- Ultrasound transducers and cables disinfection
- Patient's bed and chair disinfection
- Change disposable gloves (latex-free, polyurethane)
- Two pairs of gloves when handling dirty clothes or sheets. Hand wash for at least 20 seconds afterward.

Ultrasound scans in suspected or confirmed COVID-19 cases

Whenever possible, the obstetric visit was delayed until 14 days after the end of the respiratory symptoms or, at least, the resolution of the active disease (Table 2). If the examination could not be delayed, it was carried out at the end of the session, limiting the number of health workers and the examination time and wearing full PPE (FFP2 or FFP3 masks if available, protected by surgical mask or screen, waterproof gown, double glove, and glasses). The subsequent disinfection of the scanning room was complete, including the ultrasound machine (Table 4).

Results

From March 19th to May 22nd, 2020, 1842 obstetric appointments were scheduled (Figure 1). One thousand four hundred ten (76.5%) were face-to-face appointments and 23.4% were telephone appointments (432 patients). Of the telephone appointments, 417 (96.5%) were telephone calls according to clinical protocol, 7 (1.6%) corresponded to patients that had been advised to stay home as they had a positive item at the first triage, and 8 (1.9%) corresponded to patients who communicated that they were COVID-19 confirmed cases at the first triage. Of the face-to-face scheduled appointments, 137 (9.7%) patients did not attend because they feared getting infected; they were contacted by phone, and a follow-up was arranged. Six (0.5%) women contacted the hospital to report COVID-19 symptoms, and they were rescheduled according to protocol. 44 (3.1%) did not attend and did not answer phone calls, so they were lost to follow up. 1223 (86.7%) attended face-to-face appointments and had a second triage. 44 (3.6%) screened positive, of whom 32 (72.7%) were rescheduled, and 12 (27.3%) were seen on the day.

In 43 (97.7%) of the screened positive pregnant women, an rRT-PCR-SARS-CoV2 test was performed, and 2 of them tested positive. Additionally, 67 screened negative patients at first and second triages, had a planned cesarean section or induction of labor within the study period, and were tested by rRT-PCR-SARS-CoV2 on the day of the appointment according to protocol; none of them tested positive.

In this period, no symptoms of COVID-19 were reported among health care professionals in the outpatient obstetric service, where 12 doctors, 7 nurses/auxiliary nurses, and 3 receptionists worked daily. Anti-SARS-CoV2 IgG and IgM antibodies were only detected in one nurse following universal health care workers' screening, performed at the end of the study period. However, the onset of her symptoms occurred before she started to work in our unit.

Discussion

Main findings

The main findings of this study were that, first, a preventive protocol can be quickly implemented following an emergent disease outbreak, but this protocol must be

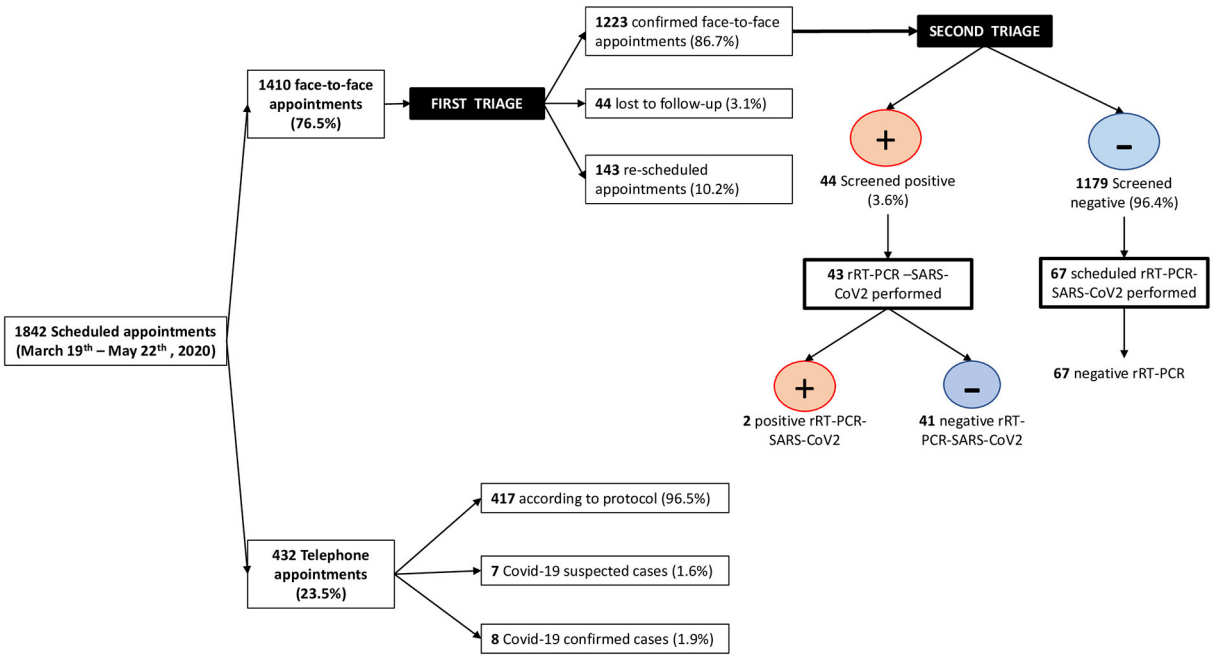

FIGURE 1
Patients diagram flow.

evolving to incorporate new scientific knowledge; second, the implementation of this new protocol in our obstetric outpatient service transformed about 23% of our face-to-face appointments into telephone calls; and third, as a result of the implemented preventive measures, only one health care worker was infected during the first peak of the pandemic.

Research in context

In Madrid region, official sources pointed out that 11,660 health care professionals, including 3,464 were doctors and 5,789 were nurses or auxiliary nurses, had tested positive by rRT-PCR-SARS-CoV2 (9.772 at hospitals and 1.678 at primary care), and 19 of them had died due to COVID-19 disease by June 15th, 2020 (7).

Two seroprevalence studies carried out at two major referral hospitals in Madrid reported that about 21% and 17% of their health care workers presented anti-SARS-CoV2 antibodies by May and June 2020, respectively (8, 9). The Spanish Ministry of Health sponsored a national seroprevalence study reporting an overall prevalence of antibodies in Spain of 4.6% and in Madrid region in particular of 11.5% in May 2020 (10), confirming that, similarly to other studies, the infection was more prevalent between health care professionals than in the general population (9, 11, 12). However, this was not translated into a higher proportion of infected professionals in our department; our only positive result corresponded to a nurse that was initially working in the emergency department, who presented with symptoms and, after recovery, was transferred to our unit.

Torrejón de Ardoz was a hotspot during the first pandemic's peak and one of the first places where people suffered from COVID-19 disease in Spain. The seroprevalence study carried out in the city showed that about 20% of the population presented anti-SARS-CoV-2 IgG, and about 23% presented any kind of antibody (IgM and IgG) by June 5th, 2020 (6). This study pointed out how severely affected this city was in comparison to the rest of Madrid region. If about 17% of the women of fertile age in the city were exposed to the virus during the study period, we could assume that about 300 (17% of the 1,842 appointments) of the scheduled women at our obstetric service were infected including about 200 (17% of 1,223) who had face-to-face appointments. However, we only identified 44 women as high risk of having COVID-19 in our triage system, and only two had a positive result from the rRT-PCR-SARS-CoV2 for the SARS-CoV2 test. A likely explanation for this lower rate is that first, asymptomatic patients were not tested, and second, most women with symptoms stayed at home. These results highlight the beneficial effect of the early implementation of our preventive protocol. Unfortunately, many other studies have reported delayed actions and much higher rates of infected professionals (4).

Strengths and limitations

One of the biggest concerns for implementing such a protocol was the decreased quality of care and the subsequent worsening in the perinatal outcomes. However, since that was not the aim of our study, we are not reporting on this. Another limitation relates to the lack of universal testing in pregnant women, which would have been crucial for assessing the usefulness of our protocol in terms of patient safety. However, antibody testing is not a definitive test to determine disease since false positives and negatives may occur.

However, our study presents some significant strengths. First, it is a complete cohort where all scheduled appointments were carefully reviewed, allowing accurate reporting on the protocol consequences in our obstetric service. Second, although not a diagnostic test, all health care professionals at our institution received universal screening for anti-SARS-CoV2 antibodies, which provides invaluable information regarding contagious rate.

Clinical implications

Since the early implementation of preventive measures was crucial to prevent the spread of the disease, our study has demonstrated the feasibility of rapidly rearranging all appointments within a unit by joining efforts from several professionals (doctors, nurses, and other health workers). Therefore, if a new infection outbreak happened in the future, we would be able to protect health workers and our pregnant population.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization, methodology, and writing—original draft: MR, IF-B, and MG. Data curation and formal analysis: MR and IF-B. Investigation and writing—review and editing: MR, IF-B, EF, MA, BS, and MG. Project administration: MG and BS. Supervision: IF-B, MG, and BS. Validation: MR, IF-B, MG, and BS. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. *WHO Coronavirus (COVID-19) Dashboard*. Available online at: https://covid19.who.int (accessed March 18, 2022).

2. Jamieson DJ, Steinberg JP, Martinello RA, Perl TM, Rasmussen SA. Obstetricians on the coronavirus disease 2019 (COVID-19) front lines and the confusing world of personal protective equipment. *Obstet Gynecol*. (2020) 135:1257–63. doi: 10.1097/AOG.0000000000003919

3. Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Schünemann HJ, et al. Physical distancing, face masks, and eye protection to

prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. *Lancet Lond Engl.* (2020) 395:1973–87. doi: 10.1016/S0140-6736(20)31142-9

4. Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. *N Engl J Med*. (2020) 382:2081–90. doi: 10.1056/NEJMoa2008457

5. Wei WE, Li Z, Chiew CJ, Yong SE, Toh MP, Lee VJ. Presymptomatic transmission of SARS-CoV-2 - Singapore, January 23-March 16, 2020. *MMWR Morb Mortal Wkly Rep*. (2020) 69:411–5. doi: 10.15585/mmwr.mm6914e1

6. El Estudio de Seroprevalencia de Torrejón de Ardoz revela una prevalencia de anticuerpos IgG del 20,18% | Ayuntamiento de Torrejon. Available online at: https://www.ayto-torrejon.es/noticia/nota-de-prensa/el-estudio-de-seroprevalencia-de-torrejon-de-ardoz-revela-una-prevalencia-de (accessed March 18, 2022).

7. Actualizacion_137_COVID-19.pdf. Available online at: https://www.sanidad.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/Actualizacion_137_COVID-19.pdf (accessed February 10, 2022).

8. El Marañón finaliza el estudio más grande de Europa sobre seroprevalencia de COVID-19. *Hospital General Universitario Gregorio Marañón*. Available online at: https://www.comunidad.madrid/hospital/gregoriomaranon/noticia/maranon-finaliza-estudio-grande-europa-seroprevalencia-covid-19 (accessed July 5, 2020).

9. Cantero M, Millán-Pérez R, Muñez E, Gómez-Lozano N, Anel-Pedroche J, Parra LM, et al. SARS-CoV-2 seroprevalence among all healthcare workers in a tertiary hospital in Spain. *Infect Dis Lond Engl*. (2022) 54:8–15. doi: 10.1080/23744235.2021.1963468

10. Pollán M, Pérez-Gómez B, Pastor-Barriuso R, Oteo J, Hernán MA, Pérez-Olmeda M, et al. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. *Lancet Lond Engl*. (2020) 396:535–44. doi: 10.1016/S0140-6736(20)32266-2

11. Cabezón-Gutiérrez L, Custodio-Cabello S, Palka-Kotlowska M, Oliveros-Acebes E, García-Navarro MJ, Khosravi-Shahi P. Seroprevalence of SARS-CoV-2-specific antibodies in cancer outpatients in Madrid (Spain): A single center, prospective, cohort study and a review of available data. *Cancer Treat Rev*. (2020) 90:102102. doi: 10.1016/j.ctrv.2020.102102

12. Escribano Ceruelo E, Espinel Ruíz MA, Ortega López-Peláez M, Fernández Garoz B, Asensio Antón J, Jiménez García R. Seroprevalencia de infección frente a SARS-CoV-2 en trabajadores de la salud en un hospital monográfico pediátrico en Madrid (España). *Enferm Infecc Microbiol Clin*. (2021) 40:326–9. doi: 10.1016/j.eimc.2020.12.011

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Application of modified subtotal resection of adenomyosis combined with LNG-IUS and GnRH-a sequential therapy in severe adenomyosis: A case series

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Background and Objective: Adenomyosis focus resection has always been the main surgical method for patients with uterine preservation, but its curative effect and surgical method are still controversial. We improved this method on the basis of the "double-flap method" and combined it with the levonorgestrel intrauterine delivery system (LNG-IUS) and gonadotropin-releasing hormone agonist (GnRH-a) sequential treatment to determine the clinical effect and feasibility of this scheme in the treatment of severe adenomyosis.

Methods: This is a retrospective review. A total of 64 patients with severe adenomyosis were treated in the Department of Gynecology of Changzhou Second People's Hospital, which is affiliated to Nanjing Medical University, from December 2017 to September 2021. The transabdominal approach and laparoscopic approach were adopted for the purposes of treatment in this study. Hence, the patients were subdivided into the transabdominal approach subgroup and the laparoscopic approach subgroup. The hemoglobin, visual analog score (VAS) score, menstruation score, and other indices of each patient before and after treatment were observed, recorded, and analyzed.

Results: All 64 patients underwent the operation successfully. After the completion of sequential treatment, the CA125 decreased significantly 1 month after the operation, the average uterine volume significantly reduced, the hemoglobin value increased to a certain extent 3 months after the operation, and the menstrual score and dysmenorrhea during the first menstruation were significantly lower than they were before the operation. After the treatment, the therapeutic results of the transabdominal approach subgroup and endoscopic approach subgroup were compared on the basis of the observed indices, and no significant difference was observed ($P > 0.05$). Only one patient had a downward movement of the LNG-IUS, and

the vaginal ultrasound showed that the upper end of the LNG-IUS was approximately 1.5 cm from the bottom of the uterine cavity. The average follow-up period was 24.02 ± 11.77 months, and no lesion progression was found in any patients.

Conclusion: For patients suffering from severe adenomyosis who have no pregnancy plans and require uterine preservation, transabdominal or laparoscopic subtotal resection of the focus of adenomyosis, combined with the LNG-IUS + GnRH-a sequential treatment, may be a safe and effective alternative when conservative treatments such as drugs fail.

KEYWORDS

severe adenomyosis, subtotal resection of adenomyosis, levonorgestrel intrauterine delivery system, gonadotropin-releasing hormone agonist, dysmenorrhea

Introduction

Adenomyosis (AM) is a disease caused by the invasion of the endometrium into the myometrium. It is an estrogen-dependent disease (1). The clinical symptoms are progressive secondary dysmenorrhea, increased menstruation, and enlarged uterine volume, and some patients may also suffer from infertility (2). It is reported that the prevalence rate is 5%–70% (3). The radical treatment of AM is total hysterectomy, which will cause impacts on women's physical and mental conditions and life after hysterectomy to varying degrees, so it is crucial to preserve the uterus. The most commonly used operation to preserve the uterus is local focus resection. However, the high recurrence in the long term and the improvement in clinical symptoms after focal resection are worthy of attention (4–6).

Many drugs can be used to treat AM, but they cannot cure the disease, and it is easy for the disease to relapse and progress after drug withdrawal (1). Related clinical studies have confirmed that both the levonorgestrel intrauterine delivery system (LNG-IUS) and the gonadotropin-releasing hormone agonist (GnRH-a) have certain efficacy in the treatment of AM, but they both have their own adverse reactions (7–11). Because of the high recurrence and unsatisfactory clinical effect of a single treatment approach for AM, clinicians have begun to adopt combined interventions such as high-intensity focused ultrasound (HIFU) combined with the LNG-IUS (12), local focus resection with the LNG-IUS (13), and HIFU with GnRH-a (14). However, with the increase in follow-up time, the recurrence rate also increases (14, 15–17).

We found that the "double-flap method" was more effective in the operation of preserving the uterus (18–20), but this method is suitable for patients with pregnancy intention after an operation, so a part of the myometrium will still be preserved. For patients who still have a strong desire to retain the uterus after the failure of drug treatment, this study improves the surgical method to reduce the recurrence among patients after treatment. During the operation, the focus of adenomyosis is resected as much as possible, and a part of the uterine cavity is remodeled to consolidate the curative effect and reduce the recurrence by sequential treatment with the LNG-IUS and GnRH-a after the operation. The purpose of this study was to preliminarily determine the efficacy of postoperative combined drugs in the treatment of severe adenomyosis.

Data and methods

General data

A total of 64 patients with severe adenomyosis treated in the Department of Gynecology, the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, from December 2017 to September 2021 were selected. The patients suffered from severe adenomyosis as determined by auxiliary examination, and the postoperative pathological results supported the diagnosis of adenomyosis. According to the guidelines of the International Federation of Obstetrics and Gynecology, the extent of the lesion was determined. If the uterus volume affected by the lesion is <25%, it is called mild, 25%–50% is called moderate, and >50% is called severe (21).

(1) Case inclusion criteria: (1) The patient had a strong desire to preserve the uterus. (2) The conservative treatment with drugs failed. (3) The patient had no pregnancy plan. (4) The patient voluntarily accepted this procedure and signed the informed consent form.

(2) Case exclusion criteria: (1) The patient suffered from primary dysmenorrhea. (2) The patient had a malignant tumor of the reproductive system. (3) The patient was unwilling to accept GnRH-a treatment or was lost during follow-up.

Surgical steps

Transabdominal surgery group: Make a median longitudinal incision, pull the uterus out of the pelvic cavity, wrap it with a cotton pad soaked in normal saline, and determine the location of the lesion by touching the uterus.

Inject diluted pituitrin into the normal myometrium near the focal tissue (with close attention paid to blood pressure fluctuations) (Figure 1A). If the uterine leiomyoma is to be removed at the same time (Figure 1B), make a longitudinal incision with an electrotome at the location of the focus of adenomyosis to reach the uterine cavity (Figure 1C). Resect the focal lesion from the seromuscular layer separately on the myometrium flaps (Figure 1D), and retain approximately 5 mm–10 mm of the flaps for suture (Figure 1E). The lesions around the uterine cavity should be removed as clean as possible to avoid postoperative recurrence (Figures 1F,G). Finally, the endometrium and the left and right muscle layers within 5 mm were preserved as the "uterine center" (Figure 1H). Use the LNG-IUS placed during the operation as the "ruler" to reshape the uterine cavity at a depth of approximately 7–8 cm (Figure 1I). Suture the uterine cavity (Figure 1J). Align both sides of the sarcoplasmic layers and remove the extra length of these layers (Figure 1K). Suture the seromuscular layers on both sides with the "Baseball Stitching Technique" to complete the uterine plastic surgery (Figures 1L–N).

Laparoscopic surgery group: The procedure is basically the same as that of the transabdominal group. Before the operation, the location and scope of the focus were evaluated by gynecological examination, a transvaginal ultrasound, and MRI. During the operation, the focus can be resected by a rational use of energy instruments such as an ultrasonic scalpel. The specimen needs to be packed in a specimen bag and then slowly removed from the puncture hole around 1.5 cm in diameter. The "tumor-free principle" should be observed during specimen collection. Polyglactin 910: synthetic absorbable surgical suture (Model: 2-0) was used to close the uterine cavity. Polyglactin 910: synthetic absorbable surgical suture (Model: 1-0) was used to close the seromuscular layer.

After completion of either the transabdominal or laparoscopic surgery, wash the pelvic and abdominal cavity with warm saline to reduce the possibility of endometrial implantation, close the abdominal cavity layer by layer, and place drainage tubes in the pelvic cavity when necessary.

Postoperative management

No special postoperative treatment was required for the patients. After discharge, GnRH-a injection was given on the first day of menstruation. If the menstruation did not occur due to the placement of the LNG-IUS, the first injection can be administered according to the previous menstrual cycle. Administer three to six injections according to the patient's age, disease condition, and other factors, with an interval of 28 days and regular follow-up (a total of 27 patients received 6 injections of GnRH-a, and 37 patients received 3 injections of GnRH-a).

Observed indices

The indices before, during, and after the operation were recorded to evaluate the therapeutic effect. The indices to be observed include the following: (1) operation time and intraoperative blood loss; (2) hemoglobin value at preoperative and 3 months postoperative; (3) CA125 at preoperative and 1 month postoperative; (4) dysmenorrhea score at preoperative and the first menstrual period after GnRH-a injection; dysmenorrhea score calculated by using visual analog score (VAS) where the pain scale was subdivided into 10 grades; "no pain" was indicated on the left side of the scale, and "the maximum pain you could imagine" was designated on the right side of the scale; (5) menstrual volume score at the preoperative and the first menstrual period after GnRH-a injection, scored with the pictorial blood loss assessment chart (PBAC) (22); (6) uterine volume estimated by transvaginal ultrasound at preoperative and 3 months postoperative where the uterus size is estimated using the elliptical volume formula, which is $0.52 \times \text{length} \times \text{thickness} \times \text{width}$ of the uterus measured with transvaginal ultrasound (23); (7) regular follow-up with transvaginal ultrasound to check for any progress of AM lesions and displacement of the LNG-IUS.

Statistical analysis

The data from this study were statistically analyzed using the SPSS26.0 statistical software. The results were expressed as the mean value ± standard deviation ($\bar{x} \pm s$), though the measured variable values were not normally distributed. Then, the *t*-test was performed on the observed indices of the 64 patients before and after the operation. If $P < 0.05$, it means the difference was statistically significant.

Results

Demographic details

A total of 64 patients received and completed this combined treatment, and the baseline characteristics of all these patients are given in Table 1. The average age of the 64 patients was 42.20 ± 5.39 years. The average duration of clinical symptoms such as dysmenorrhea and menorrhagia was 5.02 ± 4.72 years, and the average BMI was 24.02 ± 3.59 kg/m^2. Among them, 36 patients had endometriosis and 18 patients had leiomyoma of the uterus, 9 patients had both, while 19 patients had only adenomyosis without uterine leiomyoma or endometriosis.

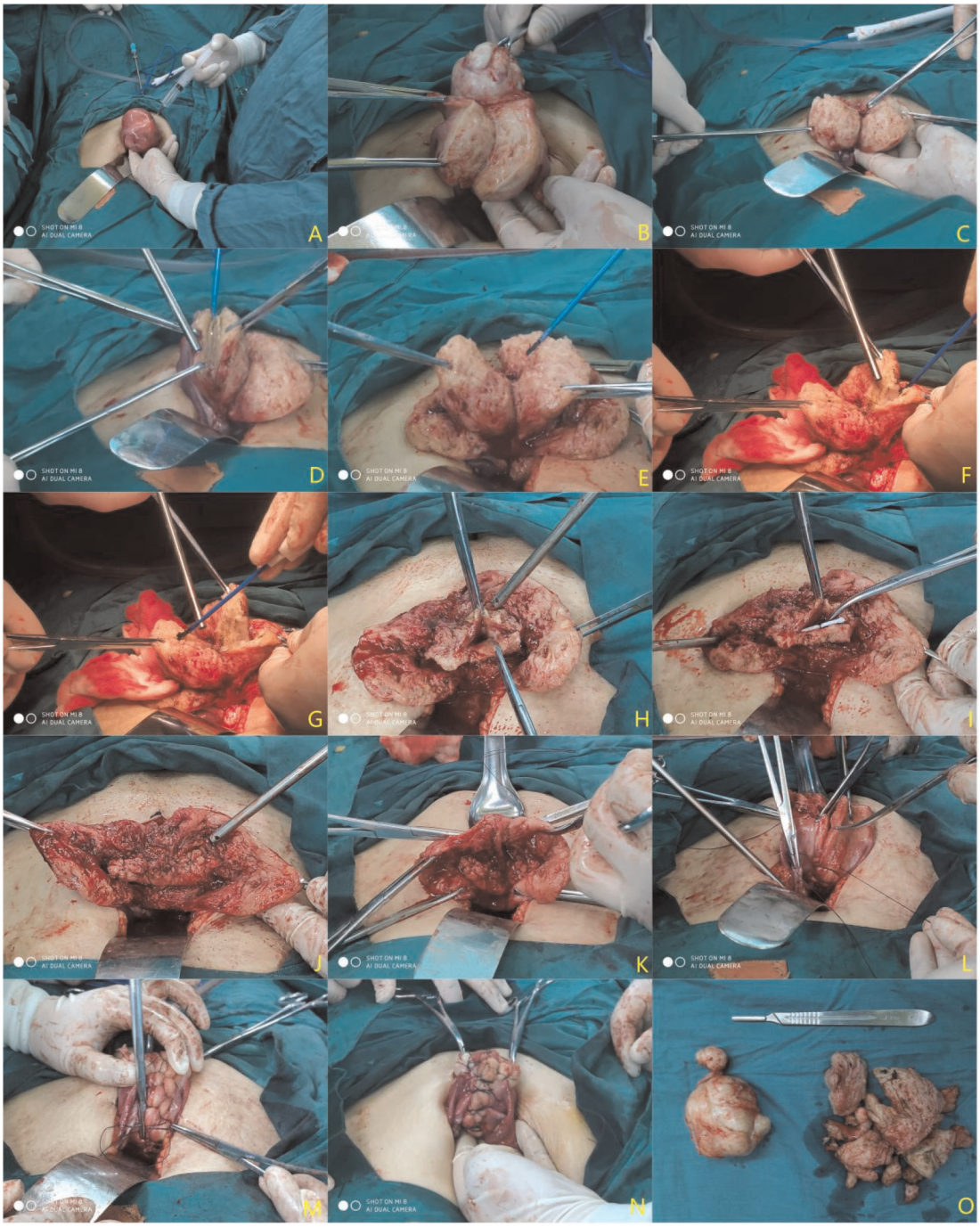

FIGURE 1
Procedure diagram of a transabdominal operation. (A) Inject diluted pituitrin; (B) remove uterine fibroids; (C) make a longitudinal incision of adenomyosis lesions to reach the uterine cavity; (D) Resect the lesion as much as possible (preserving approximately 0.5–1 cm of the plasmomuscular layer flaps); (E) treat the contralateral lesions with the same method; (F) gradually subtract the lesion to the uterine cavity and excise a part of the uterine cavity to reduce the uterine volume; (G) treat the contralateral lesions with the same method; (H) remodel the myometrium; (I) place the LNG-IUS (Manchester ring) and reshape the depth of the uterine cavity again based on the LNG-IUS length; (J) Mattress-suture the uterine cavity continuously; (K) align the sarcoplasmic layers and reduce the extra length; (L,M) suture the bilateral seromuscular layers with the "baseball stitching technique"; (N) repair the sutured uterus; (O) uterine fibroids and adenomyosis specimens resected during the operation.

TABLE 1 Basic information on 64 patients.

Characteristics	Total ($n = 64$)
Mean age ± SD, years	42.20 ± 5.39
Average time with clinical symptoms ± SD, years	5.02 ± 4.72
Preoperative BMI ± SD, kg/m^2	24.02 ± 3.59
Fertility history, *n* (%)	
$n = 0$	2 (3)
$n = 1$	41 (64)
$n \geq 2$	21 (33)
Abortion history, *n* (%)	
$n = 0$	14 (22)
$n = 1$	13 (20)
$n \geq 2$	37 (58)
Complications, *n* (%)	
Leiomyoma	18 (28)
Endometriosis	36 (56)
Leiomyoma and endometriosis	9 (14)
No leiomyoma and endometriosis	19 (30)

TABLE 2 Changes in observed indices pre-treatment and post-treatment of 64 patients ($\bar{x} \pm s$).

Observed indices	Pre-treatment	Post-treatment	*P*
Hemoglobin value (g/L)	104.77 ± 19.41 (56–144)	118.08 ± 9.67 (105–142)	.000
CA125 (U/ml)	92.64 ± 104.45 (9.38–245.8)	14.18 ± 8.95 (4.58–45.36)	.000
Dysmenorrhea score (points)	8.13 ± 0.75 (7–9)	1.36 ± 0.65 (0–3)	.000
Menstrual volume score (points)	131.42 ± 13.25 (106–166)	22.52 ± 9.18 (3–48)	.000
Uterine volume (cm^3)	173.61 ± 76.49 (76.58–340.70)	44.98 ± 16.97 (16.47–82.19)	.000

Hemoglobin value is for 3 months post-treatment; CA125 is for 1-month post-treatment; dysmenorrhea score and menstrual volume score are for the first menstrual period after GnRH-a injection; uterine volume is for 3 months post-treatment.

Pre- and post-treatment outcomes

(1) The hemoglobin value remeasured 3 months after the operation increased to a certain extent compared with that before the operation, and the difference was statistically significant ($P = 0.000$) (see Table 2). (2) A total of 50 patients out of the 64 patients before the operation tested positive for CA125. The remeasured CA125 1 month after the operation was lower than that before the operation, and the difference was statistically significant ($P = 0.000$) (see Table 2). (3) The degree of dysmenorrhea after the completion of GnRH-a sequential treatment was lower than that before the operation, and the difference was statistically significant ($P = 0.000$) (see Table 2). (4) The menstrual volume score after completion of GnRH-a sequential treatment was lower than that before the operation, and the difference was statistically significant ($P = 0.000$) (see Table 2). (5) The estimated average uterine volume re-examined 3 months after completion of the sequential treatment was smaller than that before the operation, and the difference was statistically significant ($P = 0.000$) (see Table 2). (6) During the postoperative follow-up, only one patient developed an intrauterine device migration, and the vaginal ultrasound showed that the upper end of the birth control ring was approximately 1.5 cm away from the bottom of the uterine cavity. The average follow-up lasted 24.02 ± 11.77 months, and no disease progression was observed.

Operation time and blood loss

None of the 64 patients had any complications during or after the operation. There was no significant difference in the operation time between the two subgroups ($P > 0.05$). There was a statistically significant difference in intraoperative blood loss between the two subgroups ($P = 0.000$) (see Table 3).

Pre- and post-treatment outcomes of the two subgroups

After the treatment was completed, the abdominal approach treatment of this scheme was completed, and various observation indices improved after treatment ($P = 0.000$). The laparoscopic approach treatment of this scheme was completed, and the observation indices also improved after treatment ($P = 0.000$). The differences in the observed indices between the two subgroups were not statistically significant ($P > 0.05$) (see Table 4).

Discussion

According to the data in Table 1, the average age of our 64 patients is 42.20 ± 5.39 years. This is similar to the fact that most

TABLE 3 Operation time and intraoperative blood loss of subgroups ($\bar{x} \pm s$).

Operation-related information	Subgroups		*P*
	Transabdominal surgery group ($n = 31$)	Laparoscopic group ($n = 33$)	
Operation time (min)	143.71 ± 32.51 (75–230)	134.55 ± 46.10 (70–260)	.360
Intraoperative blood loss (ml)	198.06 ± 145.93 (30–500)	54.85 ± 43.02 (20–200)	.000

TABLE 4 Changes in observed indices pre-treatment and post-treatment of a transabdominal surgery group and a laparoscopic surgery group ($\bar{x} \pm s$).

	Pre-treatment		Post-treatment		*P*	*P**
	Transabdominal surgery group ($n = 31$)	Laparoscopic surgery group ($n = 33$)	Transabdominal surgery group ($n = 31$)	Laparoscopic surgery group ($n = 33$)		
Hemoglobin value (g/L)	99.71 ± 18.40 (72–138)	109.52 ± 19.41 (79–144)	117.13 ± 10.38 (102–142)	118.97 ± 9.01 (102–135)	.000	.000
CA125 (U/ml)	111.55 ± 133.96 (11.71–749.90)	74.87 ± 63.10 (17.38–249.80)	12.54 ± 8.53 (4.58–45.36)	15.71 ± 9.18 (7.36–45.35)	.000	.000
Dysmenorrhea score (points)	8.39 ± 0.67 (7–9)	7.68 ± 1.38 (7–9)	1.23 ± 0.67 (0–2)	1.48 ± 0.62 (1–3)	.000	.000
Menstrual volume score (points)	130.29 ± 12.94 (105–162)	129.09 ± 24.06 (106–166)	21.87 ± 7.50 (3–31)	22.76 ± 10.50 (3–48)	.000	.000
Uterine volume (cm^3)	198.80 ± 80.64 (87.55–340.70)	147.20 ± 63.80 (76.58–335.95)	38.83 ± 15.14 (16.47–73.36)	49.51 ± 17.08 (14.71–80.70)	.000	.000

Hemoglobin value is for 3 months post-treatment; CA125 is for 1-month post-treatment; dysmenorrhea score and menstrual volume score are for the first menstrual period after GnRH-a injection; uterine volume is for 3 months post-treatment. *P*: Statistical analysis of a transabdominal surgery group pre-treatment and post-treatment.

**P*: Statistical analysis of a laparoscopic surgery group pre-treatment and post-treatment.

of the reported patients are over 40 years old, and the age of onset is getting younger (24–26). The average BMI value is 24.02 ± 3.59 kg/m^2, which is a bit high, and it has been reported that an increase in BMI values increases the risk of uterine leiomyoma (27, 28), but whether AM is associated with patient weight gain may be an issue worth exploring. The data indicate that two patients did not have children, one of whom had two miscarriages, and the other had no history of abortion. A total of 62 (97%) patients had a history of childbearing, and 50 (78%) had a history of miscarriage, which was also related to the fact that fertility and abortion may be the causes of AM (29). In order to reduce AM incidence, we should adopt good contraceptive measures to reduce unnecessary abortions. The data indicated that a total of 18 (28%) patients were complicated with leiomyoma, which was similar to the reported 15%–57% (30), and 36 (56%) patients were complicated with endometriosis. Some studies have suggested that the incidence of adenomyosis with deep infiltrating endometriosis (DIE) is within 6.8%–25.4% (31). The reason for this may be related to our careful exploration of pelvic endometriosis, especially the occurrence of DIE.

Hysterectomy is still the main radical method for patients with severe adenomyosis. However, the uterus is a unique organ for women, especially in China where hysterectomy is not accepted by most patients, and this mindset is also observed in Japan (32). With the progress and improvement of conservative surgical methods in recent years, the double-flap method and the triple-flap method can not only preserve the uterus but also improve the short-term effects of dysmenorrhea, excessive menstruation, and infertility (19, 20). However, the boundary between the focus of AM and normal myometrium is not clear, and the focus cannot be completely removed during the operation (33). The residual small lesions may grow slowly and recur (34, 35). A 2-year follow-up study showed that the recurrence rate of patients with adenomyosis treated with GnRH-a was 28.1%, which was lower than the 49% for treatment with surgery alone (36). The LNG-IUS can release progesterone directly into the uterine cavity. In recent years, many studies have confirmed that the LNG-IUS can relieve symptoms such as dysmenorrhea and menorrhagia in patients with AM and reduce the level of CA125 to a certain extent (9, 23, 37). However, some studies have found that the slippage rate among AM patients with a larger uterus is as high as 37.5% after the implantation of the LNG-IUS (38). It can be seen that the therapeutic effect of the LNG-IUS on AM patients with a larger uterine volume is not as good as that of AM patients with a smaller uterine volume.

We improved the method of operation by cutting the uterus vertically to the uterine cavity, eradicating AM lesions as much as possible, and reducing the uterine cavity according to the depth of the LNG-IUS. The process of removing the focus is to change the adenomyosis from a larger volume to a smaller one. The postoperative combination with the GnRH-a therapy can reduce the recurrence rate of AM to a certain extent (36). The LNG-IUS has a better therapeutic effect on AM patients with a smaller uterine volume (9, 23, 37). The therapeutic effect of this regimen may be similar to that of the LNG-IUS in the treatment of small-volume adenomyosis. During the postoperative follow-up, only one patient had a downward displacement of the LNG-IUS, as observed with transvaginal ultrasound (transvaginal ultrasound showed that the upper end of the LNG-IUS was approximately 1.5 cm from the bottom of the uterine cavity). The LNG-IUS of the other patients was normal. During the follow-up, it is suggested that the incidence of LNG-IUS displacement is temporarily much lower than that suggested in other reports (39–42). We are of the opinion that the decrease in the LNG-IUS displacement may be related to the following: intraoperative remodeling of the uterine cavity to better align the LNG-IUS with the shape of the uterine cavity; and the postoperative injection of

GnRH-a, which can reduce the uterine volume and uterine cavity again, reducing the probability of spondylolisthesis. However, it is necessary to increase the sample size and evaluate the change in the LNG-IUS slippage rate with time after the placement of the LNG-IUS. The effective time of the LNG-IUS is 5 years. If the patient is still menopausal after 5 years, a new LNG-IUS can be replaced until menopause to maintain the therapeutic effect.

It is difficult to remove the focus of adenomyosis completely because there is no obvious boundary between adenomyosis and normal myometrium. If there are residual small lesions during the operation, they may recur as time passes. A retrospective study showed that with the increase in follow-up time after surgery, the recurrence rate of patients with adenomyosis increases from the lowest (no recurrence) to the highest (close to 50%) (17). Some studies have also confirmed that GnRH-a or LNG-IUS treatment can reduce the recurrence rate (9, 23, 36, 37). Therefore, we designed this scheme, and it can be seen from **Table 2** that the patients who completed sequential treatment after a modified subtotal resection of adenomyosis showed a significant improvement in postoperative hemoglobin, CA125, dysmenorrhea, menstrual volume, and uterine volume. The average uterine volume estimated by transvaginal ultrasound significantly reduced after treatment in both the transabdominal group and the laparoscopic group. The reduction of the volume of the uterus is the inevitable result of surgical resection of the focus of adenomyosis, but the author opines that it is very important to monitor the changes in the uterus volume after the operation. During the follow-up period, if the uterus volume increases with time, we need to be on guard against recurrence. **Table 3** shows that the amount of intraoperative bleeding in the laparoscopic subgroup is lower than that in the transabdominal subgroup, which has something to do with the finer laparoscopic operation. However, there was no significant difference in operation time between the two subgroups. **Table 4** shows that there is no significant difference in the therapeutic effect between the transabdominal approach subgroup and the endoscopic approach subgroup, considering that the improvement of the endoscopic technique of the operator may achieve a result similar to that of the transabdominal approach. Longer follow-up observation is still needed.

After the improvement of this operation and the sequential treatment with the combination of two drugs, the following advantages are observed: (1) The uterus of the patient can be preserved, the effect of cutting off the ascending branch of the uterine artery on the ovary can be avoided, the length of the vagina is not reduced, and the quality of female sex life can be preserved; (2) it retains the original normal structure around the cervix, reduces the probability of injuring the ureter, bladder, and other adjacent organs during the operation, and avoids the change of micturition and defecation habits caused by the change in the pelvic structure; (3) during the operation, the uterine cavity is repaired according to the length of the LNG-IUS, which is the difference between this operation and other uterine preservation operations. Remodeling the uterine cavity can directly and effectively reduce the amount of menstruation. Placing the LNG-IUS during the operation can also help with the treatment of AM to consolidate the surgical effect and reduce recurrence. A more appropriate size of the uterine cavity can reduce slippage of the LNG-IUS to a certain extent; (4) postoperative injection of GnRH-a can further atrophy the residual lesions, reduce the probability of abnormal uterine bleeding after the placement of the LNG-IUS, and also reduce slippage of the LNG-IUS by reducing the amount of menstruation (43).

After the improvement of this procedure, the following shortcomings are observed. (1) Endometriosis is possible during the operation, so we emphasize that the uterine cavity should be closed as soon as possible to reduce the exposure time and chance. Meanwhile, after uterine remodeling, the pelvic cavity and abdominal cavity should be fully washed to reduce the possibility of residual blood and residual endometrial cells. (2) Many tissues will be resected during the surgery, making it easy to leave dead spaces when the seromuscular layer is sutured with the myometrium retained around the uterine cavity, leading to possible hematoma and infection by errhysis. Continuous mattress suture of the uterine cavity was adopted during the operation and the bilateral seromuscular layers were sutured with the "baseball stitching technique." This suture method can reduce needle bleeding while making the suture closer, so as to effectively avoid residual dead spaces.

In view of the fact that this study is a retrospective analysis, the number of cases is relatively small, and there may be bias in case selection, with a shorter follow-up period as well. We feel that more prospective studies with big sample sizes are also needed to evaluate and compare the efficacy and safety of this study with other treatment measures.

Conclusion

For patients suffering from severe adenomyosis who have no pregnancy plans and require uterine preservation, transabdominal or laparoscopic subtotal resection of the focus of adenomyosis, combined with the LNG-IUS + GnRH-a sequential treatment, may be a safe and effective alternative when conservative treatments such as drugs fail.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, and further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Kho KA, Chen JS, Halvorson LM. Diagnosis, evaluation, and treatment of adenomyosis. *JAMA*. (2021) 326(2):177–8. doi: 10.1001/jama.2020.26436

2. Horton J, Sterrenburg M, Lane S, Maheshwari A, Li TC, Cheong Y. Reproductive, obstetric, and perinatal outcomes of women with adenomyosis and endometriosis: a systematic review and meta-analysis. *Hum Reprod Update*. (2019) 25(5):592–632. doi: 10.1093/humupd/dmz012

3. Graziano A, Lo Monte G, Piva I, Caserta D, Karner M, Engl B, et al. Diagnostic findings in adenomyosis: a pictorial review on the major concerns. *Eur Rev Med Pharmacol Sci*. (2015) 19(7):1146–54.

4. Mikos T, Lioupis M, Anthoulakis C, Grimbizis GF. The outcome of fertility-sparing and nonfertility-sparing surgery for the treatment of adenomyosis. A systematic review and meta-analysis. *J Minim Invasive Gynecol*. (2020) 27 (2):309–331.e3. doi: 10.1016/j.jmig.2019.08.004

5. Tan J, Moriarty S, Taskin O, Allaire C, Williams C, Yong P, et al. Reproductive outcomes after fertility-sparing surgery for focal and diffuse adenomyosis: a systematic review. *J Minim Invasive Gynecol*. (2018) 25 (4):608–21. doi: 10.1016/j.jmig.2017.12.020

6. Huang YF, Deng J, Wei XL, Sun X, Xue M, Zhu XG, et al. A comparison of reproductive outcomes of patients with adenomyosis and infertility treated with high-intensity focused ultrasound and laparoscopic excision. *Int J Hyperthermia*. (2020) 37(1):301–7. doi: 10.1080/02656736.2020.1742390

7. Song SY, Lee SY, Kim HY, Park DB, Kim DE, Lee KH, et al. Long-term efficacy and feasibility of levonorgestrel-releasing intrauterine device use in patients with adenomyosis. *Medicine (Baltimore)*. (2020) 99(22):e20421. doi: 10.1097/MD.0000000000020421

8. Abbas AM, Samy A, Atwa K, Ghoneim HM, Lotfy M, Saber Mohammed H, et al. The role of levonorgestrel intra-uterine system in the management of adenomyosis: a systematic review and meta-analysis of prospective studies. *Acta Obstet Gynecol Scand*. (2020) 99(5):571–81. doi: 10.1111/aogs.13798

9. Sheng J, Zhang WY, Zhang JP, Lu D. The LNG-IUS study on adenomyosis: a 3-year follow-up study on the efficacy and side effects of the use of levonorgestrel intrauterine system for the treatment of dysmenorrhea associated with adenomyosis. *Contraception*. (2009) 79(3):189–93. doi: 10.1016/j.contraception.2008.11.004

10. Magon N. Gonadotropin releasing hormone agonists: expanding vistas. *Indian J Endocrinol Metab*. (2011) 15(4):261–7. doi: 10.4103/2230-8210.85575

11. Kang JL, Wang XX, Nie ML, Huang XH. Efficacy of gonadotropin-releasing hormone agonist and an extended-interval dosing regimen in the treatment of patients with adenomyosis and endometriosis. *Gynecol Obstet Invest*. (2010) 69 (2):73–7. doi: 10.1159/000258683

12. Guo Q, Xu F, Ding Z, Li P, Wang X, Gao B. High intensity focused ultrasound treatment of adenomyosis: a comparative study. *Int J Hyperthermia*. (2018) 35(1):505–9. doi: 10.1080/02656736.2018.1509238

13. Wu Q, Lian Y, Chen L, Yu Y, Lin T. Alleviation of symptoms and improvement of endometrial receptivity following laparoscopic adenomyoma excision and secondary therapy with the levonorgestrel-releasing intrauterine system. *Reprod Sci*. (2020) 27(6):1259–65. doi: 10.1007/s43032-019-00130-4

14. Pang LL, Mei J, Fan LX, Zhao TT, Li RN, Wen Y. Efficacy of high-intensity focused ultrasound combined with GnRH-a for adenomyosis: a systematic review and meta-analysis. *Front Public Health*. (2021) 9:688264. doi: 10.3389/fpubh.2021.688264

15. Haiyan S, Lin W, Shuhua H, Wang W. High-intensity focused ultrasound (HIFU) combined with gonadotropin-releasing hormone analogs (GnRHa) and levonorgestrel-releasing intrauterine system (LNG-IUS) for adenomyosis: a case series with long-term follow up. *Int J Hyperthermia*. (2019) 36(1):1179–85. doi: 10.1080/02656736.2019.1679892

16. Wang W, Ma X, Zhang W, Li Z, Wang Y, Yu Z, et al. Relapse after conservative surgery combined with triptorelin acetate versus conservative surgery only in women with focal adenomyosis: study protocol for a multicenter, prospective, randomized controlled trial. *Trials*. (2020) 21(1):364. doi: 10.1186/s13063-020-04294-2

17. Younes G, Tulandi T. Conservative surgery for adenomyosis and results: a systematic review. *J Minim Invasive Gynecol*. (2018) 25(2):265–76. doi: 10.1016/j.jmig.2017.07.014

18. Kim JK, Shin CS, Ko YB, Nam SY, Yim HS, Lee KH. Laparoscopic assisted adenomyomectomy using double flap method. *Obstet Gynecol Sci*. (2014) 57 (2):128–35. doi: 10.5468/ogs.2014.57.2.128

19. Huang X, Huang Q, Chen S, Zhang J, Lin K, Zhang X. Efficacy of laparoscopic adenomyomectomy using double-flap method for diffuse uterine adenomyosis. *BMC Womens Health*. (2015) 15:24. doi: 10.1186/s12905-015-0182-5

20. Zhu L, Chen S, Che X, Xu P, Huang X, Zhang X. Comparisons of the efficacy and recurrence of adenomyomectomy for severe uterine diffuse adenomyosis via

laparotomy versus laparoscopy: a long-term result in a single institution. *J Pain Res*. (2019) 12:1917–24. doi: 10.2147/JPR.S205561

21. Munro MG, Critchley HOD, Fraser IS, FIGO Menstrual Disorders Committee. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. *Int J Gynaecol Obstet*. (2018) 143 (3):393–408. doi: 10.1002/ijgo.12666. Erratum in: *Int J Gynaecol Obstet*. (2019 Feb) 144(2):237. doi: 10.1002/ijgo.12666

22. Herman MC, Mak N, Geomini PM, Winkens B, Mol BW, Bongers MY, et al. Is the Pictorial Blood Loss Assessment Chart (PBAC) score associated with treatment outcome after endometrial ablation for heavy menstrual bleeding? A cohort study. *BJOG*. (2017) 124(2):277–82. doi: 10.1111/1471-0528.14434

23. Cho S, Nam A, Kim H, Chay D, Park K, Cho DJ, et al. Clinical effects of the levonorgestrel-releasing intrauterine device in patients with adenomyosis. *Am J Obstet Gynecol*. (2008) 198(4):373.e1–7. doi: 10.1016/j.ajog.2007.10.798

24. Naftalin J, Hoo W, Pateman K, Mavrelos D, Holland T, Jurkovic D. How common is adenomyosis? A prospective study of prevalence using transvaginal ultrasound in a gynaecology clinic. *Hum Reprod*. (2012) 27(12):3432–9. doi: 10.1093/humrep/des332

25. Chapron C, Tosti C, Marcellin L, Bourdon M, Lafay-Pillet MC, Millischer AE, et al. Relationship between the magnetic resonance imaging appearance of adenomyosis and endometriosis phenotypes. *Hum Reprod*. (2017) 32 (7):1393–401. doi: 10.1093/humrep/dex088

26. Pinzauti S, Lazzeri L, Tosti C, Centini G, Orlandini C, Luisi S, et al. Transvaginal sonographic features of diffuse adenomyosis in 18-30-year-old nulligravid women without endometriosis: association with symptoms. *Ultrasound Obstet Gynecol*. (2015) 46(6):730–6. doi: 10.1002/uog.14834

27. Wise LA, Laughlin-Tommaso SK. Epidemiology of uterine fibroids: from menarche to menopause. *Clin Obstet Gynecol*. (2016) 59(1):2–24. doi: 10.1097/GRF.0000000000000164

28. Pavone D, Clemenza S, Sorbi F, Fambrini M, Petraglia F. Epidemiology and risk factors of uterine fibroids. *Best Pract Res Clin Obstet Gynaecol*. (2018) 46:3–11. doi: 10.1016/j.bpobgyn.2017.09.004

29. Genc M, Genc B, Cengiz H. Adenomyosis and accompanying gynecological pathologies. *Arch Gynecol Obstet*. (2015) 291(4):877–81. doi: 10.1007/s00404-014-3498-8

30. Weiss G, Maseelall P, Schott LL, Brockwell SE, Schocken M, Johnston JM. Adenomyosis a variant, not a disease? Evidence from hysterectomized menopausal women in the Study of Women's Health Across the Nation (SWAN). *Fertil Steril*. (2009) 91(1):201–6. doi: 10.1016/j.fertnstert.2007.11.025

31. Khan KN, Fujishita A, Koshiba A, Kuroboshi H, Mori T, Ogi H, et al. Biological differences between intrinsic and extrinsic adenomyosis with coexisting deep infiltrating endometriosis. *Reprod Biomed Online*. (2019) 39 (2):343–53. doi: 10.1016/j.rbmo.2019.03.210

32. Osada H, Silber S, Kakinuma T, Nagaishi M, Kato K, Kato O. Surgical procedure to conserve the uterus for future pregnancy in patients suffering from massive adenomyosis. *Reprod Biomed Online*. (2011) 22(1):94–9. doi: 10.1016/j.rbmo.2010.09.014

33. Di Spiezio Sardo A, Calagna G, Santangelo F, Zizolfi B, Tanos V, Perino A, et al. The role of hysteroscopy in the diagnosis and treatment of adenomyosis. *Biomed Res Int*. (2017) 2017:2518396. doi: 10.1155/2017/2518396

34. Louis LS, Saso S, Chatterjee J, Barsoum E, Al-Samarrai M. Adenomyosis and infertility. *Reprod Biomed Online*. (2012) 24(5):586. doi: 10.1016/j.rbmo.2012.02.013. author reply 587.

35. Maheshwari A, Gurunath S, Fatima F, Bhattacharya S. Adenomyosis and subfertility: a systematic review of prevalence, diagnosis, treatment and fertility outcomes. *Hum Reprod Update*. (2012) 18(4):374–92. doi: 10.1093/humupd/dms006

36. Wang PH, Liu WM, Fuh JL, Cheng MH, Chao HT. Comparison of surgery alone and combined surgical-medical treatment in the management of symptomatic uterine adenomyoma. *Fertil Steril*. (2009) 92(3):876–85. doi: 10.1016/j.fertnstert.2008.07.1744

37. Bragheto AM, Caserta N, Bahamondes L, Petta CA. Effectiveness of the levonorgestrel-releasing intrauterine system in the treatment of adenomyosis diagnosed and monitored by magnetic resonance imaging. *Contraception*. (2007) 76(3):195–9. doi: 10.1016/j.contraception.2007.05.091

38. Park DS, Kim ML, Song T, Yun BS, Kim MK, Jun HS, et al. Clinical experiences of the levonorgestrel-releasing intrauterine system in patients with large symptomatic adenomyosis. *Taiwan J Obstet Gynecol*. (2015) 54(4):412–5. doi: 10.1016/j.tjog.2014.05.009

39. Kriplani A, Singh BM, Lal S, Agarwal N. Efficacy, acceptability and side effects of the levonorgestrel intrauterine system for menorrhagia. *Int J Gynaecol Obstet*. (2007) 97(3):190–4. doi: 10.1016/j.ijgo.2007.01.009

40. Maldonado LY, Sergison JE, Gao X, Hubacher D. Menstrual bleeding and spotting with the levonorgestrel intrauterine system (52 mg) during the first-year after insertion: a systematic review and meta-analysis. *Am J Obstet Gynecol*. (2020) 222(5):451–468.e9. doi: 10.1016/j.ajog.2019.09.044

41. Saloranta TH, Gyllenberg FK, But A, Gissler M, Laine MK, Heikinheimo O. Free-of-charge long-acting reversible contraception: two-year discontinuation, its risk factors, and reasons. *Am J Obstet Gynecol*. (2020) 223(6):886.e1–886.e17. doi: 10.1016/j.ajog.2020.06.023

42. Bahamondes MV, de Lima Y, Teich V, Bahamondes L, Monteiro I. Resources and procedures in the treatment of heavy menstrual bleeding with the levonorgestrel-releasing intrauterine system (LNG-IUS) or hysterectomy in Brazil. *Contraception*. (2012) 86(3):244–50. doi: 10.1016/j.contraception.2011.12.005

43. Rathinam KK, Abraham JJ, S HP, S AS, Sen M, George M, et al. Evaluation of pharmacological interventions in the management of adenomyosis: a systematic review. *Eur J Clin Pharmacol*. (2022) 78(4):531–45. doi: 10.1007/s00228-021-03256-0

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Factors influencing treatment decisions in HIFU treatment of adenomyosis: A retrospective study

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Objective: To explore the influencing factors of decision-making in patients with adenomyosis, who are receiving high-intensity focused ultrasound (HIFU) treatment.
Methods: A total of 776 patients with adenomyosis were enrolled into HIFU group (241 cases) and hysterectomy group (535 cases) according to the treatment methods. The general data, clinical symptoms, marital and childbearing history, and economic status were compared between the two groups, and factors with $P < 0.05$ were introduced into multivariate logistic regression analysis to determine the determinants of patients choosing HIFU.
Results: The average age of the patients in the HIFU group was 39.1 ± 5.2 years, which was lower than that in the hysterectomy group, which was 45.1 ± 3.9 years ($P < 0.05$). The basic medical insurance for urban workers in the HIFU group was more than the hysterectomy group ($P < 0.05$). 95.9% of the hysterectomy group had no desire to have children, compared to 60.6% of the HIFU group, the difference was significant ($P < 0.05$). The treatment costs of HIFU group were significantly lower than that of hysterectomy group ($P < 0.05$). The main symptoms of the two groups were dysmenorrhea, menorrhagia, and secondary anemia. The results of multivariate logistic regression analysis showed that 31–40 years old, fertility desire, dysmenorrhea, menorrhagia, anemia and dizziness and fatigue were the influencing factors for the decision-making of HIFU for patients with adenomyosis.
Conclusion: 31–40 years old, fertility desire, dysmenorrhea, menorrhagia, anemia and dizziness and fatigue were the influencing factors for patients to choose HIFU treatment. HIFU therapy has emerged as a new option for patients with adenomyosis as an alternative to hysterectomy.

KEYWORDS
adenomyosis, HIFU, dysmenorrhea, menorrhagia, decision-making

Introduction

Adenomyosis (AM) is a common benign gynecological disease, defined as the presence of endometrial glands and stroma deep within the myometrium, causing myometrial hypertrophy and hyperplasia (1, 2). The true prevalence of adenomyosis is difficult to determine; for decades, the diagnosis of adenomyosis has been made mainly by pathology after hysterectomy, with a prevalence of about 5% to 70% (3). Over the past decade, adenomyosis can also be diagnosed without surgical intervention. Advances in imaging technology have created the possibility of non-invasive diagnosis of adenomyosis, such as magnetic resonance imaging (MRI) and transvaginal ultrasonography (TVUS). This allows the diagnosis to be made in young women, with or without clinical symptoms (4–7). Clinically, adenomyosis can result in abnormal bleeding, pelvic pain, and infertility, although approximately 30% of patients are asymptomatic (8–10). There are two types of adenomyosis: diffuse and focal (when a definite nodule is found, it can be called an adenomyoma). In addition, adenomyosis is often combined with other gynecological diseases, such as endometriosis (11, 12) and leiomyoma (13).

Adenomyosis treatment includes drug therapy, conservative surgery, interventional therapy, and hysterectomy. Hysterectomy is currently considered to be the last resort for adenomyosis (14), but it is a difficult choice for patients who want to preserve their uterus or maintain fertility. Unfortunately, approximately 50% of patients will experience relapse after conservative surgery (15). Drug therapy can effectively relieve clinical symptoms such as dysmenorrhea and menorrhagia (16).

High-intensity focused ultrasound (HIFU) is a new technology developed in recent years for non-invasive local hyperthermia treatment of tumors. It is widely used in gynecological diseases and has a good curative effect on uterine fibroids and adenomyosis (17, 18). The therapeutic mechanism of HIFU therapy is to focus the ultrasound beam generated by an external transducer on the target lesion in the body. The mechanical effect of ultrasound is transformed into thermal effect and cavitation effect. The purpose of HIFU in the treatment of adenomyosis is to selectively ablate adenomyosis lesions to relieve the symptoms. It relies on highly focused ultrasound energy to precisely destroy uterine adenomyosis in a non-invasive, bloodless manner (19). Patients treated with HIFU had significantly fewer symptoms of adenomyosis and recovered at a relatively high pregnancy rate after the treatment (20, 21). However, due to the unclear boundary of adenomyosis, some patients' symptom relief only lasts for a certain period, Liu et al. showed that 26% of patients relapsed after HIFU treatment, and the median time to relapse was 12 months (22). It should be noted that HIFU treatment is mainly suitable for symptomatic patients with lesions larger than 3 cm (23, 24).

Currently, there is no guideline for the management of adenomyosis, especially the uterine-sparing treatment of these adenomyosis presents formidable challenges to the gynecologist. Therefore, this study aimed to explore the factors influencing a patient's decision to undergo HIFU by extracting raw medical records, which can provide a basis for exploring optimized treatment strategies and clinical management options for patients with adenomyosis.

Materials and methods

Study design

This cross-sectional retrospective study was conducted at the First Hospital of Chongqing Medical University. We reviewed all patients with adenomyosis (ICD-10: n80.001) who were admitted to hospital and received treatment from January 2013 to December 2020. Inclusion criteria were as follows: (1) premenopausal women; (2) typical symptoms: dysmenorrhea, menorrhagia; (3) diagnosis of adenomyosis by clinical evaluation, vaginal ultrasound and/or MRI (**Figure 1**).

The exclusion criteria were: (1) no intervention on the day of admission and discharge; (2) incomplete electronic medical record description information; (3) postmenopausal women with abnormal uterine bleeding or/and lower abdominal pain; (4) patients who received treatments other than hysterectomy and HIFU; (5) patients with suspected or confirmed uterine malignancy; (6) patients with acute pelvic inflammatory disease.

After deliberation by the ethics committee of Chongqing Medical University (Ethics Approval Number, 2021–006), it is unnecessary to sign the informed consent form. However, it shall be implemented in strict accordance with the general provisions of the Declaration of Helsinki. Besides, all patient information is strictly confidential.

Data extraction

The age of each patient was calculated from the date of birth recorded in the case record to the date of hospitalization. At the same time, the clinical data of all patients were collected through a medical history system. These data included the patients' age, reproductive desire, work status, symptoms, marital status, abortion, deliver, cesarean section, medical insurance, and medical expenses.

Statistical analysis

SPSS 22.0 statistical software (IBM SPSS, USA) was used for the data analysis. Quantitative data are presented as mean ± SD, while count data are presented as [n (%)]. The $\chi 2$ test was used

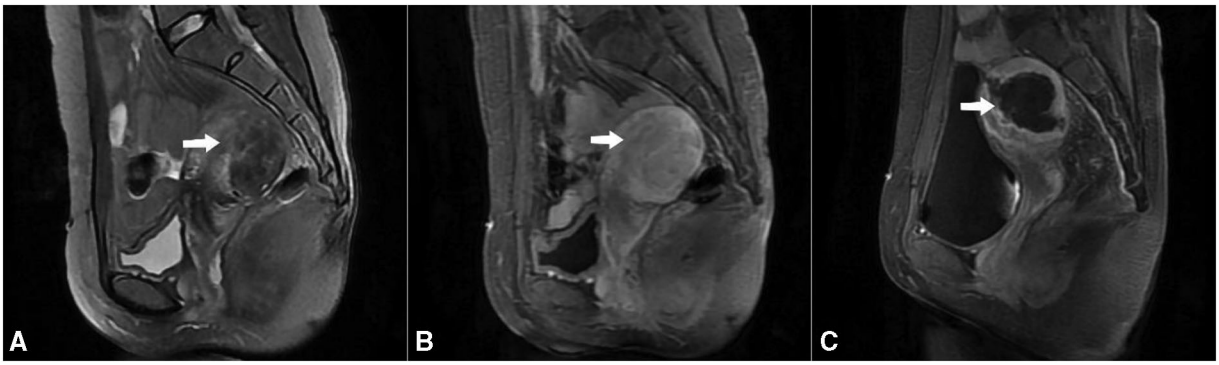

FIGURE 1
Mr images obtained from a patient with adenomyosis. (A) T2WI shows a well-defined adenomyosis lesion, which is a poorly defined low-signal lesion with scattered punctate and patchy high-signal foci located in the posterior uterine wall (arrow); (B) Contrast-enhanced MRI showed perfusion of the adenomyotic lesion (arrow); (C) Post-treatment T1-weighted contrast-enhanced image shows that the non-perfused volume ratio was 83.5% (arrow).

to compare differences between groups and $P < 0.05$ was considered statistically significant. In addition, multivariate logistic regression analysis was used to determine the influencing factors of patients' choice of HIFU.

Results

There was a total of 973 patients diagnosed with adenomyosis on admission, excluding 127 patients who received drug treatment, 42 patients who received lesion resection, and 29 patients with abnormal uterine bleeding or lower abdominal pain in postmenopausal women. The remaining 776 patients, including 535 (57.5%) patients who underwent hysterectomy and 241 (42.5%) who underwent HIFU treatment, were included in this study.

Adenomyosis-related symptoms

Among the 776 patients, 626 (80.7%) complained of dysmenorrhea, 497 (64%) menorrhagia, 427 (55%) secondary anemia and 230 (29.6%) lower abdominal pain (Figure 2).

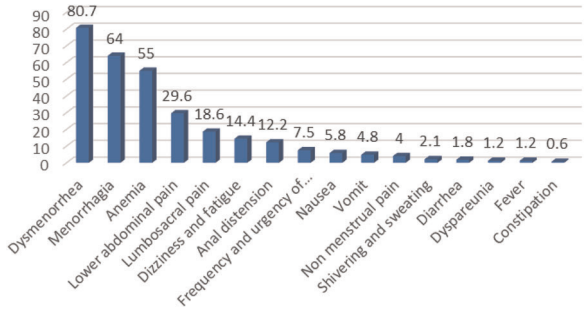

FIGURE 2
Symptoms of patients with adenomyosis (%).

General conditions of patients and treatment decisions

The patients were enrolled into two groups according to the treatment method. The mean age of patients in the hysterectomy group was 45.1 ± 3.9 years (range = 31–52 years), and the HIFU group was 39.1 ± 5.2 years (range = 25–52 years), the difference was significant ($t = 17.704$ $P < 0.001$).60.6% of the HIFU group were younger than 40 years old, and only 11.6% were in the hysterectomy group. There was a statistically significant difference in age distribution between the two groups ($\chi 2 = 211.722$, $P < 0.001$). Meanwhile, the HIFU group had a desire to have children in 60.6%, which was significantly higher than the hysterectomy group (4.1%) ($\chi 2 = 312.346$, $P < 0.001$).In addition, patients with jobs in the HIFU group accounted for 74.4%, which was significantly higher than that in the hysterectomy group (50.3%); while 23.7% of the patients in the HIFU group had temporary job, which was significantly lower than that in the hysterectomy group (41.1%) ($\chi 2 = 42.656$, $P < 0.001$) (Table 1).

Adenomyosis-related symptoms and treatment decisions

The main clinical manifestations of hospitalized patients were dysmenorrhea, menorrhagia, secondary anemia, and lower abdominal pain. Compared with the two treatment decisions, dysmenorrhea accounted for 90.1% in the HIFU group, which was significantly higher than that in the

TABLE 1 Comparison of basic conditions of patients with adenomyosis [*n*(%)].

	HIFU (*n* = 241)	Hysterectomy (*n* = 535)	*P* value
Age			0.000
≤30 years	12 (5)	0 (0)	
31–40 years	134 (55.6)	62 (11.6)	
41–50 years	93 (38.6)	432 (80.7)	
> 50 years	2 (0.8)	41 (7.7)	
Reproductive desire			0.000
Yes	146 (60.6)	22 (4.1)	
No	95 (39.4)	513 (95.9)	
Work status			0.000
Patients with jobs	180 (74.7)	275 (51.4)	
Temporary job	58 (23.7)	220 (41.1)	

TABLE 2 Comparison of related symptoms in patients with adenomyosis [*n*(%)].

	HIFU	Hysterectomy	*P* value
Dysmenorrhea	218 (90.5)	408 (76.3)	0.000
Menorrhagia	126 (52.3)	371 (69.3)	0.000
Anemia	93 (38.6)	334 (62.4)	0.000
Lower abdominal pain	63 (26.1)	167 (31.2)	0.174
Lumbosacral pain	46 (19.1)	98 (18.3)	0.842
Dizziness and fatigue	14 (5.8)	98 (18.3)	0.000
Anal distension	33 (13.7)	62 (11.6)	0.409
Frequency and urgency of micturition	13 (5.4)	45 (8.4)	0.184
Nausea	22 (9.1)	23 (4.3)	0.012
Vomit	21 (8.7)	16 (3)	0.001
Non menstrual pain	8 (3.3)	23 (4.3)	0.692
Shivering and sweating	6 (2.5)	10 (1.9)	0.590
Diarrhea	9 (3.7)	5 (0.9)	0.015
Dyspareunia	5 (2.1)	4 (0.7)	0.145
Fever	1 (0.4)	8 (1.5)	0.287
Constipation	1 (0.4)	4 (0.7)	1.000

hysterectomy group (75.9%) ($\chi2 = 21.470$, $P < 0.001$); Menorrhagia in the HIFU group were 52.1%, which was significantly lower than that in the hysterectomy group (69.3%) ($\chi2 = 21.009$, $P < 0.001$);The secondary anemia covered 38.8% in the HIFU group, which was significantly lower than that in the hysterectomy group (61.9%) ($\chi2 = 38.161$, $P < 0.001$).At the same time, other symptoms included dizziness and fatigue, urinary frequency and urgency, nausea, vomiting, diarrhea and dyspareunia, and the difference between the two groups was statistically significant (all $P < 0.05$) (Table 2).

Marital and reproductive Status and treatment decisions

The patients who have childbirth history of the HIFU group was 79.3%, which was lower than that of the hysterectomy group (92.3%), and the difference was statistically significant ($\chi2 = 27.475$, $P < 0.001$). There was no significant difference in marital status, history of abortion, and childbirth between the two groups ($P > 0.05$) (Table 3).

Economic situation and treatment decisions

The basic medical insurance for urban workers in the HIFU group (71.4%) was higher than that in the hysterectomy group (53.6%), while the basic medical insurance for urban residents in the HIFU group (24.5%) was lower than that in the hysterectomy group (40.7%). ($\chi2 = 25.793$, $P < 0.001$). The proportion of HIFU treatment costs less than ¥25,000 was 62.2%, while that in the hysterectomy group was 19.4%. There was a statistically significant difference in the distribution of treatment costs between the two groups, and the hysterectomy group was higher ($\chi2 = 230.024$, $P < 0.001$) (Table 4).

TABLE 3 Comparison of marital and reproductive status of patients with adenomyosis. [*n*(%)].

	HIFU	Hysterectomy	*P* value
Marital status			0.384
Married	230 (95.4)	518 (96.8)	
Divorce	9 (3.7)	16 (3)	
Unmarried	2 (0.8)	1 (0.2)	
Abortion	209 (89)	476 (89)	0.367
Deliver	191 (79.3)	494 (92.3)	0.000
Cesarean section	56 (23.2)	115 (21.5)	0.588

TABLE 4 Comparison of economic situation of patients with adenomyosis [*n*(%)].

	HIFU	Hysterectomy	*P* value
Medical insurance			0.000
Basic medical insurance for employee	172 (71.4)	287 (53.6)	
Basic medical insurance for residents	60 (24.9)	233 (43.5)	
Commercial medical insurance	9 (3.7)	15 (2.8)	
Treatment costs (CNY)			0.000
≤15,000	80 (33.2)	7 (1.3)	
15,000–25,000	70 (29)	86 (18.1)	
25,000–50,000	91 (37.8)	342 (63.9)	
> 50,000	0 (0)	100 (18.7)	

TABLE 5 Factors influencing decision-making for HIFU treatment [*n*(%)].

	OR	OR (95% CI)	*P* value
31–40 years old	0.188	0.038-0.920	0.039
Reproductive desire	0.051	0.025-0.104	0.000
Dysmenorrhea	0.525	0.288-0.956	0.035
Menorrhagia	1.605	1.005-2.565	0.048
Anemia	1.799	1.129-2.866	0.013
Dizziness and fatigue	2.453	1.134-5.306	0.023

Factors influencing HIFU treatment decision-making

Univariate analysis was performed on the influence of patients' general information, clinical symptoms, marriage and childbearing history, economic status, etc. on treatment decisions, and statistically significant indicators were included in multivariate analysis, including age, medical insurance category, work status, reproductive requirements, and birth history., dysmenorrhea, menorrhagia, anemia, nausea, vomiting, diarrhea, dizziness and fatigue, $P < 0.05$ was used to screen the patients with adenomyosis Influencing factors for choosing HIFU.

The results showed that between 31 and 40 years old (OR = 0.188, $P = 0.039$), fertility requirements (OR = 0.051, $P < 0.001$), dysmenorrhea (OR = 0.525, $P = 0.035$), menorrhagia (OR = 1.605, $P = 0.048$), secondary anemia (OR = 1.799, $P = 0.013$), and dizziness and fatigue (OR = 2.453, $P = 0.023$) were the influencing factors for HIFU decision-making in patients with adenomyosis (**Table 5**).

Discussion

Adenomyosis is a common chronic gynecological disease. Treating adenomyosis remains a global challenge, and most women want to protect their uterus while effectively relieving symptoms and improving their quality of life. The problem that this study attempts to solve is to find out the characteristics of the population who choose HIFU treatment and hysterectomy treatment, and the factors influencing the decision-making of patients choosing HIFU treatment. The results show that patients under the age of 40, who have jobs, have basic medical insurance for urban workers, and have fertility requirements are more inclined to choose HIFU; However, patients who are older than 40 years old, have no fixed jobs, have basic medical insurance for urban residents, and have no desire to have children tend to choose hysterectomy. In addition, the HIFU group had fewer treatment costs compared to hysterectomy.

In clinical practice, we found that many factors may affect patients' choice for HIFU treatment. In this study, patients treated with HIFU were significantly younger than the hysterectomy group ($P < 0.001$), with a range of age 31–40 years (55.6%), meanwhile there was also a statistical difference in fertility requirements between patients treated with HIFU and the hysterectomy group ($P < 0.001$), with 60.6% of patients treated with HIFU having fertility requirements. More and more young women were diagnosed, mainly because the diagnosis now was based on imaging diagnoses such as TVUS and MRI (9, 20). At the same time, with the change in women's concept of fertility, more and more women choose to give birth after the age of 30 and retain the uterus, and symptom relief are their primary concerns when seeking treatment options. Therefore, as a non-invasive treatment, HIFU has become the preferred treatment method for women of childbearing age between 31 and 40 years old. There are multiple clinical case reports of improved fertility after HIFU treatment (25, 26). The benefit of HIFU treatment for patients with adenomyosis deserves further study.

Severe dysmenorrhea and menorrhagia are considered as the most important symptoms affecting patients' quality of life. The main purpose of adenomyosis treatment is to relieve symptoms and improve the quality of life of patients. HIFU has been used to treat adenomyosis for many years. Recently, more and more gynecologists in China consider HIFU as a routine treatment for patients with adenomyosis. The results of 3–12 months' follow-up of patients with adenomyosis treated with HIFU showed that the clinical effective rate of improving dysmenorrhea or menorrhea was about 80% (18, 27). And combined treatment regimen with GnRHa and LNG-IUS after HIFU can significantly improve long-term outcomes (28). Although hysterectomy can also solve the patient's symptom problems, it brings many serious side effects, such as loss of reproductive function, impaired pelvic anatomical integrity, impaired neural network systems, and the gonadal endocrine axis (29, 30). Therefore, hysterectomy is mainly suitable for older patients, who have no fertility requirements, severe symptoms, and poor drug treatment effects or drug contraindications. HIFU may be a better choice for patients who have fertility requirements and want to relieve symptoms. However, HIFU technology as a way to treat adenomyosis, its comprehensive management plan which needs further study, to improve its long-term efficacy and reduce recurrence.

Another important finding of this study was that work status and medical insurance category were significantly associated with the choice of HIFU treatment in patients. 74.7% of the patients who received HIFU treatment were working and had a high level of basic medical insurance for urban workers. The main reason may be that the Patients with jobs have less time controllability than who with

temporary job. Considering the postoperative recovery time, HIFU has more advantages than hysterectomy. Another aspect is that the proportion of anyone at work who have received higher education is relatively high, they have a deeper understanding of health awareness and medical knowledge and are more inclined to new technologies with fewer side effects (23). In addition, adenomyosis is still at risk of recurrence after HIFU treatment and the possibility of getting secondary interventions is high. Therefore, financial freedom and independent decision-making ability have become important factors affecting treatment decisions. Patients with jobs are more inclined to choose less traumatic and repeatable treatments.

The main concern of patients when they visit the clinic, besides the cure rate of the disease, is the actual cost of medical care. This study found that the medical cost of HIFU treatment was significantly lower than that of hysterectomy ($P < 0.001$), and 62.2% of patients spent less than 25,000 CNY. Therefore, HIFU is inexpensive than hysterectomy. Evaluating the cost of care not only helps healthcare providers and healthcare systems utilize limited healthcare resources, it also provides a way to maximize benefits to patients and healthcare systems.

This study is a retrospective study, there is no unified path design for patient selection, and it is difficult to avoid the influence of physicians' own technical knowledge on patients' treatment choices. Due to the possibility of skin and subcutaneous tissue burns during HIFU treatment, the limitation of large abdominal scarring in the path of the ultrasound beam remains (31). Although research has shown that scar patches are safe and effective in relieving abdominal scarring in patients with uterine and adenomyosis treated with MRgHIFU (32). But this study did not consider the effect of this factor on treatment decisions in patients with adenomyosis, which is one of the study's limitations.

Conclusion

The results of this study show that HIFU is safe and effective in the treatment of adenomyosis, and the cost is lower than that of hysterectomy. Age 31–40, fertility desire, dysmenorrhea, menorrhagia, anemia, and dizziness and fatigue were the factors influencing patients' treatment decision to choose HIFU. In conclusion, HIFU treatment can keep the uterus while relieving symptoms. It has become one of the new choices for patients with adenomyosis, and younger (31–40 years old) working patients who are willing to choose HIFU treatment. Meanwhile, prospective studies on patient self-report scales are needed in the future to optimize patient treatment decisions.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Haifu Hospital of Chongqing Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

ZQ, CJY, and CWZ contributed to conception and design of the study. ZQ organized the database. ZQ, YMJ performed the statistical analysis. ZQ, wrote the first draft of the manuscript. ZQ, YMJ, HY, JL, and YJW wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Donnez J, Donnez O, Dolmans MM. Introduction: uterine adenomyosis, another enigmatic disease of our time. *Fertil Steril*. (2018) 109(3):369–70. doi: 10.1016/j.fertnstert.2018.01.035

2. Senturk LM, Imamoglu M. Adenomyosis: what is new? *Women's Health*. (2015) 11(5):717–24. doi: 10.2217/whe.15.60

3. Protopapas A, Grimbizis G, Athanasiou S, Loutradis D. Adenomyosis: disease, uterine aging process leading to symptoms, or both? *Facts, Views Vision in ObGyn*. (2020) 12(2):91–104.

4. Kishi Y, Suginami H, Kuramori R, Yabuta M, Suginami R, Taniguchi F. Four subtypes of adenomyosis assessed by magnetic resonance imaging and their specification. *Am J Obstet Gynecol*. (2012) 207(2):114.e1–7. doi: 10.1016/j.ajog.2012.06.027

5. Van den Bosch T, Van Schoubroeck D. Ultrasound diagnosis of endometriosis and adenomyosis: state of the art. *Best Pract Res Clin Obstet Gynaecol*. (2018) 51:16–24. doi: 10.1016/j.bpobgyn.2018.01.013

6. Loring M, Chen TY, Isaacson KB. A systematic review of adenomyosis: it is time to reassess what we thought we knew about the disease. *J Minim Invasive Gynecol*. (2021) 28(3):644–55. doi: 10.1016/j.jmig.2020.10.012

7. Chapron C, Vannuccini S, Santulli P, Abrão MS, Carmona F, Fraser IS, et al. Diagnosing adenomyosis: an integrated clinical and imaging approach. *Hum Reprod Update*. (2020) 26(3):392–411. doi: 10.1093/humupd/dmz049

8. Abbott JA. Adenomyosis and abnormal uterine bleeding (Aub-a)-pathogenesis, diagnosis, and management. *Best Prac Res Clin Obstet Gynaecol*. (2017) 40:68–81. doi: 10.1016/j.bpobgyn.2016.09.006

9. Pinzauti S, Lazzeri L, Tosti C, Centini G, Orlandini C, Luisi S, et al. Transvaginal sonographic features of diffuse adenomyosis in 18–30-year-old nulligravid women without endometriosis: association with symptoms. *Ultrasound Obstet Gynecol*. (2015) 46(6):730–6. doi: 10.1002/uog.14834

10. Bourdon M, Santulli P, Marcellin L, Maignien C, Maitrot-Mantelet L, Bordonne C, et al. Adenomyosis: an update regarding its diagnosis and clinical features. *J Gynecol Obstet Hum Reprod*. (2021) 50(10):102228. doi: 10.1016/j.jogoh.2021.102228

11. Di Donato N, Montanari G, Benfenati A, Leonardi D, Bertoldo V, Monti G, et al. Prevalence of adenomyosis in women undergoing surgery for endometriosis. *Eur J Obstet Gynecol Reprod Biol*. (2014) 181:289–93. doi: 10.1016/j.ejogrb.2014.08.016

12. Eisenberg VH, Arbib N, Schiff E, Goldenberg M, Seidman DS, Soriano D. Sonographic signs of adenomyosis are prevalent in women undergoing surgery for endometriosis and may suggest a higher risk of infertility. *Biomed Res Int*. (2017) 2017:8967803. doi: 10.1155/2017/8967803

13. Brucker SY, Huebner M, Wallwiener M, Stewart EA, Ebersoll S, Schoenfisch B, et al. Clinical characteristics indicating adenomyosis coexisting with leiomyomas: a retrospective, questionnaire-based study. *Fertil Steril*. (2014) 101(1):237–41. doi: 10.1016/j.fertnstert.2013.09.038

14. Li X, Liu X, Guo SW. Clinical profiles of 710 premenopausal women with adenomyosis who underwent hysterectomy. *J Obstet Gynaecol Res*. (2014) 40(2):485–94. doi: 10.1111/jog.12211

15. Younes G, Tulandi T. Conservative surgery for adenomyosis and results: a systematic review. *J Minim Invasive Gynecol*. (2018) 25(2):265–76. doi: 10.1016/j.jmig.2017.07.014

16. Farquhar C, Brosens I. Medical and surgical management of adenomyosis. *Best Pract Res Clin Obstet Gynaecol*. (2006) 20(4):603–16. doi: 10.1016/j.bpobgyn.2006.01.012

17. Fan HJ, Zhang C, Lei HT, Cun JP, Zhao W, Huang JQ, et al. Ultrasound-Guided high-intensity focused ultrasound in the treatment of uterine fibroids. *Medicine (Baltimore)*. (2019) 98(10):e14566. doi: 10.1097/md.0000000000014566

18. Zhang X, Li K, Xie B, He M, He J, Zhang L. Effective ablation therapy of adenomyosis with ultrasound-guided high-intensity focused ultrasound. *Int J Gynaecol Obstet*. (2014) 124(3):207–11. doi: 10.1016/j.ijgo.2013.08.022

19. Stewart EA, Gedroyc WM, Tempany CM, Quade BJ, Inbar Y, Ehrenstein T, et al. Focused ultrasound treatment of uterine fibroid tumors: safety and feasibility of a noninvasive thermoablative technique. *Am J Obstet Gynecol*. (2003) 189(1):48–54. doi: 10.1067/mob.2003.345

20. Guo Q, Xu F, Ding Z, Li P, Wang X, Gao B. High intensity focused ultrasound treatment of adenomyosis: a comparative study. *Int J Hyperthermia*. (2018) 35(1):505–9. doi: 10.1080/02656736.2018.1509238

21. Parazzini F, Mais V, Cipriani S, Busacca M, Venturini P. Determinants of adenomyosis in women who underwent hysterectomy for benign gynecological conditions: results from a prospective multicentric study in Italy. *Eur J Obstet Gynecol Reprod Biol*. (2009) 143(2):103–6. doi: 10.1016/j.ejogrb.2008.12.010

22. Liu X, Wang W, Wang Y, Wang Y, Li Q, Tang J. Clinical predictors of long-term success in ultrasound-guided high-intensity focused ultrasound ablation treatment for adenomyosis: a retrospective study. *Medicine (Baltimore)*. (2016) 95(3):e2443. doi: 10.1097/md.0000000000002443

23. Zhang L, Rao F, Setzen R. High intensity focused ultrasound for the treatment of adenomyosis: selection criteria, efficacy, safety and fertility. *Acta Obstet Gynecol Scand*. (2017) 96(6):707–14. doi: 10.1111/aogs.13159

24. Keserci B, Duc NM, Nadarajan C, Huy HQ, Saizan A, Wan Ahmed WA, et al. Volumetric mri-guided, high-intensity focused ultrasound ablation of uterine leiomyomas: asean preliminary experience. *Diagnostic Intervent Radiol*. (2020) 26(3):207–15. doi: 10.5152/dir.2019.19157

25. Huang YF, Deng J, Wei XL, Sun X, Xue M, Zhu XG, et al. A comparison of reproductive outcomes of patients with adenomyosis and infertility treated with high-intensity focused ultrasound and laparoscopic excision. *Int J Hyperthermia*. (2020) 37(1):301–7. doi: 10.1080/02656736.2020.1742390

26. Zhou CY, Xu XJ, He J. Pregnancy outcomes and symptom improvement of patients with adenomyosis treated with high intensity focused ultrasound ablation. *Zhonghua fu Chan ke za zhi*. (2016) 51(11):845–9. doi: 10.3760/cma.j.issn.0529-567X.2016.11.009

27. Haiyan S, Lin W, Shuhua H, Wang W. High-Intensity focused ultrasound (hifu) combined with gonadotropin-releasing hormone analogs (gnrha) and levonorgestrel-releasing intrauterine system (lng-ius) for adenomyosis: a case series with long-term follow up. *Int J Hyperthermia*. (2019) 36(1):1179–85. doi: 10.1080/02656736.2019.1679892

28. Li X, Zhu X, He S, Jiang Z, Li H, Tian X, et al. High-intensity focused ultrasound in the management of adenomyosis: long-term results from a single center. *Int J Hyperthermia*. (2021) 38(1):241–7. doi: 10.1080/02656736.2021.1886347

29. Ryann Louie A, Armstrong JA, Findeiss LK, Goodwin SC. Comparison of sexual dysfunction using the female sexual function Index following surgical treatments for uterine fibroids. *Case Rep Obstet Gynecol*. (2012) 2012:368136. doi: 10.1155/2012/368136

30. Barber EL, Harris B, Gehrig PA. Trainee participation and perioperative complications in benign hysterectomy: the effect of route of surgery. *Am J Obstet Gynecol*. (2016) 215(2):215.e1–7. doi: 10.1016/j.ajog.2016.02.022

31. Hindley J, Gedroyc WM, Regan L, Stewart E, Tempany C, Hynyen K, et al. Mri guidance of focused ultrasound therapy of uterine fibroids: early results. *AJR Am J Roentgenol*. (2004) 183(6):1713–9. doi: 10.2214/ajr.183.6.01831713

32. Keserci B, Duc NM. Volumetric magnetic resonance-guided high-intensity focused ultrasound ablation of uterine fibroids through abdominal scars: the impact of a scar patch on therapeutic efficacy and adverse effects. *J Ther Ultrasound*. (2017) 5:22. doi: 10.1186/s40349-017-0100-4

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The severity of depression is associated with pelvic inflammatory diseases: A cross-sectional study of the United States National Health and Nutrition Examinations from 2013 to 2018

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Purpose: As depression in patients with pelvic inflammatory diseases (PID) has received increasing attention in recent years, this study aims to investigate the relationship between depression severity and risk factors for pelvic inflammatory disease, and to provide new perspectives in the treatment of PID.

Patients and methods: Multivariate regression was used to evaluate the association between pelvic inflammatory disease and the severity of depression. Females who participated in the United States National Health and Nutrition Examination Survey (NHANES) from 2013 to 2018 were included. In addition, risk factors for PID and depression were also included in the analysis as adjustment factors.

Results: The risk of developing PID was associated with depressive status (odds ratio, OR 1.10, 95% confidence interval, CI 1.08–1.12), especially in people with severe depression (odds ratio, OR 6.34, 95% confidence interval, CI 3.72–10.79). Subgroup analysis showed differences in the risk of PID among people with different characteristics.

Conclusion: This study showed that there may be a potential positive association between depressive status and the prevalence of PID in the United States adult female population. Depression should be actively looked for in all patients with PID and treated appropriately

KEYWORDS

pelvic inflammatory diseases, NHANES, depression severity, cross-sectional study, inflammatory state

Introduction

Pelvic inflammatory disease is a common clinical syndrome of female reproductive tract, which is usually caused by untreated pathogenic microorganism infection, which may lead to important reproductive sequelae, including tubal infertility, chronic pelvic pain, ectopic pregnancy and so on (1). The etiology of pelvic inflammatory diseases (PID)is complicated (2, 3). Anaerobes, viruses, and mycoplasma are also involved in sexually transmitted infections (4). The prevalence of sexually transmitted infection-related diseases in high-income countries is estimated at 40% due to PID (5). Clinical signs and symptoms do not clearly indicate PID, and some women of childbearing age show no signs of infected reproductive organs, which severely affects their physical and mental health (1).

Research indicates that inflammation plays a role in the pathophysiology of depression. Inflammation, or inflammatory reaction, is caused by the activation of the immune system, usually characterized by local reactions caused by stimulation, injury, or infection, accompanied by symptoms such as redness, swelling, heat, and pain (6). Redness, swelling, heat, and pain were commonly associated with local reactions caused by stimulation, injury, or infection (7). In patients with severe depression, the abnormal expression of glucocorticoid receptors is related to inflammation (8). Furthermore, patients with depression are at risk for congenital and adaptive immune system disorders, etc. Inflammation is conducive to a decreased antidepressant response to depression (9). Most PID can be treated with antibiotics. Nonetheless, the therapeutic effect is not optimal because of drug resistance and side effects (10). There is limited clinical evidence on depression states and inflammatory disorders such pelvic inflammatory disease, despite a huge corpus of research on inflammation levels and depressive states.

The United States (US) National Health and Nutrition Survey (NHANES)is one of several health-related programs conducted by the NCHS to inform the public on the health and nutritional status of diseases and conditions as well as provide information on the prevention of the diseases or conditions. Health policy decisions were made using this information to estimate the prevalence of various diseases and conditions (11). The NHANES database has many perfect and standardized physiological and psychological data such as depression index questionnaire and medical history collection. Considering that depression is closely related to inflammatory factors, the relevant data of NHANES database are included in the research and analysis. The study aims to determine whether depression is associated with the prevalence of PID to shed light on new ideas for the clinical treatment of PID.

Materials and methods

Study population

We used data on NHANES participants from 2013 to 2018 for this study. Female participants aged 12 years and older were eligible. The Research Ethics Review Committee of the National Center for Health Statistics (NCHS) approved the NHANES project, and the data in NHANES were collected by professional investigators of NCHS. No application is required to use the database and it is available to any researcher who meets the requirements for use. All patient information in the database is anonymous, and all participants are aware of and consent to the data collection activities.

Primary exposure

The Patient Health Questionnaire of NHANES database, which consists of nine items, was administered for depression screening. “Almost every day,” “a few days,” “more than half of the days,” and “not at all” were scored 0–3 according to the nine-item instrument. The total score is calculated by adding up the scores in each item, ranging from 0 to 27. PHQ-9 scores and Proposed Treatment Actions were used to define the rating criteria for depression, depression is classified according to the score of depression index:None (0–4), Mild (5–9), Moderate (10–14), Moderately Severe (15–19), Severe (20–27).

Outcomes

Prevalence of PID was assessed based on the NHANES Reproductive Health Questionnaire, where RHQ078 asked, "Ever treated for a pelvic infection/PID?" Participants who answered "Yes" were categorized as the PID group.

Covariates

NHANES investigators prespecified options for race/ethnicity based on a written questionnaire. Another included a multiracial option. Race/ethnicity and Education level were included in the analysis because it is known to be independently associated with PID. According to guidelines published by the US Centers for Disease Control and Prevention, a z score for age categorizes body mass index as normal. Whether there was a regular menstrual cycle in the past 12 months, and the number of leukocytes and neutrophils in serum were taken from NHANES questionnaire data and laboratory data, respectively, and were included in the study as risk factors for PID events.

Statistical analysis

Continuous variables were expressed as means and standard deviations in normal distributions or as medians (quartiles) in skewed distributions. Among the measurements, we used a one-way ANOVA (normal distribution), K-W test (skewed distribution) and chi-square test (categorical variables) to assess whether there was any significant difference between means and proportions.

Multivariate logistic regression analysis and curve fitting was used to assess the association of the primary outcome: prevalence of PID, with the Depression Severity. By adjusting different risk factors step by step, we tested different models (Models 1–3). Model 1 was Unadjusted, Model 2 was adjusted for age, education, and race; Model 3 was further adjusted for Regular menstruation and BMI; Based on these data, an adjusted odds ratio (OR) is calculated with 95% confidence intervals (CI). The strengthening the reporting of observational studies in epidemiology (STROBE) statement advised simultaneous presentation of results from unadjusted, minimally adjusted, and fully adjusted analyses. The covariance in the model adjusts at least 10% of the matched OR values. All analyses were carried out using R ([1]The R Foundation) and EmpowerStats (X&Y Solutions, Inc., Boston, MA, USA). Statistical significance was defined as *P* values less than 0.05 (two-sided).

1 http://www.R-project.org

Participant characteristics

A total of 5,432 subjects were included in this analysis after excluding males (n = 14,452) and those with missing prevalence of PID (n = 9,516) (**Figure 1**). Age at participation was 38.1 ± 12.4 years (**Table 1**). The Depression Score level of 314 PID patients in the 2013–2018 NHANES was 6.5 (6.3) 4.0 (0.0–25.0), Mean (SD) Median (Min-Max)/N (%). Patients with PID had a significantly higher Depression score than those with Non-PID (**Table 1**).

Univariate analysis of prevalence of pelvic inflammatory diseases

The increase in age was significantly correlated with the occurrence of prevalence of PID (OR1.03, 95%CI 1.02–1.04). Further, women with irregular menstrual cycles had a lower risk of developing prevalence of PID (OR 0.51, 95%CI 0.40–0.64; **Table 2**).

Associations between prevalence of pelvic inflammatory diseases and the depression score

After further adjustment for age, race/ethnicity, education, body mass index, menstrual cycle, white blood cell, segmental, neutrophils factors. In multiple logistic regression analysis and curve fitting, we found that there was a significant correlation between depression index and the prevalence of PID. A multifactor regression analysis revealed a continuous relationship between prevalence of PID and Depression (**Figure 2** and **Table 3**).

Association between prevalence of pelvic inflammatory diseases and the depression severity

Results of multivariate logistic regression analysis and curve fitting showed a correlation between the prevalence of PID and depression (**Figure 2**). Multivariate logistic regression analysis and curve fitting revealed that prevalence of PID risk increased with depression severity. Age, race/nationality, education, body mass index, menstrual cycle, white blood cells and segmented neutrophils as risk factors for PID were included in the study as adjustment factors. The results of multivariate Logistic regression analysis and curve fitting showed that the prevalence of mild depression was higher than that of non-depression (OR 1.50, 95%CI 1.12–2.00). In addition, with the increase of depression index and the aggravation of depression, the

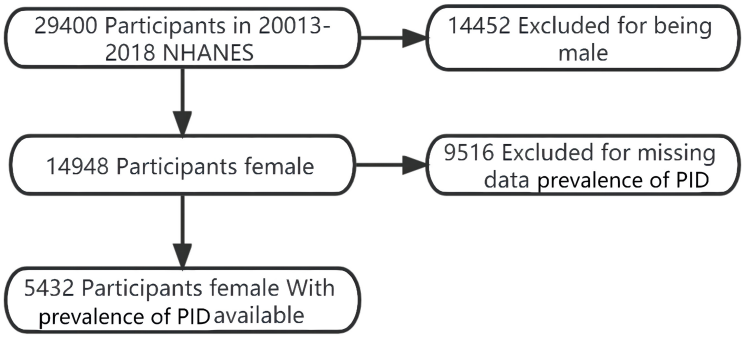

FIGURE 1
Flowchart of study participant selection: from 2013 to 2018 NHANES. A total of 26,026 individuals remained after satisfying inclusion and exclusion criteria.

TABLE 1 Characteristics of participants (N = 5432).

Prevalence of PID	Overall (n = 5432)	Non-PID (n = 5118)	PID (n = 314)	Standardize diff. (CI)	P-value	P-value*
Age (years, mean ± SD)	38.1 ± 12.4	37.8 ± 12.4	42.3 ± 11.2	0.4 (0.3, 0.5)	< 0.001	< 0.001
Race n (%)				0.3 (0.1, 0.4)	< 0.001	–
Non-Hispanic White	1809 (33.3%)	1697 (33.2%)	112 (35.7%)			
Mexican American Other Hispanic	1498 (27.6%)	1439 (28.1%)	59 (18.8%)			
Non-Hispanic Asian Other race	912 (16.8%)	864 (16.9%)	48 (15.3%)			
Non-Hispanic Black	1213 (22.3%)	1118 (21.8%)	95 (30.3%)			
Education n (%)				0.2 (0.1, 0.2)	< 0.001	
High school below	837 (15.4%)	520 (13.6%)	317 (19.8%)			
High school graduate or above	4595 (84.6%)	3312 (86.4%)	1283 (80.2%)			
Depression score	3.8 (4.6)	3.6 (4.4)	6.5(6.3)	0.5(0.4,0.7)	< 0.001	< 0.001
Mean (SD) Median (Min-Max)/N (%)	2.0 (0.0-27.0)	2.0 (0.0-27–0)	4.0(0.0,25.0)			
Depression severity				0.5 (0.4, 0.6)	< 0.001	–
None	3421(63.0%)	3281 (64.1%)	140 (44.6%)			
Mild	1285 (23.7%)	1205 (23.5%)	80 (25.5%)			
Moderate	445 (8.2%)	401 (7.8%)	44 (14.0%)			
Moderately severe	185 (3.4%)	156 (3.0%)	29 (9.2%)			
Severe	96 (1.8%)	75 (1.5%)	21 (6.7%)			
Regular menstruation				0.2 (0.1, 0.2)	< 0.001	
No	1599 (29.4%)	1039 (27.1%)	560 (35.0%)			
Yes	3833 (70.6%)	2793 (72.9%)	1040 (65.0%)			
BMI (mean ± SD)	29.9 ± 8.3	29.8 ± 8.3	31.3 ± 8.8	0.2 (0.1, 0.3)	0.002	0.002
WBC	7.6 ± 2.3	7.6 ± 2.3	7.6 ± 2.5	0.0 (−0.1, 0.1)	0.967	0.698
Segmented neutrophils	4.5 ± 1.8	4.5 ± 1.8	4.4 ± 2.1	0.0 (−0.1, 0.1)	0.652	0.194

CI, confidence interval, OR, odds ratio; PID, pelvic inflammatory disease; WBC, white blood cell count (1,000 cells/ul); BMI, body mass index (1,000 cell/uL, mean ± SD). P-value: Obtained by t-test or chi-square test. P-value*: For continuous variables, Kruskal–Wallis rank test, Fisher exact for categorical variables, with expects <10.

correlation between prevalence of PID and depression may be more significant (OR 6.34, 95%CI 3.72–10.79). There was a positive correlation between the degree of depression and the prevalence of PID. This conclusion is also supported by the linear relationship in the smooth curve fitting of the two (Figure 3).

It is worth noting that in the smooth curve fitting analysis, the non-linear correlation between the subjects with different depression index and their segmented neutrophil count was observed: when the depression index was higher than a numeric value, the higher the depression index was, the higher the segmented neutrophil count in blood was, and there was a

TABLE 2 Univariate analysis for prevalence of pelvic inflammatory diseases.

Covariate	Statistics	OR (95% CI)	*P*-value
AGE (years, mean ± SD)	38.09 ± 12.36	1.03 (1.02, 1.04)	< 0.0001
RACE *n* (%)			
Non-Hispanic white	1809 (33.30%)	Ref	
Mexican American Other Hispanic	1498 (27.58%)	0.62 (0.45, 0.86)	0.0039
Non-Hispanic Asian Other race	912 (16.79%)	0.84 (0.59, 1.19)	0.3318
Non-Hispanic black	1213 (22.33%)	1.29 (0.97, 1.71)	0.0808
EDUCATION *n* (%)			
high school below	837 (15.41%)	Ref	
High school graduate or above	4595 (84.59%)	0.83 (0.62, 1.12)	0.2206
Regular menstruation			
No	1599 (29.44%)	Ref	
Yes	3833 (70.56%)	0.51 (0.40, 0.64)	< 0.0001
BMI (mean ± SD)	29.89 ± 8.35	1.02 (1.01, 1.03)	0.0020
Depression score	3.75 ± 4.59	1.10 (1.08, 1.12)	< 0.0001
Depression severity			
None	3421 (62.98%)	Ref	
Mild	1285 (23.66%)	1.56 (1.17, 2.06)	0.0022
Moderate	445 (8.19%)	2.57 (1.80, 3.66)	< 0.0001
Moderately severe	185 (3.41%)	4.36 (2.83, 6.70)	< 0.0001
Severe	96 (1.77%)	6.56 (3.93, 10.96)	< 0.0001
WBC	7.57 ± 2.30	1.00 (0.95, 1.05)	0.9668
SN	4.46 ± 1.83	0.99 (0.92, 1.05)	0.6516

CI, confidence interval; OR, odds ratio; PID, Pelvic inflammatory disease; WBC, White blood cell count (1,000 cells/ul); BMI, body mass index; SN, Segmented neutrophil.

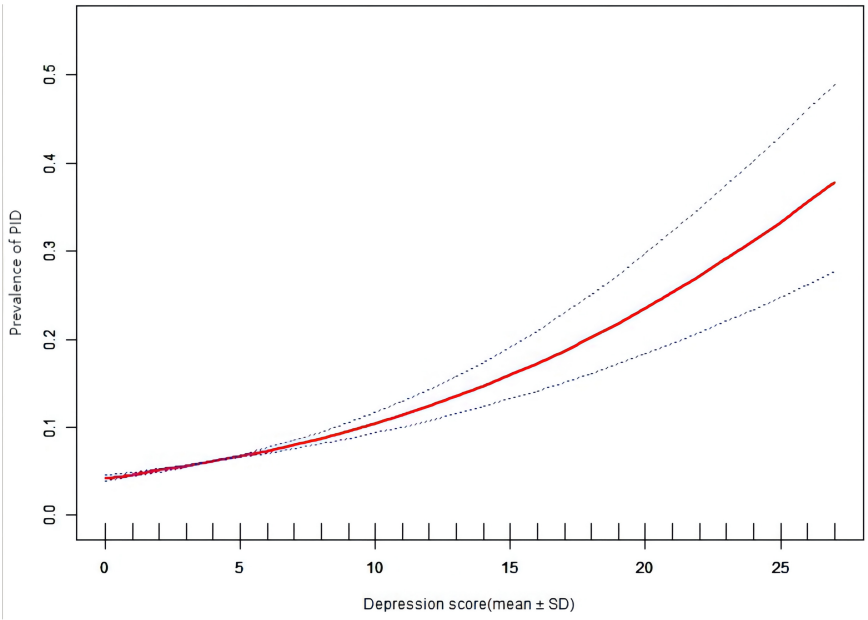

FIGURE 2
Prevalence of pelvic inflammatory diseases (PID) vs. depression score: association PID and depression score: A linear association between PID and depression score was found in a generalized additive model (GAM). The solid red line represents the smooth curve fit between variables. Blue bands represent the 95% of confidence interval from the fit. All adjusted for age, education, race, BMI, Regular menstruation, WBC, Segmented neutrophils.

TABLE 3 Relationship between depression severity and prevalence of pelvic inflammatory diseases.

Outcome	Crude model		Model I		Model II	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Depression score (mean ± SD)	1.10 (1.08, 1.12)	< 0.0001	1.10 (1.08, 1.12)	< 0.001	1.10 (1.08, 1.12)	< 0.0001
Depression-severity *n* (%)						
None	Ref		Ref		Ref	
Mild	1.56 (1.17, 2.06)	0.0022	1.48 (1.11, 1.97)	0.0081	1.50 (1.12, 2.00)	0.0060
Moderate	2.57 (1.80, 3.66)	< 0.0001	2.33 (1.62, 3.35)	< 0.0001	2.35 (1.64, 3.38)	< 0.0001
Moderately Severe	4.36 (2.83, 6.70)	< 0.0001	4.01 (2.57, 6.27)	< 0.0001	4.01 (2.56, 6.28)	< 0.0001
Severe	6.56(3.93,10.96)	< 0.0001	6.36 (3.74, 10.82)	< 0.0001	6.34(3.72,10.79)	< 0.0001

CI, confidence interval. Model I adjusted for age, education, and race. Model II adjusted for age, education, race, BMI, Regular menstruation, WBC, Segmented neutrophils.

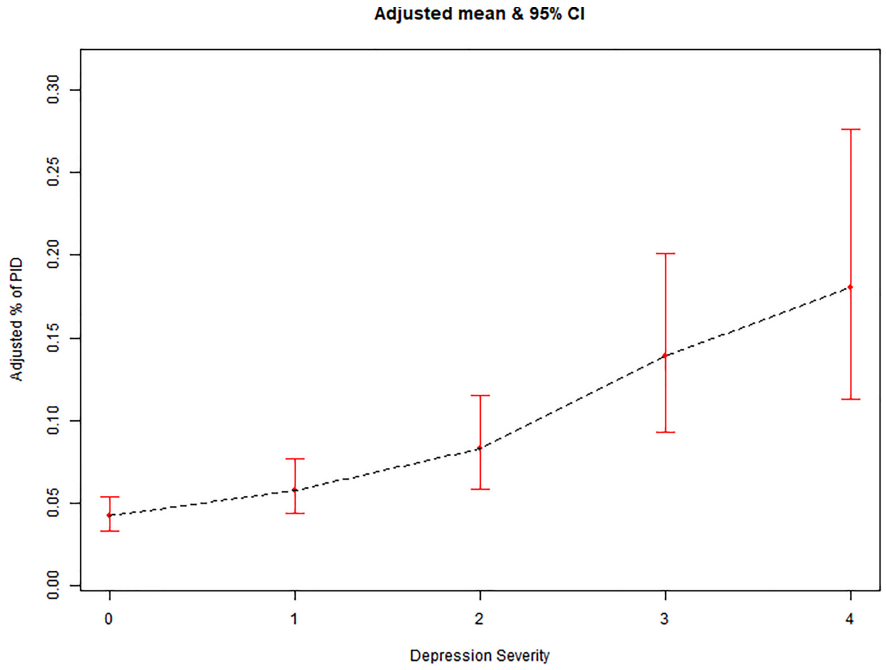

FIGURE 3
Prevalence of pelvic inflammatory diseases (PID) vs. depression severity: association PID and depression severity: A linear association between PID and Depression Severity was found in a generalized additive model (GAM). 0 = Non, 1 = Mild, 2 = Moderate, 3 = Moderately Severe, 4 = Severe.

positive correlation between them. Unfortunately, we did not calculate the turning value of the depression index, this is also the focus of our further research on the relationship between the two in the future. That may partly explain why people with depression have such a high risk of prevalence of PID (Figure 4).

Subgroup analysis

We used subgroup analysis and interaction testing to further understand this outcome. The age range was separated into three categories: under 20, 20–49, and above 49. According to WHO guidelines, BMI was categorized as 18.5, 18.5–24.9, 25.0–29.9, and 30.0 kg/m^2. This study determined if the association between prevalence of PID and the Depression Score still applied to each subgroup based on age, gender, race, BMI, menstrual cycle status, and smoking exposure. There was an interaction between prevalence of PID and the Depression Score across menstrual cycles, age, BMI, and racial groups, according to the findings. We found a greater correlation between prevalence of PID and the Depression Score in the population of women of reproductive age between 20 and 49 years of age compared to patients younger than 20 years of age and those older than 49 years of age, with an effect value and 95% confidence interval of (OR 1.109, 95% CI 1.083–1.135).

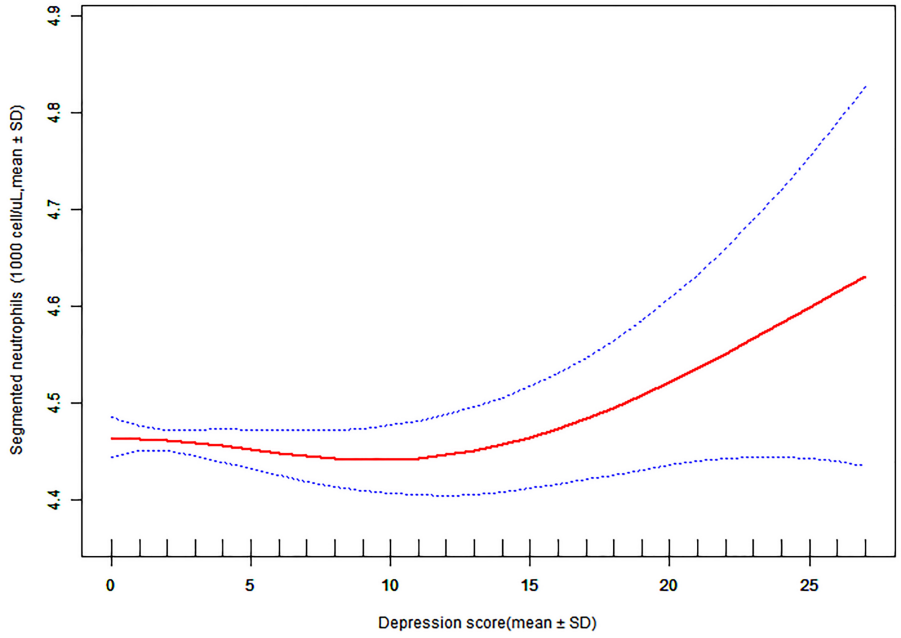

FIGURE 4
Association depression score and segmented neutrophils: A threshold, non-linear association between depression severity and segmented neutrophils were found in a generalized additive model (GAM).

When compared to other ethnic groups, depression was more linked with the prevalence of pelvic inflammatory disease in the Non-Hispanic-Asian population, with an effect value and 95% confidence interval of (OR 1.134, 95% CI 1.081–1.190). There was no significant difference between prevalence of PID and Depression Score in smokers versus non-smokers (**Figure 5**).

Discussion

With the increase in depression score and the aggravation of Depression severity, we found that the prevalence of PID was not significantly correlated with BMI, race, and education level. When compared with the non-Depression group, the OR of the Severe-Depression group increased the most (OR 6.43, 95%CI 3.72–10.79), followed by the Moderately Severe group (OR 4.01, 95%CI 2.56–6.28) and the Moderate group (OR 2.35 95%CI 1.64–3.38). The prevalence of PID increased 6.34 times, 4.01 times, and 2.35 times, respectively.

In addition, we also analyzed the potential mechanism of depression scores on the occurrence of PID in women. For every 1 increase in depression scores, the risk of pelvic inflammation was 1.10 times higher than before. Interestingly, although there was no difference between WBC and Segmented neutrophils in the prevalence of PID group and Non-PID Group, we found a non-linear relationship between them in smooth curve fitting between Segmented neutrophils and Depression Severity: when the depression score was less than a numeric value, there was no correlation between the depression index and the serum Segmented neutrophils equivalent, but when the depression index was more than numeric value and gradually increased, the Segmented neutrophils equivalent increased, and there was a positive correlation between them. In previous studies, there has been a close relationship between depression and inflammatory factors. A persistently activated hypothalamus-pituitary adrenal (HPA) axis combined with excessive cortisol release impair the sensitivity of glucocorticoid receptors (GR) and increases the activity of the pro-inflammatory immune response. It may be inferred that the serum segmented neutrophils equivalent will increase abnormally if the severity of depression is increased.

A series of symptoms are often accompanied by PID, such as abnormal leucorrhea, fever, and abdominal pain, which can be completely cured when the disease is treated with antibiotic. Pelvic inflammation caused by low autoimmunity and drug resistance is often accompanied by intermittent abdominal pain and low back pain in patients. Chronic pain and depression are very common diseases, and one disease increases the risk of the other. An array of physiological and behavioral processes is involved in depression and pain. Under chronic stressful conditions, or even after a stressful event, the hypothalamic-pituitary-adrenal (HPA) axis can be overactivated or activated. A variety of antidepressants have been proven to relieve chronic pain in patients (12). In comparison with healthy controls, depression patients display an up-regulation of inflammation markers in peripheral and central nervous system

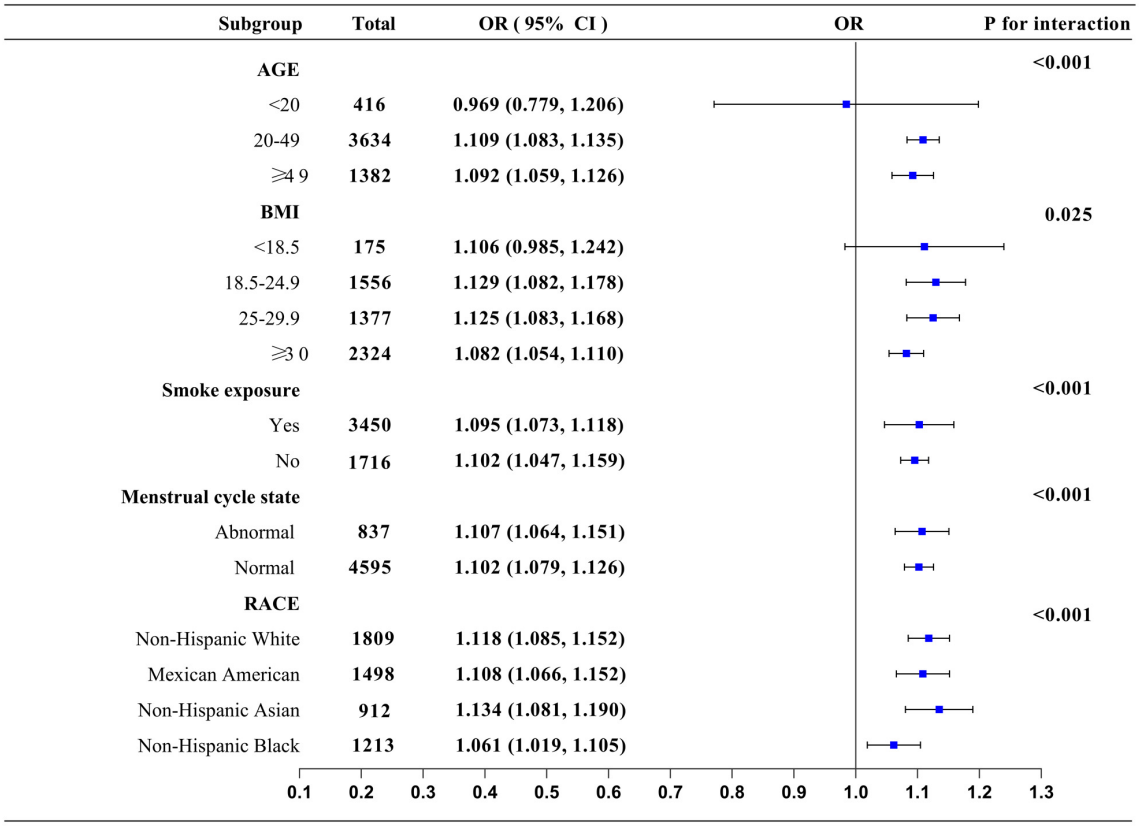

FIGURE 5
Subgroup analysis: Forest plot showing the OR and 95%CI of incidence of pelvic inflammatory diseases risk in patients with different degrees of depression in different subgroups.

tissues, including elevated concentrations of pro-inflammatory cytokines and immune mediators in cerebrospinal fluid (13). However, there is little evidence that there is a correlation between depression and PID, and there is little literature on the correlation between the severity of depression and PID. Our results are supported by data that show that the correlation between the severity of depression and PID is biologically reasonable. Due to the secondary nature of the analysis, we are unable to collect new data, which may result in residual confusion in the unmeasurable covariates. For the lack of serum C-reactive protein (CRP) data, we choose to ignore this covariate for analysis. In addition, limited information is available regarding the treatment, prognosis, and duration of specific PID. In this study, the population is large and representative. Severity and outcome variables of depression, as well as PID, were also assessed in a standardized manner.

Our research has a number of advantages. Firstly, a large sample of public databases was applied, which enhances the authority and reliability of the data. Secondly, the application of multi-factor regression analysis allows for the inclusion of more risk factors in the analysis, which enhances the credibility of the results, and finally, the relatively large sample size allows for more objective conclusions.

Inevitably, there are some limitations to our study. Firstly, cross-sectional analysis can only examine the distribution of risk factors for PID in a specific population at a specific time, and the study population is limited to adult women in the USA.

Conclusion

According to this study, depression severity among women in the US was associated with pelvic inflammatory disease. Even after adjusting for possible confounding factors, this correlation persists. Diagnosis and treatment of concomitant depression should be strongly considered in patients with PID.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by National Health and Nutrition Examination Survey (NHANES). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XY and JL obtained funding. TH and RC designed the study. TH and PL collected the data, involved in data cleaning, mortality follow-up, and verification. TH and XY analyzed the data. RC and TH drafted the manuscript. All authors contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript and have read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Kreisel KM, Llata E, Haderxhanaj L, Pearson WS, Tao G, Wiesenfeld HC, et al. The burden of and trends in pelvic inflammatory disease in the United States, 2006–2016. *J Infect Dis.* (2021) 224:S103–12. doi: 10.1093/infdis/jiaa771

2. Savaris RF, Fuhrich DG, Maissiat J, Duarte RV, Ross J. Antibiotic therapy for pelvic inflammatory disease. *Cochrane Database Syst Rev.* (2020) 8:CD010285. doi: 10.1002/14651858.CD010285.pub3

3. Lewis J, Horner PJ, White PJ. Incidence of pelvic inflammatory disease associated with mycoplasma genitalium infection: evidence synthesis of cohort study data. *Clin Infect Dis.* (2020) 71:2719–22. doi: 10.1093/cid/ciaa419

4. Mitchell CM, Anyalechi GE, Cohen CR, Haggerty CL, Manhart LE, Hillier SL, et al. Etiology and diagnosis of pelvic inflammatory disease: looking beyond gonorrhea and chlamydia. *J Infect Dis.* (2021) 224:S29–35. doi: 10.1093/infdis/jiab067

5. Hillier SL, Bernstein KT, Aral S. A review of the challenges and complexities in the diagnosis, etiology, epidemiology, and pathogenesis of pelvic inflammatory disease. *J Infect Dis.* (2021) 224:S23–8. doi: 10.1093/infdis/jiab116

6. Green C, Shen X, Stevenson AJ, Conole ELS, Harris MA, Barbu MC, et al. Structural brain correlates of serum and epigenetic markers of inflammation in major depressive disorder. *Brain Behav Immun.* (2021) 92:39–48. doi: 10.1016/j.bbi.2020.11.024

7. Orsolini L, Pompili S, Tempia Valenta S, Salvi V, Volpe U. C-Reactive protein as a biomarker for major depressive disorder? *Int J Mol Sci.* (2022) 23:1616.

8. Chiang TI, Hung YY, Wu MK, Huang YL, Kang HY. TNIP2 mediates GRbeta-promoted inflammation and is associated with severity of major depressive disorder. *Brain Behav Immun.* (2021) 95:454–61. doi: 10.1016/j.bbi.2021.04.021

9. Ting EY, Yang AC, Tsai SJ. Role of Interleukin-6 in depressive disorder. *Int J Mol Sci.* (2020) 21:2194. doi: 10.3390/ijms21062194

10. Hu L, Chen Y, Chen T, Huang D, Li S, Cui S, et al. A systematic study of mechanism of sargentodoxa cuneata and patrinia scabiosifolia against pelvic inflammatory disease with dampness-heat stasis syndrome via network pharmacology approach. *Front Pharmacol.* (2020) 11:582520. doi: 10.3389/fphar.2020.582520

11. Chen, TC, Clark J, Riddles MK, Mohadjer LK, Fakhouri T. National health and nutrition examination survey, 2015–2018: sample design and estimation procedures. *Vital Health Stat 2.* (2020) 1–35.

12. Kimura LF, Novaes LS, Picolo G, Munhoz CD, Cheung CW, Camarini R, et al. How environmental enrichment balances out neuroinflammation in chronic pain and comorbid depression and anxiety disorders. *Br J Pharmacol.* (2022) 179:1640–60. doi: 10.1111/bph.15584

13. Beurel E, Toups M, Nemeroff CB. The bidirectional relationship of depression and inflammation: double trouble. *Neuron.* (2020) 107:234–56. doi: 10.1016/j.neuron.2020.06.002

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Jain point laparoscopic entry in contraindications of Palmers point

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Background: This study was conducted to assess the efficacy of the Jain point to overcome the contraindications of Palmer's point. The Jain point lies on the left side of the abdomen at the L4 level, 10–13 cm lateral to the umbilicus. Due to its anatomical location, the Jain point is free from adhesions because postsurgical adhesions are encountered usually in the midline or the right side.

Methods: This is a retrospective study conducted at a high-volume tertiary care referral center for advanced gynecological laparoscopic surgery, enrolling 8,586 patients who underwent laparoscopy at the center from January 2011 to March 2022. In this paper, we analyze 2,519 patients with a history of previous surgeries, who were operated using the Jain point.

Results: In the 2,519 patients with a history of previous surgeries, the Jain point port was found to be adhesion free, regardless of the location of the scars, the number and type of previous surgeries, and those in whom Palmer's point was contraindicated. No major complications were reported, except for one case (0.04%) of small bowel injury, which was managed intraoperatively. The Jain point continued to function as the main ergonomic working port.

Conclusion: The Jain point offers an alternate safe entry port in previous surgery cases for laparoscopic surgeons of various specialties, like general surgeons, urologists, oncologists, and bariatric surgeons, to overcome the contraindications of Palmer's point. The Jain point also acts as the main ergonomic working port, whereas Palmer's point becomes redundant after initial entry.

KEYWORDS

Jain point, laparoscopic entry port, left lateral port, non-umbilical entry, Palmer's point, laparoscopy in previous surgery, Hasson Technique, laparoscopic entry

Introduction

Adhesions require a highly evolved surgical intervention. Adhesions and their associated complications have piqued both the medical and the legal fraternity in recent years (1). Laparoscopic techniques have revolutionized the field of gynecological surgeries and have taken a significant leap ranging from diagnostic procedures to complex intricate surgeries. However, previous surgeries lead to adhesions, which significantly challenge safe entry in laparoscopy. Generally, first blind entry is through

the umbilicus, which is the most common site for surgical adhesions. The incidence of intra-abdominal adhesions after laparotomy is 30%–90% (2). Most complications in laparoscopy occur during primary access when the trocar passes through the abdominal wall (3), and the rate is 0.4 per 1,000 cases for gastrointestinal injury and 0.2 per 1,000 cases for major vascular injury (4). This makes laparoscopic entry a significant burden on the healthcare system in previous surgery cases.

In 1974, R. Palmer devised a port that has acted as a savior in the aforementioned surgical situations (5); this lies 3 cm below the left subcostal margin in the midclavicular line and has been approved by experts across all subspecialties of endoscopy. Although generally safe, it has contraindications in cases of bloated stomach, upper abdominal masses, hepatosplenomegaly, and upper abdominal scars, causing a dilemma for laparoscopic surgeons, thus necessitating another entry port. The relatively newly devised ports such as the Lee–Huang point and 9th intercostal space are both in the upper abdomen, where the contraindications of Palmer's point persist.

The Jain point was devised in the mid-abdomen to avoid adhesions of the upper abdomen that contraindicate the previously described entry ports. The Jain point is 10–13 cm lateral to the umbilicus and outside the main surgical field avoiding the vessel, viscera, adhesions, and small and large bowel (**Figures 1A,B**). The Jain point, in effect, simulates the position of a referee on a tennis court, sitting outside at mid court, watching the movement of the ball on either side of the court with equal agility. In our context, it is outside the surgical field, and thus, applicable for scars in the upper, mid, and lower abdomen (**Figures 2A,B**) (6).

Sharp (7), in his recent article in UpToDate titled "Overview of Gynaecological Laparoscopic surgery and Non-umbilical Entry Site", strongly advocates non-umbilical entry in previous surgery cases, large pelvic masses, extremes of body mass index (BMI), pregnancy, very lax abdomen, and umbilical hernia. We adopted the concept of non-umbilical entry ahead of time as the Jain point is a non-umbilical entry port, at the L4 level,10-13cm lateral to umbilicus away from both, the viscera on the left side (the spleen, kidney, and bloated stomach), which are located higher up at T10 to L1, and the sigmoid colon, which has physiological adherence at the pelvic brim at the lower end. This leaves a wide nascent area on the left side from L1 to the pelvic brim, which is free from the vessel, viscera, adhesions, and bowel (VVAB) (8) (**Figure 3**) where the Jain point is located. The Jain point has the potential to avoid injury to the major retroperitoneal vessel (MRV). It also avoids superior epigastric and superficial epigastric vessels that are located within 5 cm of the midline. Located at the mid-abdomen, it reaches the depth of the pelvis or upper abdomen, and hence, continues to function as the main ergonomic working port throughout the surgery (**Figures 4A,B**).

This paper outlines the study of the Jain point as an alternate entry site in patients with a history of previous surgery and those in whom Palmer's point is contraindicated. For quick reference, we have tabulated the differences between the Jain point and Palmer's point (**Table 1**).

The Jain point has a single very prominent bony landmark, the ASIS, which lies in the sterile surgical field, whereas Palmer's point is located by the clavicle which lies in the unsterile surgical field. Harry Reich, in his foreword for the book, "Non-Umbilical Laparoscopic Entry Ports", published in the year 2020 (9),

TABLE 1 Differences between Jain point and Palmer's point.

Primary port	Palmer's point	Jain point
Point proposed	1974	2011
Bony Landmarks	Two landmarks 1. Mid clavicle 2. Subcostal margin	One prominent bony landmark, i.e. the ASIS (anterior superior iliac spine)
Learning curve	Short	Short: eases the tension from beginner's mind
Time spent in port creation	Short	Short
Use as the main working port	No, becomes redundant after entry	Yes, becomes main ergonomic working port
Contraindications	1. Bloated stomach 2. Hepatosplenomegaly 3. Upper quadrant scars 4. Large upper quadrant masses 5. Suspected postinflammatory adhesions	No known contraindications
Entry from the right side	Cannot be made due to the risk of liver laceration	Can be used as a mirror image on the right side
Incidence of bowel injury in previous surgery	Injury to the bloated stomach likely but largely unreported	0.04%
Use in previous upper abdominal surgical scars	Not applicable in big upper abdominal scars	Can be used in upper abdominal scars
Use in cases with a history of infectious pathologies	Entry associated with the potential risk of visceral injury in case of upper abdominal adhesions	Safe entry in suspected upper abdominal adhesions
Use as first blind port routinely	Not reported	Reported by Jain et al.

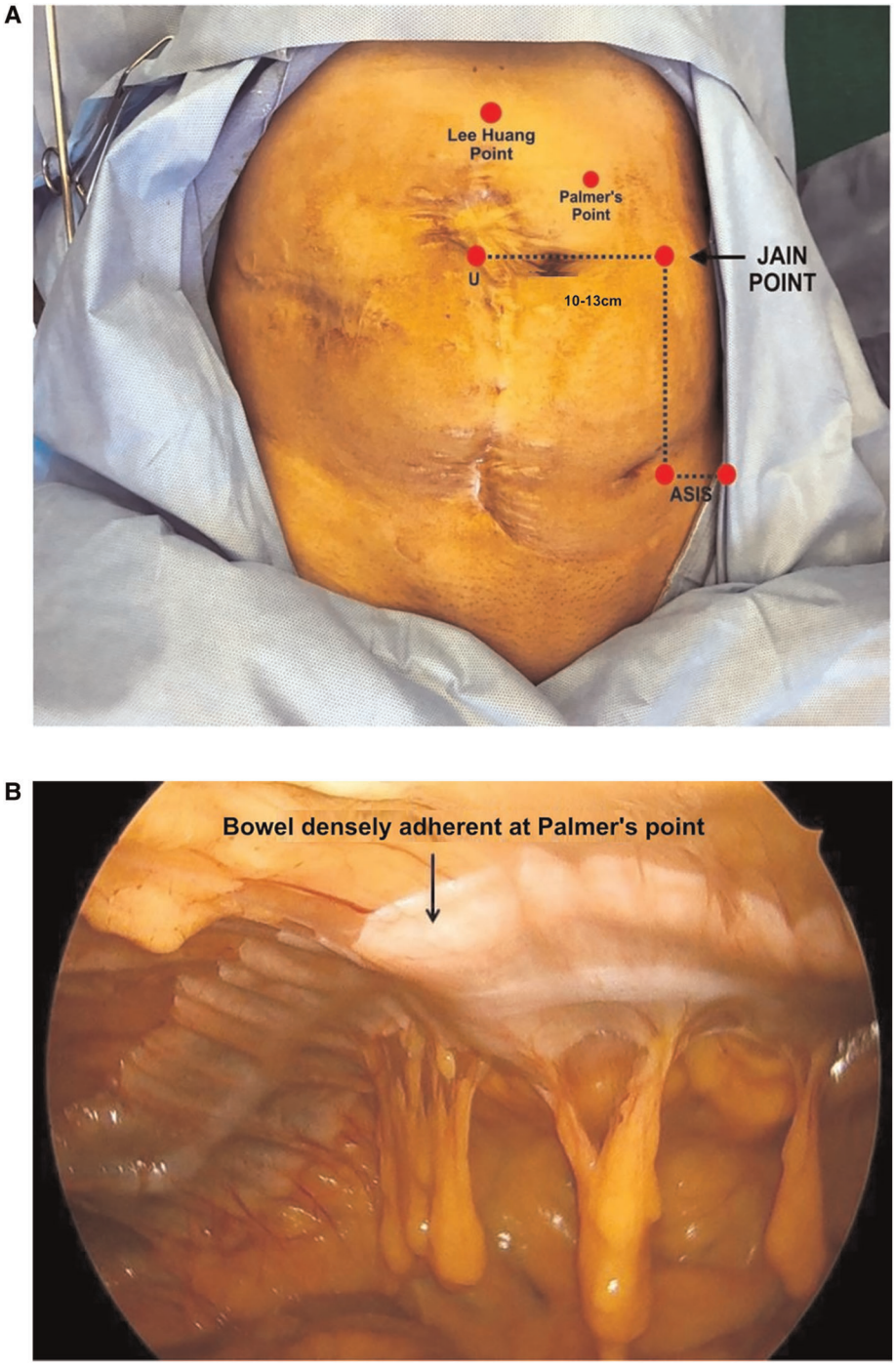

FIGURE 1
(A) Surface marking of a Jain point showing the distance from the umbilicus and the left lower port. The patient developed septicemia after surgery, following which multiple surgeries were done for colostomy and colostomy closure. (B) Finger pressing at Palmer's point from the abdominal wall, showing bowel loops stuck over the upper abdomen. The Jain point avoids Type IIA bowel adhesions.

mentions that the Jain point with a prominent bony landmark is the lowest of all entry ports and may be best for routine use. The left lateral Jain point located in the mid-abdomen can be utilized as the main ergonomic working port for both the upper and the lower abdomen (10), whereas Palmer's point becomes redundant after initial entry. With the Jain point being away from the viscera, complications associated with postinflammatory patients suspected with a high adhesion

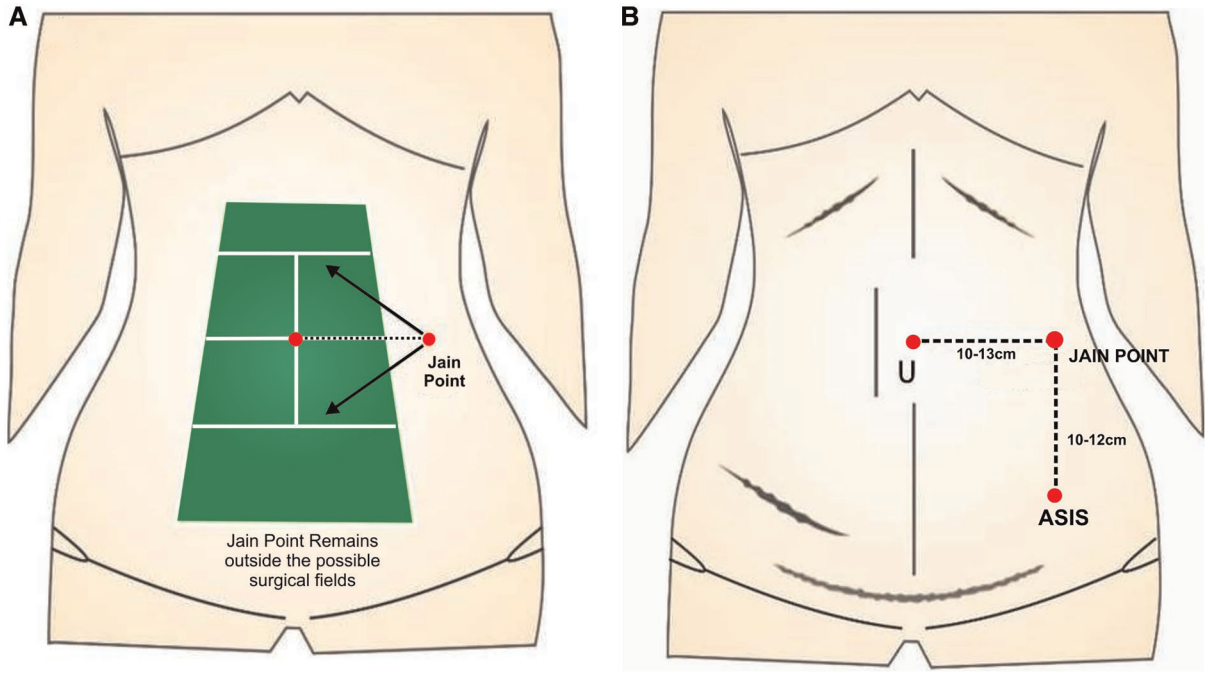

FIGURE 2
(A) Concept of a Jain point; it mimics the position of a referee on a tennis court who is sitting outside the surgical field. (B) Jain point is equally applicable for the upper-, mid-, and lower-abdomen scars.

score (classified as Type IIA adhesions) even without surgery do not occur (11). These cause omental and bowel adhesions affecting the upper abdomen, which can contraindicate Palmer's point. The Jain point can be used for all BMI patients, including low BMI patients (12) with previous surgery, whereas Palmer's point has limitations with low BMI patients due to its proximity to the left kidney (13).

Material

We collected the data of 8,586 patients who underwent laparoscopic surgery at our center from January 2011 to March 2022. Their history and operative notes were carefully recorded. The patients' age, BMI, indication of previous surgery (gynecologic or surgical), number of previous surgeries, mode of previous surgery (open or laparoscopic), and incisions of previous surgeries were tabulated. Complications were defined as events that significantly altered the planned procedure, deviated from the normal postoperative course, delayed discharge, or led to a prolongation of recuperation. Complications directly related to the entry technique that occurred intraoperatively, and discovered up to 2 weeks postoperatively, were recorded. Lastly, patients were followed up for any incisional hernia at the Jain point.

Note: To avoid inflation of data, cases of patients with multiple surgeries were counted only once when tabulating data for the mode of surgery, indication of surgery, and type of incision. For instance, if a patient had undergone laparotomy with a right paramedian incision and a cesarean section with a Pfannenstiel incision, only the right paramedian incision was considered, because the probability of having paraumbilical adhesions is more with this type of surgery and incision.

Method

The preoperative preparation comprises a low residual diet for 48 h prior to surgery and mechanical bowel preparation in all previous open surgery cases. In patients with acute clinical conditions necessitating laparoscopic, diagnostic, or therapeutic procedures, Jain point entry is made without a long bowel preparation protocol after the anesthetist administers nasogastric tube. As many procedures in the study group have been done notably in ectopic pregnancies, T.O. abscess, and the torsion of the ovary, the surgery is performed under general anesthesia, with the patient lying in the dorsal lithotomy position. The entire abdomen is inspected and previous incision sites are noted. To locate the Jain point, the ASIS, which is a prominent fixed bony landmark in the sterile surgical field, is marked and a vertical line is drawn 2.5 cm medial to the ASIS up to the level of the umbilicus. Then, a horizontal line is drawn at the upper

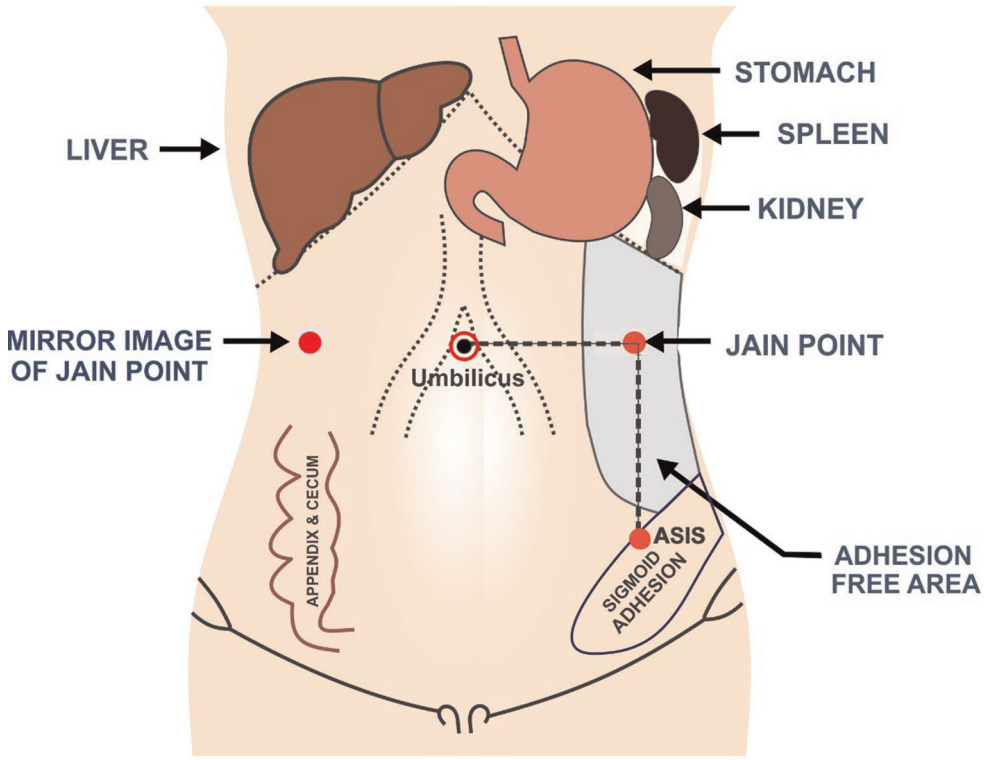

FIGURE 3
Jain point is at the L4 level, 10-13 cm lateral to umbilicus and away from both the viscera on the left side (spleen, kidney, and bloated stomach) and the sigmoid colon in a wide nascent area on the left side from L1 to pelvic, which is free from vessel, viscera, adhesions, and bowel.

margin of the umbilicus. The point where the two lines meet is the "Jain point". In effect, the entry point is located approximately 10–13 cm lateral to the umbilicus, depending on the patient's body type, BMI, and central obesity.

Notably, the abdominal wall is not lifted, avoiding unequal forces being applied during entry and zigzag track, providing a precise appreciation of layer-by-layer entry. The same technique is applied for thin or obese patients. The Veress needle is preferred, and it is entered perpendicular to the skin. Two pops are clearly heard, the first when the needle passes through the aponeurosis of the external oblique muscle and the second when the needle passes through a fused aponeurosis of the transverse abdominal muscle and internal oblique muscle, after which the needle encounters resistance as it enters the peritoneal cavity. Safety checks are done, the pneumoperitoneum is created, and the 5 mm trocar and telescope are inserted. The area below the entry point is inspected to rule out any injury to the bowel or vessel. Then, a 360° check of the abdominal cavity is done. A note is made of adhesions and their scoring and location, especially in the upper abdomen, to look for adhesions below Palmer's point and the right and left hypochondria to check for any subdiaphragmatic adhesions. Then, a 10 mm telescope is entered at an adhesion-free area according to the mandate of the surgery. The Jain point provides a working distance of 10–12 cm from the left lower port for good ergonomic working, becoming the main ipsilateral ports throughout the surgery. General surgeons and urologists have used them according to their convenience either as a camera port or as a working port later on in the course of surgery.

Results

The results of the study spanning 11 years and 8,586 cases highlight the safety of the Jain point as a routine entry port in previous surgery cases. This paper is restricted to analyzing the results in 2,519 patients who had previous surgeries and the Jain point's possible role in the contraindications of Palmer's point. The demographic profile of the patients, such as BMI, number of previous surgeries, types of scars, and indication of previous surgeries, is tabulated in Tables 2–5, respectively. The indication of previous surgery was found to be a very important factor to predict the adhesions preoperatively.

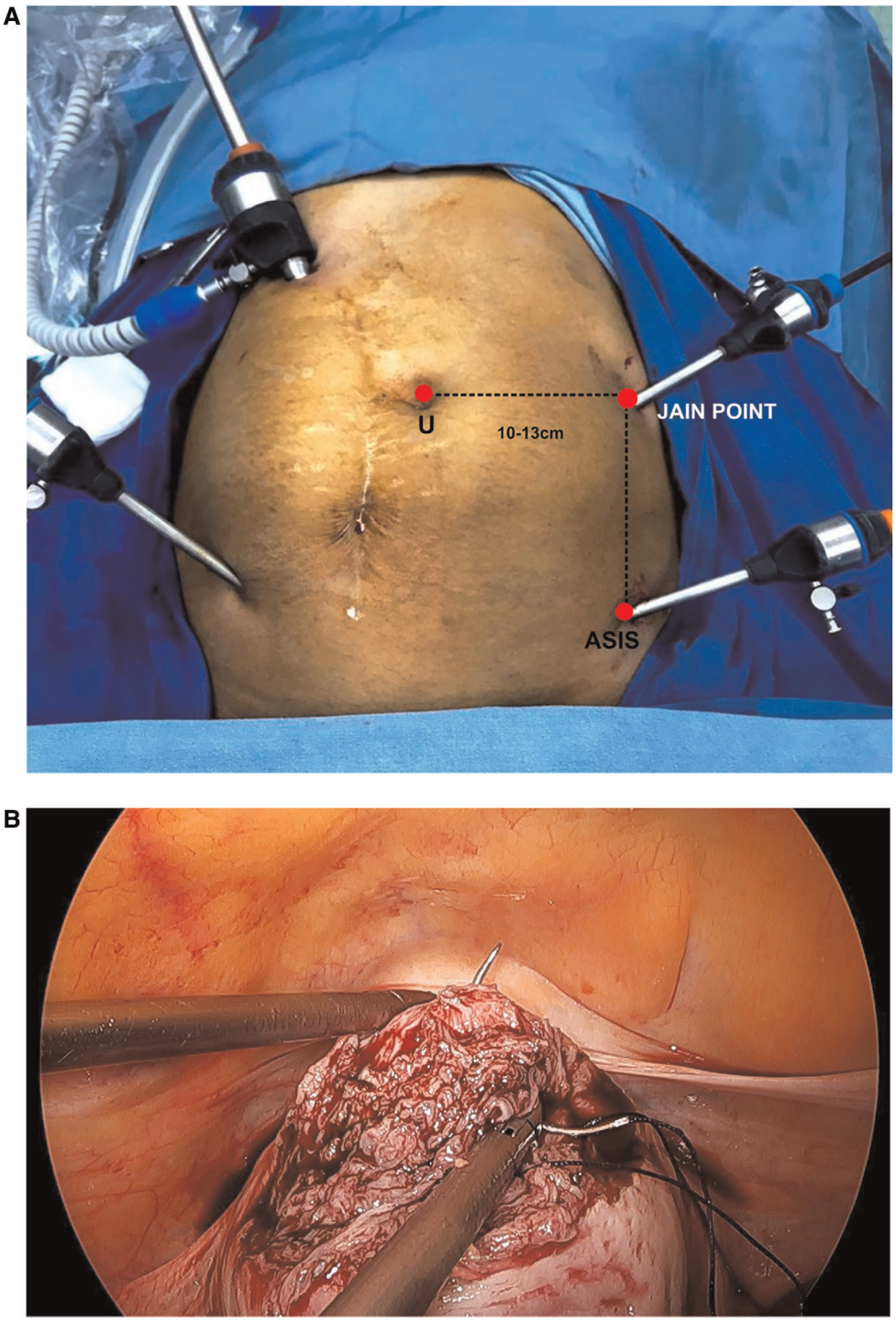

FIGURE 4
(A) 10 mm port inserted under the direct vision of the Jain point port, which becomes the main working port. (B) Ipsilateral ports making the myomectomy and suturing ergonomic.

Table 2 shows the distribution pattern of the 2,519 patients with previous surgery, according to their BMI, which ranged from <18.5 to ≥40 kg/m^2. Our study reveals that overall, in patients with a history of previous surgery, we operated on more patients in the obesity group (54%), superseding the normal BMI group (42%). Keeping with the global trend of obesity, a majority of the patients in our study had a high BMI, who included 960 overweight patients, 395 obese

TABLE 2 Distribution of previous surgery cases according to body mass index.

BMI	Numbers
<18.5	83 (3.29%)
≥18.5 to <25	1,039 (41.24%)
≥25 to <30	960 (38.11%)
≥30 to <40	395 (15.68%)
≥40	42 (1.66%)
Total	2519

BMI, body mass index.

TABLE 3 Distribution of cases according to the number of surgeries in the past.

Number of previous surgeries	Prev. laparotomy	Prev. laparoscopy
Prev. 1 surgery = 1,907 (75.70%)	817	1090
Prev. 2 surgery = 457 (18.14%)	389	68
Prev. 3 surgery = 122 (4.84%)	116	6
Prev. 4 and more surgery = 33 (1.31%)	32	1
Prev. total cases = 2519	1,354 (53.75%)	1,165 (46.24%)

TABLE 4 Distribution of patients according to the type of scar of previous surgery.

Transverse scar	Vertical scar	Mc Burney	Kocher's scar	Lap scars	Other scars
828 (32.87%)	427 (16.95%)	50 (1.98%)	44 (1.75%)	1,165 (46.25%)	5 (0.2%)

Note: other scars: Chevron scar = 3, gunshot wound = 2.

patients, and 42 morbidly obese, while only 83 (3.29%) were underweight.

Table 3 shows the distribution pattern of the 2,519 patients based on the number of surgeries in the past. A total of 1,354 patients had previous laparotomy and 1,165 had previous laparoscopy as the mode of surgery. The maximum number of patients in our study (75.7%) had one previous surgery. Of these, 817 patients underwent open surgeries and 1,090 laparoscopic surgeries. A total of 18.1% patients (457) had two previous surgeries. Among these, 389 had laparotomy and 68 laparoscopies. The percentage of patients who underwent multiple surgeries was 6.1, including 122 patients who had three previous surgeries, while 33 patients had a history of four or more surgeries. Thus, in the previous laparotomy group, we had almost 600 patients with two or more previous surgeries, while in the laparoscopy group, most had one previous surgery.

Table 4 shows the distribution pattern of patients based on the type of scar of previous surgery. A total of 32.8% (828) of the patients had previous incision as transverse. Some patients had a long horizontal incision at the level of the umbilicus, given during the neonatal period. A total of 16.9% (427) patients had vertical scars, with a few patients having non-classical incisions such as previous drain sites, colostomy sites, incisions for renal surgeries, and long vertical incisions extending from the epigastrium up to the pubic symphysis in prior surgery for intestinal obstruction, burst abdomen, septicemia, and other complex pathologies. We also had patients with atypical abdominal scar marks, with prior ectopia vesicae and Hirschsprung's disease in the early neonatal period. A total of 1.98% (50) patients had a Mc Burney scar, 1.7% (44) had Kocher's scar, and 3 had Chevron incision, while 2 had bizarre incisions related to gunshot wound surgery. A total of 46.25% (1,165) patients in our study had previous laparoscopic entry ports at multiple sites.

TABLE 5A Patient's profile depending on the type and indication of previous gynae surgery.

Previous Gynae surgery ($n = 2121$) (84.20%)		
Indications of surgery	**Laparotomy (1168) (55%)**	**Laparoscopy (953) (45%)**
LSCS	838	–
Ectopic pregnancy	92	79
Endometriosis	12	217
Myomectomy	72	158
Hysterectomy	19	18
Infectious pathologies	3	183
T.O. mass/abscess	22	52
Ovarian cyst	54	49
Mullerian anomalies	–	8
Infertility workup	8	149
Ligation	24	25
Others, including pelvic floor repair and Tubo tubal reanastomosis	24	15

LSCS, lower-segment cesarean section.

Table 5: We split the previous surgery patients into those with gynae indication (Table 5A) constituting 84.2% (2,121 out of 2,519) and general surgery cases (Table 5B) constituting 15.79% cases (398 out of 2,519).

Table 5A: In the gynae group, open procedure with 55% (1,168 out of 2,121) was 10% more prevalent than the laparoscopic procedure with 45% (953 out of 2,121). In the laparotomic approach, previous cesarean sections constituting 71.74% (838 out of 1,168) were the most common, followed by ectopic pregnancy (8%, i.e., 92 out of 1,168), both of which had a substantial rate of adhesions. Endometriosis (1%) and myomectomy (6%) were a formidable group for readhesion formation and *de novo* adhesions. Dense adhesions at the entry point and the surgical site were noted in previous

hysterectomy patients (1.6%) presenting for prolapse and posthysterectomy adnexal masses, ovarian remnant syndrome, and ovarian residual syndrome. Patients with previous surgery for infectious pathologies such as genital Koch's, septic abortion, and pelvic inflammatory disease had very advanced adhesions.

Table 5B: General surgery patients, in contrast to the gynae group, underwent more previous laparoscopies (53.26%, 212 out of 398) than previous laparotomies (46.7%, 186 out of 398) done by the open procedure. Cholecystectomy and appendectomy were the most common indications. We operated upon 13 patients with mesh hernia repairs, 7 with Hirschsprung's disease, and 5 with a high imperforate anus, which were managed in infancy by colostomy and then by the colon pull-through procedure. We encountered scars going from the pubic symphysis to the xiphisternum in midline laparotomies for indications such as Koch's abdomen [the center is located in North India, which has the world's highest prevalence of Koch's (14–17)], which, at times, necessitated bowel resection and reanastomosis and second surgery for colon pullback. These patients had a high score of adhesions. In patients in whom there were multiple scars and/or drain sites on the left side, a mirror image of the Jain point was made from the right side where there is no risk of liver injury.

No significant entry-related complications were reported in the study with the use of the Jain point as the primary port. We encountered minor complications like preperitoneal insufflation or omental emphysema, although failed entry was a less-encountered problem. In some patients with omental adhesions involving the entire abdomen, a few entries were made through the omentum, which did not incite any bleeding or require additional interventions like suture or coagulation. No vascular injury was encountered intraoperatively, no surgery was converted to laparotomy, and no mortality was noted. There was no incidence of hematoma formation after surgery, and no incisional hernia was noted at the Jain point in the long-term follow-up.

Major complications were restricted to one case (across all 8,586 patients) of small bowel entry in a patient with transverse scar exactly at the level of the umbilicus due to a laparotomy performed in childhood. We strongly suspected bowel adhesions and performed an MRI, which, however, failed to report bowel loops underneath the scar. This complication was recognized immediately, the bowel loop was extracted by widening the port, and the bowel was sutured and reposited. The patient did well postoperatively and was discharged in 3 days. The major complication rate in our study of 2,517 cases of patients with previous surgeries is 0.04%, and the overall rate for the entire number of patients entered by using the Jain point is 0.011%.

About one-third of the entries were made by fellows and trainees, with 8–10 initial cases under the supervision of senior consultants, and the remaining completely independently, demonstrating the short learning curve and reproducibility of the procedure (Table 6).

TABLE 5B Patient's profile depending on the type and indication of previous general surgery.

Previous abdominal general surgery ($n = 398$) (15.79%)		
Indications of surgery	**Laparotomy (186) (46.7%)**	**Laparoscopy (212) (53.26%)**
Appendectomy	51	59
Cholecystectomy	43	84
Renal surgery	3	1
Intestinal obstruction	25	–
Intestinal perforation	7	–
Mesh hernia repair	9	4
Septicemia	6	–
Hirschsprung's disease	7	–
Colon pull-through		
High imperforate anus	5	–
Other	30	64

TABLE 6 Entry made through Jain point.

Entry made by	No. of cases	Percentage
Senior consultant	2,978	34.68
Junior consultant	2,846	33.14
Fellows	2,762	32.16

Discussion

Palmer advocated the insertion of the Veress needle three centimeters below the left subcostal margin in the midclavicular line (called Palmer's point) in previous surgery cases. Palmer's point has enjoyed many years of use worldwide by all practitioners of endoscopic surgery, like gynecologists, general surgeons, or urologists. But as the complexities of surgical indications and the number of previous surgeries have increased, many contraindications of Palmer's point have emerged, such as hepatosplenomegaly, portal hypertension, gastropancreatic masses, huge gynecological masses forming in the upper abdomen, and upper abdominal scars on the left side due to previous splenic or gastric surgery. Even in patients with no previous surgery, making an entry through Palmer's point is challenging in those with Type IIA adhesions due to previous infectious pathology leading to bowel and omental adhesions in the upper quadrant of the abdomen, as encountered in Koch's abdomen (18–21), and previous septicemia.

To overcome these limitations, a few other non-umbilical ports were designed, namely the Lee–Huang point (22) and left 9th intercostal space (23). The Lee–Huang point was

primarily devised for para-aortic lymph node dissection. Lying midway between the xiphoid process and the umbilicus, it had the benefits of higher location and central vision and a wider working space, thereby avoiding periumbilical adhesions. Although this point was extensively used in patients with previous surgeries, it was not free from complications. In a series of 188 cases, 2 omental injuries from primary port insertion and 1 colon injury were reported. Similarly, the entry point from the left 9th intercostal space in the anterior axillary line at the superior surface of lower rib was also used for Veress needle insertion. It had a failure rate of 0.39%, and the risk of splenic injury and bleeding from subcostal artery limited its use (24). Although these points had their advantages, being located in the upper abdomen, they shared the same contraindications as Palmer's point (25).

The open Hasson technique is widely practised to remove the adhesions of previous surgeries. In this technique, blunt trocar is introduced through the vertical incision at the center of the umbilicus and pneumoperitoneum is created. Although this method took into account error-free controlled entry into the abdominal cavity, it failed to tackle the Type IIA adhesions where the bowel was densely adherent to the parietal peritoneum. A meta-analysis of 5,284 patients undergoing operative laparoscopy through this method reported primary access injuries, 1 bowel injury, 21 wound infections, 4 minor hematomas, and 1 umbilical hernia (26). It also has drawbacks such as a longer time to create a port and difficulty in maintaining the pneumoperitoneum during surgery due to leakage of gas. Also, its use is not well defined in patients with extreme BMI, becoming technically difficult to reach the rectus sheath with increased abdominal fat (27, 28).

The Jain point is shown to be safe for entry in patients with upper abdominal scars where entry through Palmer's point was not feasible. We reported one notable case of a patient with a large upper abdomen, in whom Chevron incision® was made where Palmer's point was contraindicated and entry was made using the Jain point (29). We reported another study containing 106 cases of patients with scars in the upper abdomen, where entry was made through the Jain point (30). In that study, the bowel was found stuck completely over Palmer's point in several patients with previous infectious pathologies (31), almost making a second layer of the peritoneum (**Figure 1B**). In these patients, the Jain point was used for laparoscopic entry and found to be free from adhesions. In a few patients, omental adhesions were noted, but these did not incite any bleeding during the entry of a 5 mm port and therefore did not necessitate a suture or cauterization.

In our study of 8,586 cases, the complication rates were 0.01% overall and 0.04% in previous surgery cases, across all age groups (8–76 years) and BMI ranges (12.66–58.11 kg/m^2), which were lower than those in the aforementioned studies. This can be explained by the Jain point's lateral location on the left side, 10-13 cm from the midline, inherently avoiding MRV injury. The Jain point is located at the L4 level, while all the viscera, namely, the stomach, spleen, and kidney, come up to the T12 L1 level, leaving a large nascent area till the pelvic brim where the sigmoid colon adheres. Even an adherent and distended sigmoid colon remains much lower for it to become vulnerable to trocar injury from the Jain point. Surgeons making primary entry do not encounter small or large bowel adhesions and the abovementioned formidable structures. It is very important to stay far lateral, and only being paraumbilical does not guarantee complete safety against bowel adhesions.

Unlike Palmer's point, the Lee–Huang point, and the 9th intercostal space that become redundant after initial entry, the Jain point can be used as an ergonomic working port throughout the surgery as noted by HT Sharp. Beyond just gynecologists, the point is even more versatile for general, bariatric, and oncosurgeons who commonly operate on patients having scars in all quadrants of the abdomen. The Jain point is used as a camera or working port (32), as in cholecystectomy, appendicectomy, and evaluation of patients with pain in the abdomen and hernia repairs. It can be valuable in bariatric surgery as the study indicates the Jain point's safety in high BMI patients. Oncosurgeons, while using it as a primary procedure or with second-look procedures after neoadjuvant chemotherapy, have found it safe in the context setting of advanced adhesion scores in such indications (33). The mirror image of the Jain point can be used from the right side without incurring the risk of liver laceration, making it a viable port in the lateral position for urological procedures and, in general, surgical indications where scars or drain sites are present over the Jain point on the left side.

The Jain point has a short learning curve and is easily reproducible, due to the ease of locating it by a single prominent bony landmark, the ASIS, and an easy insertion technique, as demonstrated in our study, where one-third of laparoscopic entries were made by endoscopy fellows.

The Jain point has been referenced by researchers and laparoscopic surgeons in publications on laparoscopic entry noting the benefits of the Jain point in previous surgery cases. Wasson et al. (34) recommend the use of the Jain point in patients in whom adhesive disease is suspected. Bedaiwy et al. (35) have documented the benefit of the Jain point, particularly in patients with suspected periumbilical adhesions, to enhance the safety of the subsequent 10 mm supra-umbilical port entry. Einarsson et al. (36), in a recent textbook of Minimally Invasive Gynecology, describe the Jain point as an alternative to Palmer's point on the left side mid-abdomen, 2.5 cm medial to the ASIS. Reynolds (37) has highlighted in his thesis that the Jain point is proposed as an alternate entry site when the first three options (umbilicus,

Palmer's point, and the Lee–Huang point) are not viable. Eamudomkarn et al. (38), in their recent publication, have cited the benefits of the Jain point over other points, as it is located lower and lateral than Palmer's and Lee–Huang points, avoiding injury to the viscera. Salcedo et al. (39) have described the use of the Jain point in laparoscopy in pregnancy, which is in line with our observation of over nine such surgeries done in pregnancy, where the feature of laterality gives more space for the gravid uterus.

Some publications such as "Clinical Perspective Concerning Abdominal Entry Techniques" by Recknagel et al. (40) and "Abdominal entry in laparoscopic surgery" by Pepin (41) mention the Jain point as a viable entry port in previous upper abdominal scars and previous surgery patients but have inaccurately depicted the Jain point as being located "directly lateral to the umbilicus, and 2.5 cm medial to a line drawn vertically upwards from left ASIS". Contrarily, the Jain point derives its safety features by staying 10–13 cm lateral from the umbilicus where the risk of bowel adhesions is mitigated and it avoids injury to the superior and superficial epigastric vessels that lie within 5 cm of the midline. It is important to mark the surface of the Jain point properly by locating the ASIS and the remaining 2.5 cm from it and drawing a vertical line upward at the level of the umbilicus to gain the maximum benefits of safety and ergonomics. To further increase the safety of the Jain point, entry can be made through optical trocars that clearly show the different layers of the abdominal wall and parietal peritoneum as entry is made, and they can also detect bowel injury (42). To obtain a view before entry, disposable shielded trocars, called Ternamian™ threaded trocars (43), can be used. Mulayim et al. (44) have reported direct trocar entry from the Jain point. Reusable trocars have been reported to be safe in our series. How one makes an entry through this point is a matter of personal choice or institutional practice norms.

In conclusion, this study demonstrates the safety of the Jain point as a first blind entry port across all age groups and BMI ranges, with a low complication rate of 0.04% for previous surgery cases and an overall low complication rate of 0.01%, significantly lower than those in similar studies for other entry ports. The Jain point has no known contraindications and can be used by gynecologists, urologists, oncologists, and general and bariatric surgeons to overcome the contraindications of Palmer's point.

Strength of the study

Sample size is a crucial consideration for quality research. This study includes 8,586 cases recorded over 11 years, and none of the previous studies have contained such a large number of patients and such a large time span.

Limitation of the study

Although we have a large case series and a study period of 11 years, our study is retrospective in nature.

Conclusion

Due to its anatomical location, the Jain point is a feasible entry option with low complication rates in situations where other ports have limitations. The port is safe for all types of previous scars in the upper, middle, and lower abdomen and can be used in all ranges of BMI. As per surgical need it can be used as a mirror image from the right side. Located in the mid-abdomen, it doubles up as the main ergonomic working port. It has no known contraindications. The Jain point can be used as an entry port for all practitioners of laparoscopy in previous surgery cases of patients in whom Palmer's point is contraindicated.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Vardhman Trauma and Laparoscopy Centre Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors were involved in carrying out the study. NJ and SS drafted the manuscript; SLPB and VJ contributed to the editing and reviewing of the manuscript. All authors contributed to the article and approved the submitted version.

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All authors were involved in carrying out the study. Dr Nutan Jain and Dr Sakshi Srivastava drafted the manuscript; Dr S. Lakshmi Prasanna Bayya and Dr Vandana Jain contributed to the editing and reviewing of the manuscript. All statistical analyses were carried out by Dr K.G. Arora and Aarti Jain. A very special thanks to Amol Kothari and Mansi J Kothari for helping with the editing. The authors would like to pay their gratitude to Mr Vishram Singh, Miss Asha Rathi, Mr Abhishek

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Schreinemacher MH, ten Broek RP, Bakkum EA, van Goor H, Bouvy ND. Adhesion awareness: a national survey of surgeons. *World J Surg*. (2010) 34 (12):2805–12. doi: 10.1007/s00268-010-0778-8

2. Szomstein S, Lo Menzo E, Simpfendorfer C, Zundel N, Rosenthal RJ. Laparoscopic lysis of adhesions. *World J Surg*. (2006) 30(4):535–40. doi: 10.1007/s00268-005-7778-0

3. Tinelli A, Malvasi A, Schneider AJ, Keckstein J, Hudelist G, Barbic M, et al. Primo accesso addominale in laparoscopia ginecologica: quale tecnica utilizzare? [First abdominal access in gynecological laparoscopy: which method to utilize?]. *Minerva Ginecol*. (2006) 58(5):429–40. Italian

4. Taskforce for Abdominal Entry. Principles of safe laparoscopic entry. *Eur J Obstet Gynecol Reprod Biol*. (2016) 201:179–88. doi: 10.1016/j.ejogrb.2016.03.040

5. Palmer R. Safety in laparoscopy. *J Reprod Med*. (1974) 13(1):1–5

6. Jain N, Sareen S, Kanawa S, Jain V, Gupta S, Mann S. Jain point: a new safe portal for laparoscopic entry in previous surgery cases. *J Hum Reprod Sci*. (2016) 9 (1):9–17. doi: 10.4103/0974-1208.178637

7. Sharp HT. Overview of gynecologic laparoscopic surgery and non-umbilical entry sites. In: T Falcone, editors. Wolters Kluwers (2019). p. 10. UpToDate.

8. Jain N, Jain V, Chandi A, Srivastava S, Singh S, Vasundhara N. Jain point: an alternate laparoscopic non-umbilical first blind entry port to avoid vessel, viscera, adhesions and bowel (VVAB). *Updates Surg*. (2021) 73(6):2321–9. doi: 10.1007/s13304-021-01099-z

9. Reich H. Foreword. In: N Jain, editors. *Non-umbilical laparoscopic entry ports*, 1st ed. New Delhi: Jaypee Brothers Medical Publishers (2020).

10. Mohapatra GSS, Bhusan B. Comparative study of different entry sites in laparoscopic surgery: which is safest? *IOSR J. Dent. Med. Sci. (IOSR-JDMS)*. (2017) 16(1):64–6. doi: 10.9790/0853-1601086466

11. Diamond MP. Reduction of de novo postsurgical adhesions by intraoperative precoating with sepracoat (HAL-C) solution: a prospective, randomized, blinded, placebo-controlled multicenter study. The Sepracoat Adhesion Study Group. *Fertil Steril*. (1998) 69(6):1067–74. doi: 10.1016/s0015-0282(98)00057-0

12. Jain N, Sareen S, Kanawa S, Jain V, Gupta S, Mann S. Jain point: A new safe portal for laparoscopic entry in previous surgery cases. *J. Hum. Reprod. Sci*. (2016) 9(1):9–17. doi: 10.4103/0974-1208.178637

13. Giannios NM, Gulani V, Rohlck K, Flyckt RL, Weil SJ, Hurd WW. Left upper quadrant laparoscopic placement: effects of insertion angle and body mass index on distance to posterior peritoneum by magnetic resonance imaging. *Am J Obstet Gynecol*. (2009) 201(5):522.e1-5. doi: 10.1016/j.ajog.2009.07.017

14. Debi U, Ravisankar V, Prasad KK, Sinha SK, Sharma AK. Abdominal tuberculosis of the gastrointestinal tract: revisited. *World J Gastroenterol*. (2014) 20(40):14831–40. doi: 10.3748/wjg.v20.i40.14831

15. Gupta N, Sharma JB, Mittal S, Singh N, Misra R, Kukreja M. Genital tuberculosis in Indian infertility patients. *Int J Gynaecol Obstet*. (2007) 97 (2):135–8. doi: 10.1016/j.ijgo.2006.12.018

16. Sharma JB, Roy KK, Pushparaj M, Gupta N, Jain SK, Malhotra N, et al. Genital tuberculosis: an important cause of Asherman's syndrome in India. *Arch Gynecol Obstet*. (2008) 277(1):37–41. doi: 10.1007/s00404-007-0419-0

17. "India records 2.15 m new TB patients in 2018". The Nation. 2019-03-26. Retrieved 2019-03-27.

18. Jain N, Kanwar M. Laparoscopy in genital Tuberculosis. In: N Jain, editors. *State of the art atlas of endoscopic surgery in infertility and gynaecology*. New Delhi, India: Jaypee Brothers (2004). p. 425–39.

19. Jain N. A rare case of encapsulated caseous ball. *J Minim Invasive Gynecol*. (2007) 14:557–8. doi: 10.1016/j.jmig.2007.03.006

20. Sharma JB, Roy KK, Gupta N, Jain SK, Malhotra N, Mittal S. High prevalence of Fitz-Hugh-Curtis syndrome in genital tuberculosis. *Int J Gynaecol Obstet*. (2007) 99(1):62–3. doi: 10.1016/j.ijgo.2007.03.024

21. Sharma JB, Roy KK, Pushparaj M, Kumar S, Malhotra N, Mittal S. Laparoscopic findings in female genital tuberculosis. *Arch Gynecol Obstet*. (2008) 278(4):359–64. doi: 10.1007/s00404-008-0586-7

22. Lee CL, Huang KG, Jain S, Wang CJ, Yen CF, Soong YK. A new portal for gynecologic laparoscopy. *J Am Assoc Gynecol Laparosc*. (2001) 8(1):147–50. doi: 10.1016/s1074-3804(05)60565-8

23. Lam KW, Pun TC. Left upper quadrant approach in gynecologic laparoscopic surgery using reusable instruments. *J Am Assoc Gynecol Laparosc*. (2002) 9(2):199–203. doi: 10.1016/s1074-3804(05)60132-6

24. Agarwala N, Liu CY. Safe entry techniques during laparoscopy: left upper quadrant entry using the ninth intercostal space–a review of 918 procedures. *J Minim Invasive Gynecol*. (2005) 12(1):55–61. doi: 10.1016/j.jmig.2004.12.026

25. Tulikangas PK, Nicklas A, Falcone T, Price LL. Anatomy of the left upper quadrant for cannula insertion. *J Am Assoc Gynecol Laparosc*. (2000) 7 (2):211–4. doi: 10.1016/s1074-3804(00)80042-0

26. Hasson HM. Open laparoscopy as a method of access in laparoscopic surgery. *Gynaecol Endosc*. (1999) 8:353–62. doi: 10.1046/j.1365-2508.1999.00316.x

27. Vilos GA, Ternamian A, Dempster J, Laberge PY, Vilos G, Lefebvre G, et al. Laparoscopic entry: a review of techniques, technologies, and complications. *J Obstet Gynaecol Can*. (2007) 29(5):433–47. doi: 10.1016/S1701-2163(16)35496-2

28. Dunne N, Booth MI, Dehn TC. Establishing pneumoperitoneum: Verres or Hasson? The debate continues. *Ann R Coll Surg Engl*. (2011) 93(1):22–4. doi: 10.1308/003588411X12851639107557

29. Jain N, Jain V, Agarwal C, Bansal P, Gupta S, Bansal B. Left lateral port: safe laparoscopic port entry in previous large upper abdomen laparotomy scar. *J Minim Invasive Gynecol*. (2019) 26(5):973–6. doi: 10.1016/j.jmig.2018.10.017

30. Jain N, Jain V, Gupta S. Jain point: to study the efficacy and safety in previous upper abdominal scars. *J Minim Invasive Gynecol*. (2021) 28(11): Supplement, S115. doi: 10.1016/j.jmig.2021.09.179

31. Sharma JB, Mohanraj P, Roy KK, Jain SK. Increased complication rates associated with laparoscopic surgery among patients with genital tuberculosis. *Int J Gynecol Obstet*. (2010) 109:242–4. doi: 10.1016/j.ijgo.2010.01.011

32. Gupta S, Gupta P, Jain N. Jain point in the practice of general surgery. In: Jain N. *Non-umbilical laparoscopic entry ports*, 1st ed. New Delhi: Jaypee brothers medical publishers (2020) p. 254–73.

33. Marco A, In Sociedad Espanola (SEGO). https://sego.es/views/pildorasinformativas/MARCO_ARONES_COLLANTES_JAIN_POINT.mp4

34. Carrubba AR, McKee DC, Wasson MN. Route of hysterectomy: straight stick laparoscopy. *J Gynecol Surg*. (2021) 37(2):107–11. doi: 10.1089/gyn.2020.0223

35. Bedaiwy MA, Yong PJ, Farghaly TA, Abdelhafez FF, Tan J, Pope R, et al. The effect of age and body mass index on the surgical anatomy of supraumbilical port insertion: implications for laparoscopic and robotic surgery. *Gynecol Obstet Invest*. (2018) 83(6):546–51. doi: 10.1159/000488676

36. Clark NV, Einarsson JI. 5. Laparoscopic entry techniques. In: E Saridoğan, GS Kilic, K Ertan, editors. *Minimally invasive surgery in gynecological practice: Practical examples in gynecology*. Berlin, Boston: De Gruyter (2020). p. 50–60. doi: 10.1515/9783110535204-005

37. Reynolds R. *Development of an intraperitoneal catheter placement device for use on the battlefield M.S. Thesis*. University of Nebraska-Lincoln (2021).

38. Eamudomkarn N, Luanratanakorn S, Seejorn K. Alternative access sites for abdominal entry in gynecologic laparoscopy: a literature review and narrative summary of findings. *Srinagarind Med J*. (2021) 36(2):240–5. Available from: https://li01.tci-thaijo.org/index.php/SRIMEDJ/article/view/249590

39. Salcedo AMC, Guarin CB, Jaramillo JDL, Isanoa JDL, Gutierrez DLP, Echeverri JDV. Glob. libr. women's med., ISSN: 1756-2228. doi: 10.3843/GLOWM.415713

40. Recknagel JD, Goodman LR. Clinical perspective concerning abdominal entry techniques. *J Minim Invasive Gynecol*. (2021) 28(3):467–74. doi: 10.1016/j.jmig.2020.07.010

41. Pepin K. Abdominal entry in laparoscopic surgery. *Contemp OB/GYN J*. (2020) 65(11):20–3.

42. Jirecek S, Dräger M, Leitich H, Nagele F, Wenzl R. Direct visual or blind insertion of the primary trocar. *Surg Endosc*. (2002) 16(4):626–9. doi: 10.1007/s00464-001-9089-3

43. Ternamian AM. A trocarless, reusable, visual-access cannula for safer laparoscopy; an update. *J Am Assoc Gynecol Laparosc*. (1998) 5(2):197–201. doi: 10.1016/s1074-3804(98)80091-1

44. Mulayim B, Aksoy O. Direct trocar entry from left lateral port (Jain point) in a case with previous surgeries. *J Gynecol Surg*. (2020) 36(1). doi: 10.1089/gyn.2019.0077

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Calcium channel blocker and risk of postoperation lymphatic-related complications among gynecologic malignances

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Purpose: This study was performed to assess the association of calcium channel blockers (CCB) and other potential factors with postoperative lymphatic-related morbidity in patients with cervical cancer and endometrial carcinoma.

Methods: Patients diagnosed with cervical cancer or endometrial carcinoma with pelvic lymphadenectomy between January 2017 and January 2022 were enrolled. Postoperative lymphatic-related morbidity was evaluated by calculating the lymph cyst occurrence within 3 months after surgery and the duration of pelvic drainage. Univariate analyses evaluating the risk factors for lymphatic-related morbidity were performed.

Results: Of a total of 251 patients, 52 patients were diagnosed with lymphatic cysts by B-ultrasound or computed tomography, and the duration of drainage from 110 patients exceeded the average number of days. Univariable analysis revealed that hypertension, CCB, and lymph node metastasis were independent predictors of postoperative complications.

Conclusions: This study demonstrated that CCB may be a factor associated with the incidence of postoperation lymph cysts, and CCB usage prolongs the duration of pelvic drainage.

KEYWORDS

CCB, calcium channel blocker, lymphadenectomy, lymph cyst, time of drainage, cervical cancer, endometrial carcinoma

Introduction

Gynecologic cancers, including ovarian, endometrial, and cervical cancers, are major types of malignancies for women worldwide. The incidence of cervical cancer in China is the highest among female malignant tumors (1, 2). Systematic pelvic lymph node dissection (PLND) remains an imperative surgical procedure in the treatment of gynecologic cancer. PLND not only improves staging accuracy but may also improve the prognosis.

Spontaneous contractions of smooth muscle cells in the lymphatic vessel walls are essential to maintain tissue homeostasis by draining fluid from peripheral tissues into circulation. Decreases in lymphatic pumping may reduce the velocity of lymphatic reflux and instigate lymph stasis or lymphedema. Lymphedema was first widely

studied as a postoperative complication of breast cancer because of its high incidence and irreversibility. Of the patients treated for breast cancer, 41% develop lymphedema (3). Risk factors in patients with arm lymphedema include BIM > 30, radiation, advanced stage cancer, more invasive surgery, certain chemotherapy, infection, and so on (4).

Underlying the contractions are spontaneous action potentials and associated calcium ion (Ca^{2+}) transients. Various studies have confirmed that the peacemaking mechanism relies on spontaneous transient depolarizations (STDs), which result in the opening of Ca^{2+}-activated chloride channels (5).

Lymphatic leakage that commonly developed following pelvic lymph node dissection remains to be defined (6). It can occur anywhere along the pathway of lymph, which commences in all four extremities and the abdominal and peritoneal cavities. In 1994, Geissler et al first proposed the concept of chylous ascites, which is a rare form of ascites that results from the leakage of lipid-rich lymph into the peritoneal cavity.

Lymphatic leakage could cause some clinical symptoms such as limb lymphedema, prolonged lymphatic cyst, infection, and fever. The patients' quality of life significantly deteriorated so as their sleep quality.

With the ongoing development of both laparoscopic technology and equipment, laparoscopic minimally invasive surgery is widely used in gynecological operations. Nevertheless, some studies have previously reported that CO^2 pressure and ultrasonic knife coagulation during laparoscopic surgery could lead to transient occlusion of injured lymphatic vessels (6, 7). This obstruction subsequently causes lymphatic leakage during the patient's recovery. Due to the obstruction of lymphatic circulation and the presence of cavities in the retroperitoneum, localized lymphoid cyst are easily formed in the pelvis after systematic lymphadenectomy. Therefore, placing a pelvic drainage tube could drain the accumulated lymphatic fluid, and surgeons could observe whether there is active pelvic bleeding.

Several studies have analyzed the risk factors for the development of postoperative lymphatic leakage. Reported major risk factors for lymphatic leakage include having a high body mass index (BMI), radiation therapy, and having had lymph nodes removed, with the risk increasing with the number of lymph nodes removed. However, some of these risk factors remain ambiguous (8, 9).

A recent study showed that a novel risk factor of upper extremity lymphedema was associated with the treatment of breast cancer. In 2019, Stolarz et al. studied the effect of calcium channel blockers (CCB) on the risk of postoperative lymphedema in patients with malignant breast cancers for the first time. This retrospective study revealed that CCB exposure was significantly associated with an increased risk of lymphedema (10).

Unfortunately, throughout an array of standard postoperative lymphatic leakage research studies, there is still lack of consensus of lymphatic leakage. The researchers consider that drainage tube removal is a major factor affecting the morbidity of the patients' physiological and psychological recovery as well as overall length of hospital stay. In our study, lymphatic leakage is defined as follows: the continuous drainage color of the postoperative pelvic drainage tube may be light yellow or chylous fluid, and the drainage fluid within 3–5 days postoperation is in excess of 300 ml/d, and other causes have been excluded (including urinary fistula).

Method

This study is a retrospective case–control study, and block randomization will be adopted for random grouping. The 1,195 patients diagnosed with either cervical cancer or endometrial cancer between January 1, 2017, and January 1, 2022, who were treated in our hospital with PLND including dissection of the internal iliac, external iliac, common iliac, and obturator lymph nodes on both sides, were reviewed retrospectively. A total of 217 patients were excluded because the scope of lymph node dissection was beyond the pelvic cavity. Among the 978 patients remaining, 127 had hypertension. A total of 127 patients with a nonhypertensive gynecologic malignant tumor were randomly selected as control group. Due to the absence of pelvic imaging materials within 3 months after operation, 3 patients were excluded and a total of 251 patients were included.

The patients with cervical malignant tumors and endometrial cancers were divided into groups with strict limitations on the scope of lymph node dissection. For all included patients, data regarding age, weight, height, BMI, diagnosis of cancer, preexisting chronic disease (hypertension and diabetes), number of lymph nodes removed, duration of drainage (defined as the period elapsed from the first day after surgery to the day the drainage tube was removed), postoperative drainage volume, use of different antihypertension drugs, and postoperative therapy were collected.

Patients were sorted into two groups according to whether lymphatic cyst was found by imaging 3 months after operation. Considering the postoperative hospitalization time, we also grouped the patients according to the median time of duration of pelvic drainage.

The statistical analyses were performed using the SPSS statistics version 22.0 (IBM, Armonk, NY, United States) software programs. Continuous variables were presented as the mean and SD (normally distributed variables) or median. Categorical variables were presented as numbers and percentages. Variables with a value of $P < 0.05$ in the univariate analyses were included in the subsequent

multivariate forward logistic regression analysis. Stepwise forward logistic regressions were used in multivariate analysis. Propensity score matching (PSM) was performed to eliminate the different distributions of variates among individuals in the two groups. PSM was conducted based on the logic of the propensity score and one-to-one nearest neighbor matching. The caliper was 0.02. All tests were two-sided, and differences were considered to be statistically significant at $P < 0.05$.

Result

Patient characteristics

In total, 122 patients diagnosed with cervical malignant tumors and 129 patients with endometrial cancers were enrolled in the present randomized controlled trial. With different kinds of cancer, patients were assigned to the lymph cyst group and nonlymph cyst group separately. Patient's age, BMI, hypertension, antihypertension drugs, blood routine, and biochemical indexes were similar between the two cohorts (Table 1).

TABLE 1 Patient's population.

Characteristics	Overall ($n = 251$)
Demographics	
Age	57.37 ± 10.00
BMI	24.40 ± 3.44
Cervical cancer	122 (48.6%)
Endometrial carcinoma	129 (51.4%)
Hypertension	127 (50.6%)
Diabetes	44 (17.5%)
CCB	65 (25.9%)
ACEI	23 (9.2%)
β	15 (6.0%)
Radiation	61 (24.3%)
Lymph node positivity	35 (13.9%)
Number of lymph node clearance	24.55 ± 9.88
Laboratory results	
WBC	6.97 ± 1.95
Neutrophil	4.46 ± 1.70
Lymphocyte	1.94 (1.50–2.32)
Monocyte	0.40 (0.32–0.49)
AST	24.95 ± 10.76
ALT	22.64 ± 16.22
ALB	43.20 ± 3.85
Cr	59.14 ± 12.79
Hb	125.02 ± 22.11

BMI, body mass index; CCB, calcium channel blockers; WBC, white blood cell; AST, Aspartate transaminase; ALT, Alanine transaminase; ALB, Albumin; Hb: Hemoglobin; Cr: Creatinine.

The incidence of lymph cyst in cervical cancer was 19.7% and 21.9% in endometrial carcinoma. There was no significant difference between the two groups (Figure 1).

The various lymph node dissections revealed 23.70 ± 8.5558 for cervical cancer and 25.36 ± 9.13 for endometrial malignance ($P = 0.137$). The characteristics of the two malignancies are outlined in Table 2. No difference was observed in BMI cervical cancer (CC): 24.01 ± 3.25 vs. endometrial carcinoma (EC): 24.77 ± 3.59; $P = 0.079$) and albumin (CC: 43.41 ± 4.36 vs. EC: 43.00 ± 3.29 s; $P = 0.401$) between the cervical cancer and endometrial cancer cohorts. Additionally, no significant difference was perceived regarding the duration of drainage. However, there was a statistically significant elevation in the rate of postoperation radiotherapy in the cervical cancer group (CC: 34.4% vs. EC: 14.7%, $P = 0.04$) (Table 2).

Univariate and multivariate analysis for postoperative lymph cyst

The results of the univariate and multivariate analysis of factors associated with postoperative lymph cyst (within 3 months after surgery) are shown in Tables 3 and 4, respectively. In the univariate analyses for endometrial carcinoma, hypertension (OR = 2.779, $P = 0.028$), CCB (OR = 4.415, $P = 0.001$), ACEI (OR = 4.409, $P = 0.028$), and lymph node positivity (OR = 3.389, $P = 0.027$) were associated with the postoperative lymph cyst. Regarding cervical cancer, the result demonstrated that the number of lymph nodes removed (OR = 1.053, $P = 0.049$), neutrophil (OR = 1.293, $P = 0.016$), and NLR (ratio of neutrophils to lymphocytes) (OR = 1.428, $P = 0.002$) were linked with the development of a lymphatic cyst postoperation. Multivariate logistical regression models were created and shown that radiation (OR 2.593, 95% CI 1.014–6.629, $P = 0.047$) and neutrophil (OR 1.231, 95% CI 0.991–1.530, $P = 0.060$) were significantly associated with the postoperative lymph cyst in endometrial carcinoma, CCB (OR 4.915, 95% CI 1.860–12.984, $P = 0.001$) and radiation (OR 4.756, 95% CI 1.536–14.724, $P = 0.007$).

Patient characteristics for duration of drainage

Hypertension, CCB, and lymph node metastasis were the risk factors according to the median duration of drainage ($P < 0.001$, $P = 0.002$, $P = 0.035$; Table 5).

PSM

The PSM result between two groups is shown in Table 6. Seven variables (age, BMI, radiation, white blood cell,

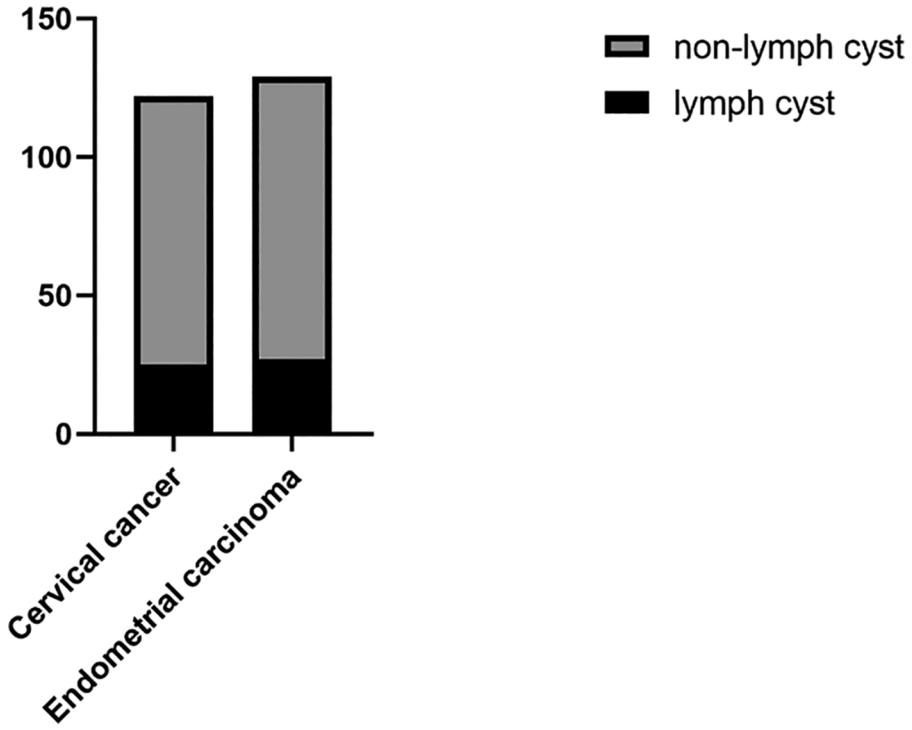

FIGURE 1
Incidence of lymph cyst.

neutrophil, CCB, and the number of lymph node clearance) were selected to calculate the propensity score. After matching, only hypertension and the use of beta receptor blockers were associated with the occurrence of lymphoid cyst.

Discussion

Calcium ion channels are present in the majority of cells of eukaryotic and prokaryotic organisms, which control a variety of cellular functions and regulate vital biological processes. Additionally, they also have been proposed to regulate a variety of biological and physiological processes, ranging from cellular secretions to electrical signaling. The discovery that nifedipine-sensitive voltage-dependent Ca^{2+} channels (VDCCs) control the regulation of the frequency of lymphatic contractions and the strength of contractions inspired researchers to attempt to develop an understanding of the relationship between lymphatic leakage and CCBs.

However, lymph node dissection was only an option for staging to particular patients, and it did not extend the survival time in patients with early-stage cancer. There is a heated debate in worldwide gynecological oncology circles about lymphadenectomy in early-stage epithelial ovarian cancer and endometrial cancer, with many beliefs in the necessity of a systematic lymphadenectomy for accurate staging. A number of research studies have reported that extensive lymph node dissection significantly increased postoperative respiratory complications and delayed patients' rehabilitation.

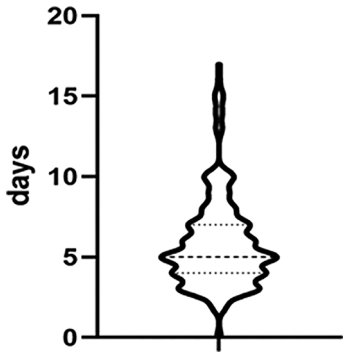

FIGURE 2
Duration of pelvic drainage..

In different studies, the rate of lymphedema complication in patients who underwent systematic pelvic lymphadenectomy for gynecologic malignancies was found to be 4%–35% (11, 12). A systematic pelvic and para-aortic lymphadenectomy still has been conventionally performed as a part of the whole procedure of surgery of gynecologic malignancies.

TABLE 2 Patients' characteristics.

Characteristics	Cervical cancer ($n = 122$)	Endometrial carcinoma ($n = 129$)	*P*-value
Demographics			
Age	57.39 ± 11.65	57.35 ± 8.18	0.977
BMI	24.01 ± 3.25	24.77 ± 3.59	0.079
Medical history			
Hypertension	61 (50.0%)	66 (51.2%)	0.854
Diabetes	22 (18.0%)	22 (17.1%)	0.839
CCB	31 (25.4%)	34 (26.4%)	0.864
ACEI	13 (10.7%)	10 (7.8%)	0.425
β	8 (6.6%)	7 (5.4%)	0.706
Radiation	42 (34.4%)	19 (14.7%)	<0.001
Lymph node positivity	18 (17.1%)	17 (13.2%)	0.737
Number of lymph node removed	23.70 ± 8.55	25.36 ± 9.13	0.137
Laboratory results			
WBC	7.19 ± 2.19	6.77 ± 1.68	0.091
Neutrophil	4.62 ± 1.98	4.31 ± 1.37	0.160
Lymphocyte	1.98 (1.40–2.40)	1.82 (1.55–2.24)	0.290
Monocyte	0.41 (0.35–0.56)	0.38 (0.30–0.47)	0.470
AST	23.92 ± 10.21	25.92 ± 11.21	0.141
ALT	20.77 ± 12.73	24.40 ± 18.82	0.076
ALB	43.41 ± 4.36	43.00 ± 3.29	0.401
Cr	59.40 ± 14.56	58.90 ± 10.92	0.759
Hb	124.79 ± 23.62	125.24 ± 20.66	0.870

BMI, body mass index; CCB, calcium channel blockers; WBC, white blood cell; AST, Aspartate transaminase; ALT, Alanine transaminase; ALB, Albumin; Hb: Hemoglobin; Cr: Creatinine.

The existing postoperative complications related to lymphatic leakage after lymph node dissection were mainly studied in breast and gynecological cancers, and the main research was focused on the long-term complication—limb lymphedema caused by regional lymph node dissection. Our study was mainly focused on the short-term adverse reactions of patients after operation including postoperative time with drainage tube, length of hospital stay, and readmission rate within 30 days.

The mechanisms of lymphedema are complex and there is no consensus. In general, it requires the following structural condition for lymphatic leakage: the interruption of the lymphatic circulation pathway and the lymphatic pressure at the damaged site being greater than the tissue fluid pressure or intrabody pressure. Removal of the retroperitoneal lymph nodes during the operation of gynecologic malignancies may result in damage to some major lymphatic vessels and trunks with high pressure and a large flow, resulting in lymphatic leakage. The consensus regarding the most critical risk factors for lymphatic leakage is that the number of removed lymph nodes and having had adjuvant radiotherapy are the most strongly correlated to lymphatic leakage.

The larger the scope of lymph node dissection, the higher the probability of lymphatic vessel injury, which is a common cause of lymphatic vessel obstruction and dilatation. A dissection spanning a larger area is also correlated with the inadequate ligation of thick lymphatic vessels or injury of local lymphatic vessels during the operation.

However, different studies have reported variable outcomes from postoperative adjuvant therapy. Biglia et al. found that neither chemotherapy alone nor the association of consecutive chemotherapy and radiotherapy was associated with an increased incidence of lower limb lymphedema (13). In addition, there have been a few studies investigating the risk factors including BMI, nutritional status, number of removed lymph nodes, lymphedema, and adjuvant radiotherapy in patients having systematic lymphadenectomy (14, 15).

Due to the declining concentration of estrogen declining in most postmenopausal women, women with high blood pressure were mainly reported in the age group of 50 or older. These women were also prone to gynecology malignant tumors (16). CCBs are becoming one the most commonly prescribed drugs, which are gaining popularity due to their fewer side effects and acceptable tolerability. As studies into the role of calcium channel in the contractile function of the lymphatics carry on, association of CCB with the rate of postoperative upper limb lymphedema has been reported in some studies (10, 17). A common mechanism of action for antihypertensive medications is the regulation of calcium signaling and smooth muscle contraction, both of which are fundamental elements in normal lymphatic function. Different calcium channel blockers have been administered in the lymphatic vessels of mice to reduce the contraction frequency and weaken the contraction intensity (5).

At present, there is no effective treatment for lymphatic leakage. Treatment is predominantly divided into conservative treatment and surgical treatment. The main conservative treatments were prohibition, nutritional support, and somatostatin. The key to surgical treatment is to find the target lost lymphatic vessels and accurately ligate them. Due to the change of pelvic anatomy after the operation, the operation is very challenging. Some new methods were proposed. Some cases have reported embolization with fibrin glue and cyanoacrylate glue, but the effectiveness of these methods has not been confirmed. How to make these complications be anticipated as well as prevented in future is our immediate priority. Our study identified a new risk factor for postoperative complications in patients with pelvic lymph node dissection. The results of this study suggest that perhaps changing the use of perioperative antihypertensive drugs

TABLE 3 Univiarate and multivariate analysis of cervical cancer for lymph cystis.

Characteristics	Univiarate		Analysis	Multivariate		Analysis
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age	1.016	0.978–1.055	0.425			
BMI	0.970	0.844–1.115	0.667			
Hypertension	1.106	0.459–2.666	0.823			
Diabetes	1.176	0.387–3.573	0.774			
CCB	1.918	0.745–4.933	0.177			
ACEI	0.680	0.141–3.285	0.631			
β	1.319	0.250–6.967	0.745			
Radiation	3.136	1.271–7.742	0.013	2.593	1.014–6.629	0.047
Lymph node positivity	1.129	0.337–3.787	0.844			
Number of lymph node clearance	1.053	1.000–1.108	0.049			
WBC	1.205	0.995–1.460	0.057			
Neutrophil	1.293	1.048–1.595	0.016	1.231	0.991–1.530	0.060
Lymphocyte	0.537	0.277–1.041	0.066			
Monocyte	1.976	0.803–4.867	0.138			
AST	1.031	0.992–1.072	0.117			
ALT	1.012	0.980–1.045	0.474			
ALB	0.909	0.808–1.024	0.117			
Hb	0.984	0.968–1.001	0.065			

BMI, body mass index; CCB, calcium channel blockers; WBC, white blood cell; AST, Aspartate transaminase; ALT, Alanine transaminase; ALB, Albumin; Hb: Hemoglobin.

TABLE 4 Univiarate and multivariate analysis of endometrial carcinoma for lymph cystis.

Characteristics	Univiarate		Analysis	Multivariate		Analysis
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age	1.041	0.988–1.096	0.130			
BMI	1.012	0.899–1.139	0.846			
Hypertension	2.779	1.115–6.927	0.028			
Diabetes	2.030	0.732–5.632	0.174			
CCB	4.415	1.796–10.853	0.001	4.915	1.860–12.984	0.001
ACEI	4.409	1.174–16.558	0.028			
β	0.001	0.001–	0.999			
Radiation	3.483	1.236–9.818	0.018	4.756	1.536–14.724	0.007
Lymph node positivity	3.389	1.146–10.025	0.027			
Number of lymph node clearance	1.046	0.998–1.096	0.061			
WBC	1.20	0.937–1.557	0.145			
Neutrophil	1.221	0.895–1.665	0.207			
Lymphocyte	1.381	0.700–2.724	0.351			
Monocyte	1.050	0.716–1.539	0.804			
AST	1.101	0.766–1.581	0.604			
ALT	1.007	0.972–1.044	0.684			
ALB	1.009	0.989–1.030	0.378			
Hb	0.975	0.856–1.110	0.698			

BMI, body mass index; CCB, calcium channel blockers; WBC, white blood cell; AST, Aspartate transaminase; ALT, Alanine transaminase; ALB, Albumin; Hb: Hemoglobin.

TABLE 5 Patient characteristics for duration of drainage.

Characteristics	Duration of drainage ≤ 5 d ($n = 141$)	Duration of drainage > 5 d ($n = 110$)	*P*-value
Demographics			
Age	56.42 ± 9.22	58.58 ± 10.84	0.089
BMI	24.30 ± 3.28	24.54 ± 3.66	0.589
Medical history			
Hypertension	56 (39.7%)	71 (64.5%)	<0.001
Diabetes	28 (19.9%)	16 (14.5%)	0.272
CCB	26 (18.4%)	39 (35.5%)	0.002
ACEI	9 (6.4%)	1412.7%)	0.084
β	7 (5.0%)	8 (7.3%)	0.444
Radiation	39 (27.7%)	22 (20.0%)	0.160
Lymph node positivity	14 (9.9%)	21 (19.3%)	0.035
Number of lymph node clearance	24.82 ± 8.95	24.21 ± 8.81	0.588
Laboratory results			
WBC	6.91 ± 2.01	7.06 ± 1.88	0.555
Neutrophil	4.41 ± 1.82	4.52 ± 1.53	0.596
Lymphocyte	1.93 (1.46–2.32)	1.95 (1.55–2.31)	0.409
Monocyte	0.40 (0.32–0.50)	0.39 (0.31–0.48)	0.273
AST	24.58 ± 11.42	25.42 ± 9.89	0.542
ALT	22.23 ± 16.95	23.16 ± 15.29	0.651
ALB	42.98 ± 4.21	43.47 ± 3.32	0.320
Hb	124.59 ± 20.27	125.58 ± 24.34	0.726

BMI, body mass index; CCB, calcium channel blockers; WBC, white blood cell; AST, Aspartate transaminase; ALT, Alanine transaminase; ALB, Albumin; Hb: Hemoglobin.

TABLE 6 Propensity score matching for cystis.

Characteristics	Before match			After match		
	Cystis group ($n = 52$)	Non-cystis group ($n = 199$)	*P*-value	Cystis group ($n = 45$)	Non-cystis group ($n = 45$)	*P*-value
Age	59.27 ± 10.91	56.87 ± 9.71	0.123	58.33 ± 11.06	62.53 ± 8.32	0.045
BMI	24.34 ± 3.77	24.42 ± 3.36	0.897	24.27 ± 4.00	24.55 ± 3.38	0.725
Hypertension	32 (61.5%)	95 (47.7%)	0.076	25 (55.6%)	38 (84.4%)	0.003
Diabetes	12 (23.1%)	32 (16.1%)	0.237	11 (24.4%)	8 (17.8%)	0.438
CCB	23 (44.2%)	42 (21.1%)	0.001	16 (35.6%)	18 (40.0%)	0.664
ACEI	7 (13.5%)	16 (8.0%)	0.228	6 (13.3%)	11 (24.4%)	0.178
β	2 (3.8%)	13 (6.5%)	0.467	1 (2.2%)	6 (13.3%)	0.049
Radiation	22 (42.3%)	39 (19.6%)	0.001	16 (35.6%)	16 (35.6%)	1
Lymph node positivity	11 (21.6%)	24 (12.1%)	0.081	9 (20.0%)	9 (20.0%)	1
Number of lymph node clearance	27.58 ± 9.08	23.76 ± 8.67	0.006	26.42 ± 7.80	24.27 ± 8.87	0.229
WBC	7.56 ± 2.30	6.83 ± 1.83	0.036	7.04 ± 1.81	7.49 ± 2.17	0.302
Neutrophil	5.05 ± 2.17	4.31 ± 1.52	0.024	4.53 ± 1.51	4.83 ± 1.93	0.413
Lymphocyte	1.80 (1.39–2.27)	1.97 (1.54–2.34)	0.554	1.77 (1.40–2.30)	1.97 (1.55–2.60)	0.366
Monocyte	0.44 (0.32–0.52)	1.80 (1.39–2.27)	0.296	0.44 (0.29–0.49)	0.39 (0.34–0.56)	0.491
AST	26.77 ± 13.52	24.47 ± 9.90	0.255	26.16 ± 13.41	23.22 ± 7.53	0.205
ALT	24.94 ± 17.54	22.04 ± 15.85	0.251	23.48 ± 15.71	19.58 ± 10.92	0.174
ALB	42.50 ± 4.30	43.38 ± 3.70	0.144	42.38 ± 4.36	42.60 ± 3.39	0.789
Cr	60.31 ± 12.57	58.84 ± 12.86	0.464	59.84 ± 12.34	62.78 ± 18.14	0.374
Hb	123.67 ± 24.98	125.37 ± 21.35	0.622	121.62 ± 25.75	126.98 ± 17.58	0.252

BMI, body mass index; CCB, calcium channel blockers; WBC, white blood cell; AST, Aspartate transaminase; ALT, Alanine transaminase; ALB, Albumin; Hb: Hemoglobin.

could affect the incidence of postoperative lymphoid cysts. However, a prospective cohort study with a larger sample size is needed to prove its reliability.

The major limitation of our study resides in several folds. First, it was a retrospective study, so a prospective study is needed to verify the accuracy of the prediction model. Second, the sample size was relatively small. There are differences in the incidence of lymphatic leakage among different types of cancer, and a larger sample size is needed for further study between groups. While some studies reported that hypertension has been associated with an increased risk of lymphedema, it remains unclear whether it is hypertension alone or hypertension treatment (17, 18). If the sample size is sufficient, it is necessary to analyze different antihypertensive drugs and rule out whether simple hypertension is an independent risk variable for postoperative lymphatic leakage-related complications.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

HJ contributed to the conception of the study and wrote the manuscript. MS, RS, and SS performed the data analyses and collection. YZ helped perform the analysis with constructive discussions. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Lortet-Tieulent J, Ferlay J, Bray F, Jemal A. International patterns and trends in endometrial cancer incidence, 1978–2013. *J Natl Cancer Inst*. (2018) 110 (4):354–61. doi: 10.1093/jnci/djx214

2. Cheng L, Guo Y, Zhan S, Xia P. Association between HLA-DP gene polymorphisms and cervical cancer risk: a meta-analysis. *BioMed Res Int*. (2018) 2018:7301595. doi: 10.1155/2018/7301595

3. Ribeiro Pereira ACP, Koifman RJ, Bergmann A. Incidence and risk factors of lymphedema after breast cancer treatment: 10 years of follow-up. *Breast*. (2017) 36:67–73. doi: 10.1016/j.breast.2017.09.006

4. Norman SA, Localio AR, Kallan MJ, Weber AL, Torpey HA, Potashnik SL, et al. Risk factors for lymphedema after breast cancer treatment. *Cancer Epidemiol Biomarkers Prev*. (2010) 19(11):2734–46. doi: 10.1158/1055-9965.EPI-09-1245

5. Lee S, Roizes S, von der Weid PY. Distinct roles of L- and T-type voltage-dependent Ca^{2+} channels in regulation of lymphatic vessel contractile activity. *J Physiol*. (2014) 592(24):5409–27. doi: 10.1113/jphysiol.2014.280347

6. Han LP, Zhang HM, Abha HD, Liu T, Zhang XP. Management and prevention of chylous leakage after laparoscopic lymphadenectomy. *Eur Rev Med Pharmacol Sci*. (2014) 18(17):2518–22. PMID: 25268098

7. Zhao Y, Hu W, Hou X, Zhou Q. Chylous ascites after laparoscopic lymph node dissection in gynecologic malignancies. *J Minim Invasive Gynecol*. (2014) 21(1):90–6. doi: 10.1016/j.jmig.2013.07.005

8. Kim JH, Choi JH, Ki EY, Lee SJ, Yoon JH, Lee KH, et al. Incidence and risk factors of lower-extremity lymphedema after radical surgery with or without adjuvant radiotherapy in patients with FIGO stage I to stage IIA cervical cancer. *Int J Gynecol Cancer*. (2012) 22(4):686–91. doi: 10.1097/IGC.0b013e3182466950

9. Biglia N, Librino A, Ottino MC, Panuccio E, Daniele A, Chahin A. Lower limb lymphedema and neurological complications after lymphadenectomy for gynecological cancer. *Int J Gynecol Cancer*. (2015) 25(3):521–5. doi: 10.1097/IGC.0000000000000341

10. Stolarz AJ, Lakkad M, Klimberg VS, Painter JT. Calcium channel blockers and risk of lymphedema among breast cancer patients: nested case-control study. *Cancer Epidemiol Biomarkers Prev*. (2019) 28(11):1809–15. doi: 10.1158/1055-9965.EPI-19-0448

11. Frey MK, Ward NM, Caputo TA, Taylor J, Worley Jr. MJ, Slomovitz BM. Lymphatic ascites following pelvic and paraaortic lymphadenectomy procedures for gynecologic malignancies. *Gynecol Oncol*. (2012) 125(1):48–53. doi: 10.1016/j.ygyno.2011.11.012

12. Carlson JW, Kauderer J, Hutson A, Carter J, Armer J, Lockwood S, et al. GOG 244—the lymphedema and gynecologic cancer (LEG) study: incidence and risk factors in newly diagnosed patients. *Gynecol Oncol*. (2020) 156 (2):467–74. doi: 10.1016/j.ygyno.2019.10.009

13. Biglia N, Zanfagnin V, Daniele A, Robba E, Bounous VE. Lower body lymphedema in patients with gynecologic cancer. *Anticancer Res*. (2017) 37 (8):4005–15. doi: 10.21873/anticanres.11785

14. Rebegea LF, Stoleriu G, Manolache N, Serban C, Craescu M, Lupu MN, et al. Associated risk factors of lower limb lymphedema after treatment of cervical and endometrial cancer. *Exp Ther Med*. (2020) 20(6):181. doi: 10.3892/etm.2020.9311

15. Lee YH, Chong GO, Kim SJ, Hwang JH, Kim JM, Park NJ, et al. Prognostic value of lymph node characteristics in patients with cervical cancer treated with radical hysterectomy. *Cancer Manag Res*. (2021) 13:8137–45. doi: 10.2147/CMAR.S332612

16. Ridner SH, Dietrich MS. Self-reported comorbid conditions and medication usage in breast cancer survivors with and without lymphedema. *Oncol Nurs Forum*. (2008) 35(1):57–63. doi: 10.1188/08.ONF.57-63

17. Tsai MK, Lai CH, Chen LM, Jong GP. Calcium channel blocker-related chylous ascites: a systematic review and meta-analysis. *J Clin Med*. (2019) 8 (4):466. doi: 10.3390/jcm804046.

18. Togawa K, Ma H, Sullivan-Halley J, Neuhouser ML, Imayama I, Baumgartner KB, et al. Risk factors for self-reported arm lymphedema among female breast cancer survivors: a prospective cohort study. *Breast Cancer Res*. (2014) 16(4):414. doi: 10.1186/s13058-014-0414-x

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