frontiers | Research Topics

Reviews in obstetrics and gynecology 2024

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Reviews in obstetrics and gynecology 2024

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Table of contents

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Editorial: Reviews in obstetrics and gynecology 2024

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Editorial on the Research Topic
Reviews in obstetrics and gynecology 2024

The field of Obstetrics and Gynecology is rapidly evolving, driven by a growing emphasis on holistic and personalized care. Recent literature suggests looking toward a patient-centered approach, which integrates the social, medical history, and individual background of the specific individual (https://doi.org/10.33178/SMJ.2024.1.18). In this Research Topic, we present reviews, systematic analyses, and case reports that reflect the breadth and complexity of modern practice. The selected works focus on novel obstetric and gynecological insights, ranging from rare diagnostic challenges to large-scale meta-analyses, offering a valuable perspective on current challenges and future directions in the field.

Case-based insights: enhancing clinical awareness in the management of rare conditions

The case reports highlight the central role of physicians in clinical practice and emphasize that obstetricians and gynecologists must remain vigilant and adaptable when addressing case-to-case variability despite the use of advanced diagnostic tools.

One such report describes a case of a simultaneous intrauterine and intramural gestation in a patient who underwent ART procedures. Heterotopic pregnancy is a rare condition that is poorly described in scientific literature and even more rarely encountered in common practice. In such a case, the ectopic gestation was uncovered thanks to further ultrasound investigations, which allowed prompt intervention and the preservation of pregnancy. While this case enriches the current knowledge on rare obstetric conditions, it stresses the tremendous role of diagnostic imaging in protecting maternal and fetal health in the early phases of gestation.

Similarly, unusual vaginal tuberculosis—a rare form of extrapulmonary infection—posed significant diagnostic challenges as reported by Bicha and colleagues, who illustrated the risk of delayed correct diagnosis. A 35-year-old Ethiopian woman was initially misdiagnosed with pelvic organ prolapse and treated for nearly a year, only to see her condition worsen. The progressive growth of the lesion prompted a more detailed investigation, and specialists established the correct diagnosis. Indeed, the initiation of targeted anti-tuberculosis therapy resulted in marked clinical improvement, underscoring the importance of maintaining diagnostic flexibility, especially in high-prevalence regions such as Ethiopia, where atypical manifestations may occur (Bicha et al.).

When it comes to managing long-term contraceptive complications, a V-shaped copper intrauterine device (IUD), embedded in the uterine wall for over 30 years, was successfully removed using hysteroscopy. The procedure, guided by preoperative imaging and performed with meticulous dissection under direct visualization, allowed clinicians to avoid more invasive surgical interventions. This case highlights the growing potential of minimally invasive techniques in managing long-standing and complex contraceptive device complications (You et al.).

Psychosocial challenges and preventive innovations in obstetrics and infertility care

Concerning physical health, this Research Topic also deals with the emotional and psychological impact of gynecological and obstetric conditions. Depression among women with infertility is a significant public health concern, especially for those women living in low-resource areas. Alongside economic issues, psychosocial factors such as lack of partner or family support and previous marital difficulties were identified as major contributors to psychological distress. Integrating mental health support into comprehensive infertility care, alongside medical interventions, is an essential factor to consider for improving the overall wellbeing of women who struggle with fertility (Tadesse et al.).

Attention must be paid also during gestation. Preventive strategies are essential in improving maternal health, particularly in reducing the risk of preeclampsia, a major contributor to maternal and fetal complications. Kumsa et al. have shown that calcium supplementation can significantly lower the incidence of this condition. Indeed, calcium plays a key role in vascular function and blood pressure regulation, and its deficiency has been strongly associated with pregnancy-related hypertension (1). The reported findings of this review strongly support calcium supplementation as a cost-effective preventive strategy: it is particularly beneficial during antenatal care in populations with low dietary calcium intake and high risk for preeclampsia.

Further insights into preeclampsia come from research on late-onset cases, a condition that develops after 34 weeks of gestation. Bayilis et al. identified several key risk factors for late-onset preeclampsia, including elevated BMI, advanced maternal age, and chronic hypertension. They suggested that low-dose aspirin may offer a promising preventive approach for high-risk pregnancies, though they emphasized the need for further studies to develop more accurate and clinically applicable predictive models for late-onset preeclampsia.

Advancements and challenges in reproductive health, oncology, and perinatal care

This Research Topic addresses key advancements and persistent challenges in reproductive health, oncology, and perinatal care, underscoring the need for dedicated attention to women living in poor conditions.

Recent findings suggest that intravaginal misoprostol may offer practical advantages over dinoprostone for labor induction. Comparative studies have shown both drugs to be similarly effective and safe, but misoprostol was associated with a significantly lower need for oxytocin augmentation. Its affordability and ease of administration make it a promising option, particularly in resource-limited settings where access to more complex treatments may be constrained (Lakho et al.).

Moreover, researchers should further investigate the late-gynecological age. In postmenopausal osteoporosis, emerging data support the use of romosozumab as an effective therapeutic option. When added to standard treatment regimens, this monoclonal antibody has been shown to significantly reduce the risk of vertebral and non-vertebral fractures while also improving bone mineral density. Notably, no substantial increase in adverse events has been observed, reinforcing its potential as a valuable addition to current management strategies (Gao et al.).

In cervical cancer research, evidence indicates that women affected by HIV are at higher risk of multiple high-risk HPV infections and developing high-grade squamous intraepithelial lesions. This increased vulnerability highlights the urgent need for improved cervical cancer screening protocols and expanded HPV vaccination efforts, especially in regions with high HPV diversity and limited healthcare access (Cassani et al.).

Finally, a detailed analysis using WHO's International Classification of Diseases for Perinatal Mortality (ICD-PM) revealed strong disparities in global perinatal outcomes. Stillbirth rates were markedly higher in low-income countries, and a considerable proportion of cases remained classified as "unspecified." These results call for enhanced data collection systems, standardized reporting practices, and targeted interventions to address preventable causes of perinatal mortality worldwide (Kumsa et al.).

Traditional therapies and methodological challenges

An analysis of clinical trials evaluating traditional Chinese medicine and natural products for endometriosis reveals both promise and limitations. While many studies incorporated key methodological elements such as randomization and blinding, most were limited by small sample sizes and inconsistent design. These findings highlight the need for more rigorous, well-powered

trials to accurately assess the potential of complementary therapies in managing chronic gynecological conditions (Zhao et al.).

Conclusion

Overall, the present Research Topic reflects the dynamic landscape of Obstetrics and Gynecology today, where technological innovation, evidence-based approaches, and global health awareness are increasingly shaping both research and clinical practice. At the same time, they underscore the critical need to integrate psychosocial and systemic perspectives, whether through better mental health support or greater inclusion of complementary medicine.

These insights contribute to a growing dialogue on how best to advance reproductive and women's health through multidisciplinary collaboration, improved methodologies, and patient-centered strategies.

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The authors declare that the work 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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Multiple human papillomavirus infection and high-grade cervical squamous intraepithelial lesions among women with human immunodeficiency virus: a systematic review and a meta-analysis

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Background: This study aimed to evaluate the prevalence of multiple high-risk (HR) human papillomavirus (HPV) infections in women with human immunodeficiency virus (HIV) compared to negative controls. This study also aimed to assess the impact of multiple HR-HPVs on the risk of high-grade squamous cervical lesions (HSILs) among women with HIV.

Methods: We performed a systematic search of PubMed/Medline, Scopus, Cochrane databases, and ClinicalTrials.gov from 1 January 2004 to 30 June 2023, including screenings and clinical studies evaluating the rates and role of multiple HPV infections in squamous intraepithelial lesions (SILs). Three reviewers independently screened the abstracts of the selected studies and extracted data from full-text articles. The data were subsequently tabulated and compared for consistency. The bias associated with each included study was evaluated according to the OSQE method.

Results: Forty-seven studies meet definitive inclusion criteria. The quality of the observations was considered low in 26 of the included studies and moderate in 21 of the included studies. In comparative screening studies, the pooled prevalence of multiple HR-HPV was 39.1% (95% CI = 33.7–44.7) among women with (n = 1734) and 21.6% (95% CI = 17.3–26.1) in those without HIV infection (n = 912) (OR = 2.33, 95% CI = 1.83–2.97, I^2 = 2.8%). The pooled ORs of HR-HPV multiple infections were similar in African (OR = 2.72, 95% CI = 1.89–3.9) and non-African countries (OR = 2.1, 95% CI = 1.46–3, p for difference = 0.96). Among women with HIV, the risk of HSIL diagnosed either by cytology or histology was higher among those with overall (OR = 2.62, 95% CI = 1.62–4.23) and HR multiple infections than those with single HPV infection (OR = 1.93, 95% CI = 1.51–2.46). Among women with HIV, the excess rates of multiple HPV infections and the excess risk of associated HSIL were consistent across studies including both HIV-naïve subjects and those on antiretroviral therapy, as well as in studies with different rates of immunocompromised women. When study quality (low vs. moderate) was used as a moderator, the results were unchanged.

Conclusion: Multiple HR-HPV infections are common among women living with HIV and are associated with an increased prevalence of HSIL. These associations were also confirmed in studies with high rates of antiretroviral therapy and low rates of immunocompromise.

Systematic Review Registration: PROSPERO [registration number: CRD42023433022].

KEYWORDS

human papillomavirus, human immunodeficiency virus, high-grade squamous cervical lesions, squamous intraepithelial lesions, meta-analysis

Introduction

Both in the general population and in subjects with squamous intraepithelial lesions (SILs), multiple human papillomavirus (HPV) infections are quite common. Even though the prevalence of multiple high-risk (HR)-HPV infections in cervical cancer ranges from 4 to 19% (1), the oncogenetic mechanism underlying the role of multiple HPV infections in the development of cervical cancer in humans is still largely unknown (2, 3). Although controversial, HPV coinfection in human immunodeficiency virus (HIV)-negative women has been associated with an increased risk of high-grade squamous cervical lesions (HSILs), suggesting the possibility of synergy between multiple HR-HPVs and cervical oncogenesis (1–3). Multiple HPV infections are three times more prevalent in Africa than they are in Asia (4), indicating that racial characteristics, HIV prevalence, HPV 16 and 18 prevalence, and low vaccination rates may all be major contributors to the excess rate of multiple HPV infections in African nations (3–5). In fact, HIV infection plays a significant role in the prevalence of multiple HPV infections in Africa (5). In the general population, HIV infection is associated with an increased risk of both overall and multiple HPV cervical infections (6). Two large meta-analyses (4, 5) have shown that in Africa, multiple HPV infections are also consistently associated with an increased risk of invasive cervical cancer mainly caused by non-vaccine HPV types. On the other hand, data on the role of multiple HPVs in the risk of precancerous cervical lesions among women infected with HIV are still lacking. The primary objective of the present meta-analysis was to evaluate the pooled rates of multiple HPV infections in women with HIV compared to HIV-negative controls in both cohort and case-control studies published in the last 20 years, including all countries. The secondary objective was to assess the role of multiple HPV infections in precancerous lesions in HIV-positive patients. For this study, we considered studies of women with HIV attending screening or colposcopy services comparing the prevalence of multiple HPV infections in HSIL subjects with controls (negative or low-grade SIL as determined by cytology or histology).

Materials and methods

Sources

This systematic review and meta-analysis was carried out according to the suggestions of the Preferred Reporting Items for Systematic Review and Meta/Analyses (PRISMA) (7). In addition, ameta-analysis of observational studies was carried out according to standard guidelines (MOOSE) (8). The protocol, including both HIV+ and HIV-subjects, was recorded on PROSPERO on 17 June 2023 (registration number: CRD42023433022). Due to the well-known protective effect of the widespread use of highly active antiviral therapy (HAART) on the prevalence/incidence of HPV infection and SIL (9), we restricted the search to the last 20 years to avoid an overrepresentation of naïve HIV+ subjects. We searched PubMed/Medline, Scopus, and Cochrane databases from 1 January 2004 to 30 June 2023. The terms used for the searches included "Human Papillomavirus" AND "Human Immunodeficiency Virus" And "Cervical Cancer" OR "Squamous Intraepithelial Neoplasia" OR "Cervical Intraepithelial Neoplasia" OR "Cervical Dysplasia" without language restrictions. First, we included cohort or case-control studies comparing the prevalence of multiple HPV infections between HIV+ and HIV-negative subjects, irrespective of recruitment protocols and type of molecular methods used to identify HPV infection. The second objective of the search was to evaluate the prevalence of multiple HPV infections in high-grade SIL diagnosed by cytology and/or histology compared to controls (low-grade SIL or negative cytology or histology) among HIV+ subjects. To avoid over-dispersion, we included in the searches only studies with at least 5 subjects for each category studied. Three reviewers (AS, MD, and CC) screened independently abstracts of the selected studies and extracted data from full-text articles. Data were subsequently tabulated and compared for consistency. The bias associated with each included study was evaluated according to the OSQE method of Drukker et al. (10). This is a bias evaluation method developed for both case-control and cohort studies and includes several domains adapted from the Newcastle–Ottawa scale, Strobe, and ROBINS-I methods. Quality items were independently assigned by two investigators (MD and CC), and discrepancies were discussed with the other authors to reach concordance.

Study selection

A total of 1,913 studies were identified and screened for potential inclusion (Figure 1). Criteria for inclusion were as follows: (a) cohort, case-control, or cross-sectional studies evaluating the prevalence of multiple HPV infections as diagnosed using HPV-DNA molecular methods among HIV-positive and HIV-negative subjects. We included subjects enrolled in the general population or convenience samples (sex workers, women attending preventive cancer centers, or sexually transmitted disease centers); (b) cohort, case-control, and cross-sectional studies evaluating the association between multiple HPV infections and severity of cervical SILs among HIV-positive women

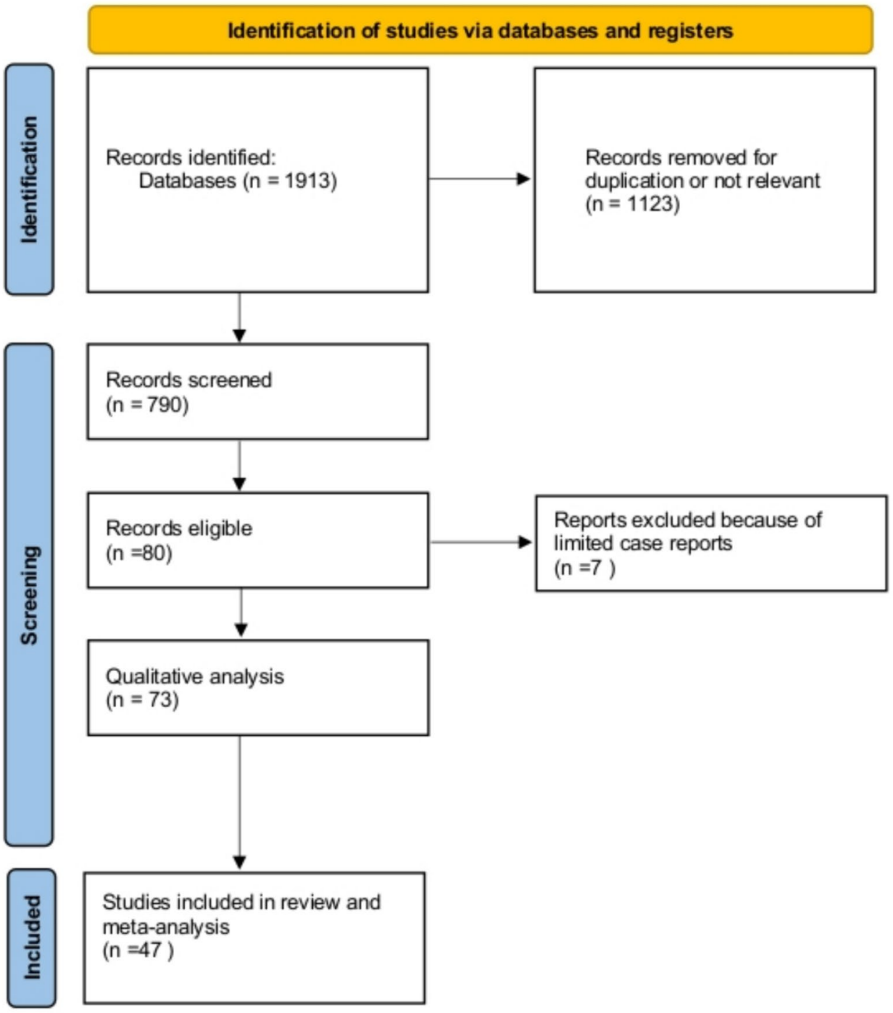

FIGURE 1
Flowchart of the study included.

attending colposcopic centers. We excluded studies enrolling pregnant subjects or women with invasive cervical cancer. In the end, 47 studies were declared eligible, and their data were abstracted and tabulated. The full list of the studies included is reported as Supplementary material. We used Stata (version 17; StataCorp, College Station, TX) to analyze the data. Random-effect models were used to compute pooled prevalences, odds ratios (ORs), and 95% confidence intervals (CIs) of the outcomes studied. Heterogeneity in the effects was evaluated using the I^2 statistics. When heterogeneity was significant (usually at $I^2 > 50\%$), we used subgroup meta-analysis. We also tested using meta-regression for the effect of moderators such as the type of SIL diagnosis (cytology vs. histology), the type of HPV infection (HR vs. overall infection), the antiretroviral treatment (no/yes), or the rate of low (<200/mL) CD4 cell counts. Finally, we checked for publication bias (small study effects) using Egger's test.

Results

In 12 studies, women were tested for HIV at the enrollment ($n = 537$) (HIV naïve), whereas the remaining 35 studies included already known HIV seropositive subjects (women living with HIV). The majority of women living with HIV (median = 83%, range 50–100) were receiving some form of antiretroviral treatment at the enrollment ($n = 3{,}550$). HPV identification and genotyping were obtained using PCR methods in all the included studies.

Figure 2 reports the prevalences of multiple HPV infections in 33 of the 47 studies (18 case-control and 15 cohort studies), including 3,944 women with HIV and 4,239 negative controls. The median age of the included subjects was 35.1 years (range 12–76). In meta-regression, median age (coefficient = 0.007 ± 0.015, $p = 0.65$) did not affect the pooled prevalence of multiple HPVs. The pooled prevalence of multiple HPV infections was higher among women with HIV (56.7, 95% CI = 49.8–63.5) compared to negative controls (38, 95% CI = 32.2–43.9) (OR = 2.3, 95% CI = 1.9–2.8) and there was a rather high heterogeneity, especially in non-African countries. In subgroup analysis, pooled ORs of multiple HPV infections were 2.59 (95% CI = 1.93–3.47) in the treatment of naïve subjects (9 studies) and 2.23 (95% CI = 1.75–2.85, p for group difference = 0.45) in those receiving some form of antiretroviral therapy (24 studies) (Supplementary material). The relationship between multiple HPV infections and HIV positivity was studied by including the proportion of subjects with

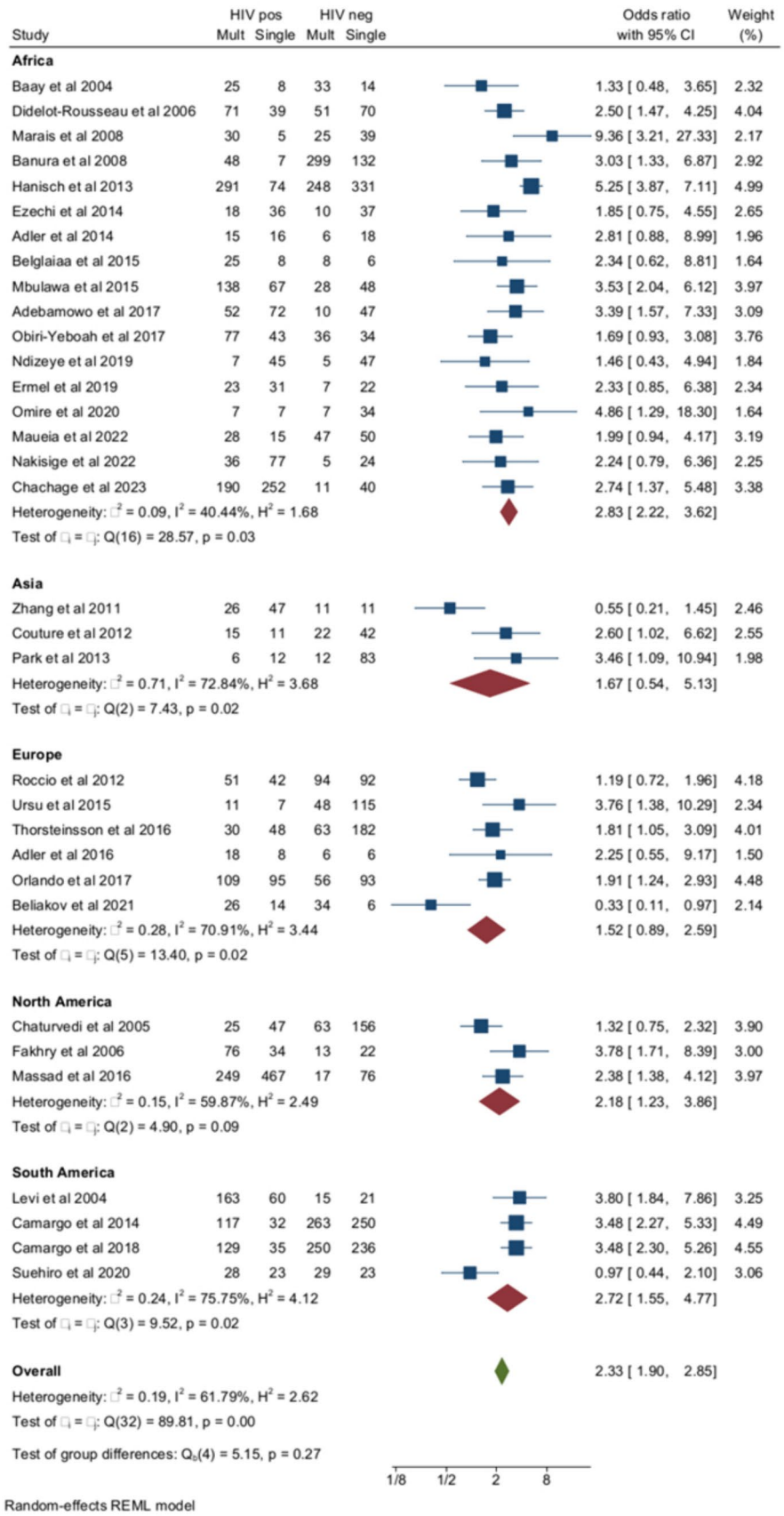

FIGURE 2
Prevalence and odds ratio (OR) of multiple human papillomavirus (HPV) infections in human immunodeficiency virus (HIV)-positive women compared to HIV-negative women.

CD4 cell counts <200/mL in each study ($n = 20$) as a moderator in a meta-regression (coefficient = 1.12 ± 0.8, $p = 0.11$) and by subgroup analysis. To check if old or newer studies influenced the outcome, we included the year of the study in meta-regression. The year of the study did not influence the rates of multiple HPVs among women with HIV compared to HIV-negative subjects (beta = −0.016, $p = 0.4$). When the risk of multiple HPV infections was stratified according to the severity of immunocompromise, the ORs of multiple HPV infections were 2.36 (95% CI = 1.58–3.51) and 2.1 (95% CI = 1.66–2.58) in studies with high (≥20%) and low (<20%) rate of subjects immunocompromised, respectively (Supplementary material).

Out of the 33 studies included in the total analysis, multiple HPV infections were evaluated as overall multiple infections (both high- and low-risk HPV) in 20 studies and as HR multiple infections in the remaining 13 studies. In studies of overall HPV infection, the pooled ORs of multiple HPV infections were higher among women with HIV compared to negative controls (Figure 3). The pooled prevalence of multiple HR-HPV was 39.1% (95% CI = 33.7–44.7) in women with HIV ($n = 1734$) and 21.6% (95% CI = 17.3–26.1) HIV-negative controls ($n = 912$) (OR = 2.33, 95% CI = 1.83–2.97) (Figure 3). Although the risk of multiple HPV infections was higher among HIV+ subjects compared to HIV-subjects for both overall and HR-HPV infections, heterogeneity of the model was lower for HR ($I^2 = 2.8\%$) than overall HPV infection ($I^2 = 77.8\%$). The small study effect was not significant according to Egger's test (Beta = −0.77, $p = 0.33$). Pooled ORs of HR-HPV multiple infection were similar in African (OR = 2.72, 95% CI = 1.89–3.9) and non-African countries (OR = 2.1, 95% CI = 1.46–3, p for difference = 0.96). Finally, the risk of multiple HR-HPV infections was similar among studies, including HIV-naïve subjects and those enrolling subjects receiving some form of antiretroviral treatment (Supplementary material).

The ORs of SIL (cytology or histology) associated with multiple HPV infections in HIV+ and HIV-subjects as opposed to unaffected controls were reported in six studies (Figure 4). The pooled prevalence of multiple HPV infections in SIL as opposed to negative controls was 52.7% (95% CI = 39.4–65.3) among women with HIV ($n = 1{,}060$) and 31.3% (95% CI = 23.5–39.6) ($n = 1{,}641$) in HIV-negative controls (OR = 2.16, 95% CI = 1.81–2.56), and the heterogeneity of the model was low ($I^2 = 0\%$). Egger's test for small studies effect was not significant (beta = −0.11, $p = 0.9$). When the analysis was restricted to histologically confirmed CIN2+ lesions (four studies), the pooled prevalence of multiple HR-HPV was 51.7% (95% CI = 40.5–62.8) among women living with HIV ($n = 421$) and 30.2% (95% CI = 23.9–36.8) in HIV-controls ($n = 522$) (OR = 2.5, 95% CI = 1.88–3.34, $I^2 = 0\%$).

Among women with HIV, multiple HPV infections were more frequent among subjects with HSILs (cytology and/or histology) than in HIV+ controls with cervical cytology or histology results ≤LSIL (Figure 5). The pooled rates of multiple HPVs were 58.9% (95% CI = 49.3–68) ($n = 747$) among HIV+ women with HSILs and 43.8% (95% CI = 36–51.9) ($n = 2053$) among HIV+ controls ≤LSIL, and the heterogeneity of the model was low ($I^2 = 34\%$). When the analysis was confined to HR-HPV, the pooled prevalence of multiple HPV infections was 53.9% (95% CI = 43–64.6) ($n = 495$) and 46.1 (95% CI = 35.4–57) ($n = 1{,}562$) among HSILs and ≤LSIL subjects, respectively. The ORs of HSILs associated with multiple infections among women with HIV were 2.62 (95% CI = 1.62–4.23) for overall multiple HPV infections (3 studies) and 1.93 (95% CI = 1.51–2.46) for HR-HPV (10 studies) (p-value for group difference = 0.1). In the analysis of the effect of multiple HR-HPV on HSILs, there were five studies from Africa and five from non-African countries. The pooled ORs of HSILs were 1.43 (95% CI = 1.07–1.92) and 2.04 (95% CI = 1.42–2.94) in African and non-African studies, respectively (p-value for group difference = 0.14). The prevalence of HPV 16 in the 13 studies included ranged from 10.2 to 34% and, in meta-regression, HPV16 prevalence did not influence overall results (p-value for interaction = 0.8). The pooled ORs of HSILs associated with multiple HPV infections were 2.1 (95% CI = 1.68–2.64) in the studies ($n = 10$) including subjects receiving antiretroviral therapy and 1.7 (95% CI = 0.71–3.61) in the few studies ($n = 3$) including naïve subjects (Supplementary material). Finally, the risk of HSILs associated with multiple HPV infections was not influenced by the different rates of immunocompromised subjects enrolled in the studies examined (Supplementary material).

Risk of bias

Tables of risk of bias compiled according to the OSQE method and including items involving representativeness, exposure, outcome, non-response, comparability, conflict of interest, and other miscellaneous potential bias factors are reported separately for cohort and case-control studies included in the analysis as Supplementary material. Given the observational nature of the included studies, the quality of the observation was considered low (higher scores in OSQE) in 26 and moderate in 21 of the included studies. Items were also included in the subsequent analysis as scores obtained by summing quality items. In the main study of multiple HPV prevalence, when the evaluation of the quality of the studies (low vs. moderate) was inserted as moderator, the ORs of multiple HR-HPV among HIV+ compared to HIV-subjects was 2.6 (95% CI = 1.74–2.74) among low-quality studies ($n = 8$) and 2.33 (95% CI = 1.83–2.97) in moderate-quality studies ($n = 5$) (p-value for group difference = 0.6). On the other hand, in the study of the association between multiple HPV infections and cervical disease, the ORs of HSILs were 1.6 (95% CI = 1.05–2.41) among the studies ($n = 4$) judged to be of low quality and 2.05 (95% CI = 1.53–2.76) in those judged to be of moderate quality ($n = 9$) (p-value for group difference = 0.4). In meta-regression, the quality of the studies included as scores did not interact significantly with the outcome measured, either as prevalence of multiple HPV infections in HIV+ compared to negative ($p = 0.33$) or prevalence of multiple infections in HSILs compared to controls ($p = 0.21$).

Discussion

The results of this meta-analysis suggest that the prevalence of multiple HPV infections, both overall and HR types, was higher among HIV+ than HIV-negative subjects in Africa and South and North American studies. The association was not significant for studies carried out in Europe and Asia, although the heterogeneity of the analysis for these countries was high, and the number of observations was limited. The excess prevalence of multiple HPV infections was confirmed for both overall and HR HPV and was also higher among women with HIV compared to HIV-negative controls with SIL or histologically confirmed CIN2+ lesions. Finally, among

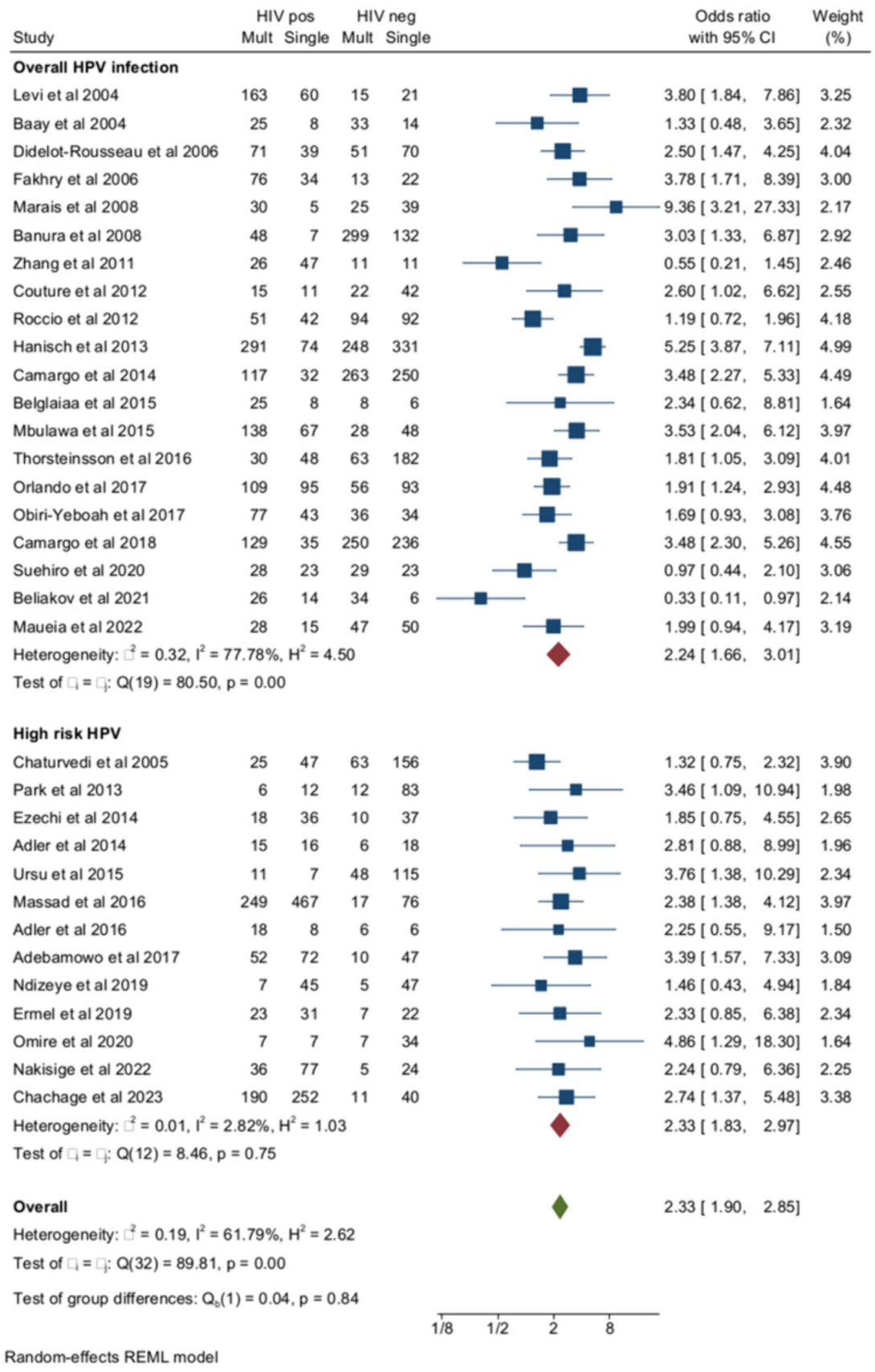

FIGURE 3
Prevalence and odds ratio (OR) of overall (high risk and low risk) multiple human papillomavirus (HPV) infections in human immunodeficiency virus (HIV)-positive women compared to HIV-negative women.

women with HIV screened for cervical neoplasia, the prevalence of multiple HPV infections, both overall and high risk, was higher among those with HSILs compared to controls with cytological or histological results ≤LSIL. The excess rate of multiple HPV infections associated with HIV was similar in studies including HIV+ naïve subjects or populations with a high rate of immunocompromise and in those enrolling known HIV-positive women receiving some form of antiviral treatment. Moreover, the excess risk of multiple infections and associated HSILs was similar across studies, including women with high or low degrees of immunocompromise.

Comparison with existing studies

Previous studies from Africa have evaluated the association between multiple HPV infections and HIV seropositivity in the general population (4, 11–13). Our meta-analysis confirms the increased risk of multiple HPV infections associated with HIV and suggests that this relationship is not limited to African studies but is also evident, although with more heterogeneity, in studies from Southern and Northern America. The association between multiple HPVs and HIV infection has been attributed to increased and prolonged exposure to HPV infection (early sexual debut and a high number of lifetime sexual partners), alongside a lower prevalence of HPV16 typical of sub-Saharan Africa (4, 14, 15). The results of this meta-analysis suggest that the association between multiple HPV cervical infections and HIV is independent of the country of origin and is similar for overall and HR-HPV cervical infections. In addition, meta-regression of published data suggests that the overall prevalence of HPV16 in the populations studied had little or no effect on the relationship between multiple HR-HPVs and overall SIL or CIN2+ lesions.

The relationship between multiple HPV infections, HIV seropositivity, and an elevated risk of cervical lesions has primarily been studied in HIV+ patients with invasive cervical cancer (5). At least two separate meta-analyses involving over 2000 cases of invasive cervical cancer from Africa suggest that the ORs of multiple HPV infections were 2–3 times greater among women with HIV than negative controls (4, 5). Interestingly, in these analyses, HPV 16 was underrepresented in HIV+ participants, while HPV 31, 35, and 68 were overrepresented in HIV-subjects (4, 5). We are not aware of any published pooled data on the connection between multiple HPV infections and cervical precancer lesions. The data from our meta-analysis indicate that multiple HR-HPV infections are linked to a higher prevalence of HSILs in women with HIV. This finding supports earlier research from Africa that multiple HPV infections could play a significant role in cervical carcinogenesis by favoring continuous and prolonged exposure to different types of HR HPVs (16).

Quality of evidence

All the studies included in this meta-analysis were observational and had many retrospectives, so the quality of observation was low or moderate. However, the strength of the relationship between multiple HPV infections and HIV seropositivity was homogeneous across studies of low and moderate quality, suggesting that the association was consistent. Although many subjects included in the analysis were receiving some form of antiretroviral therapy, we have no data on the duration of HIV infection, which could have influenced the natural history of HPV cervical infection (16, 17). Although many studies included multiple low-risk HPVs, the increased risk of HSILs associated with HR-HPV was consistent both in African and non-African countries. Finally, the excess risk of multiple infections and associated HSILs was still evident in more recent studies, including HIV+ subjects with a low degree of immunocompromise and high rates of antiretroviral therapy.

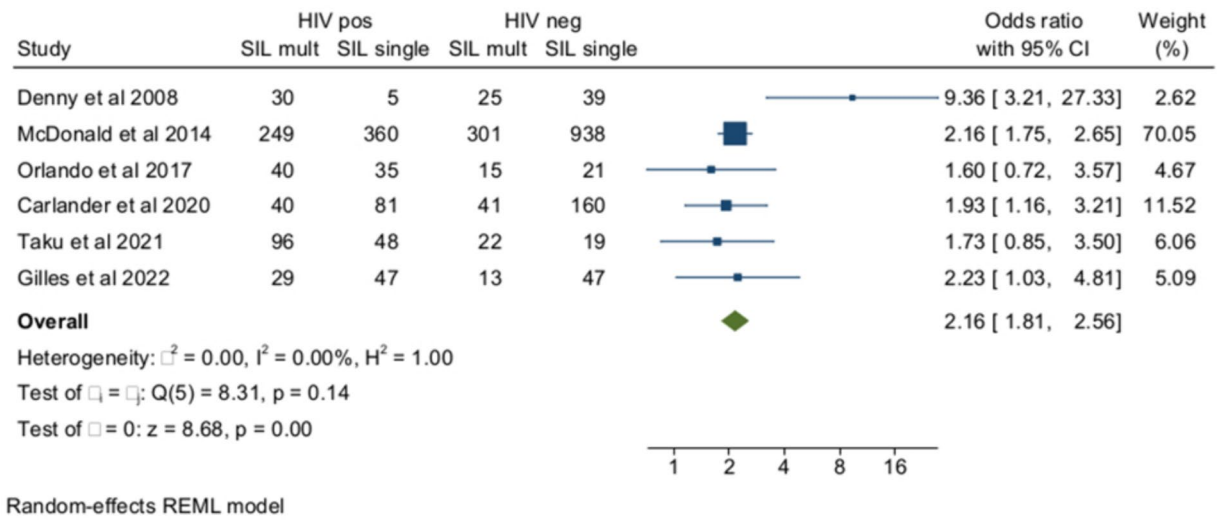

FIGURE 4
Prevalence and odds ratio (OR) of high-risk (HR) multiple human papillomavirus (HPV) infections in human immunodeficiency virus (HIV)-positive women compared to HIV-negative women.

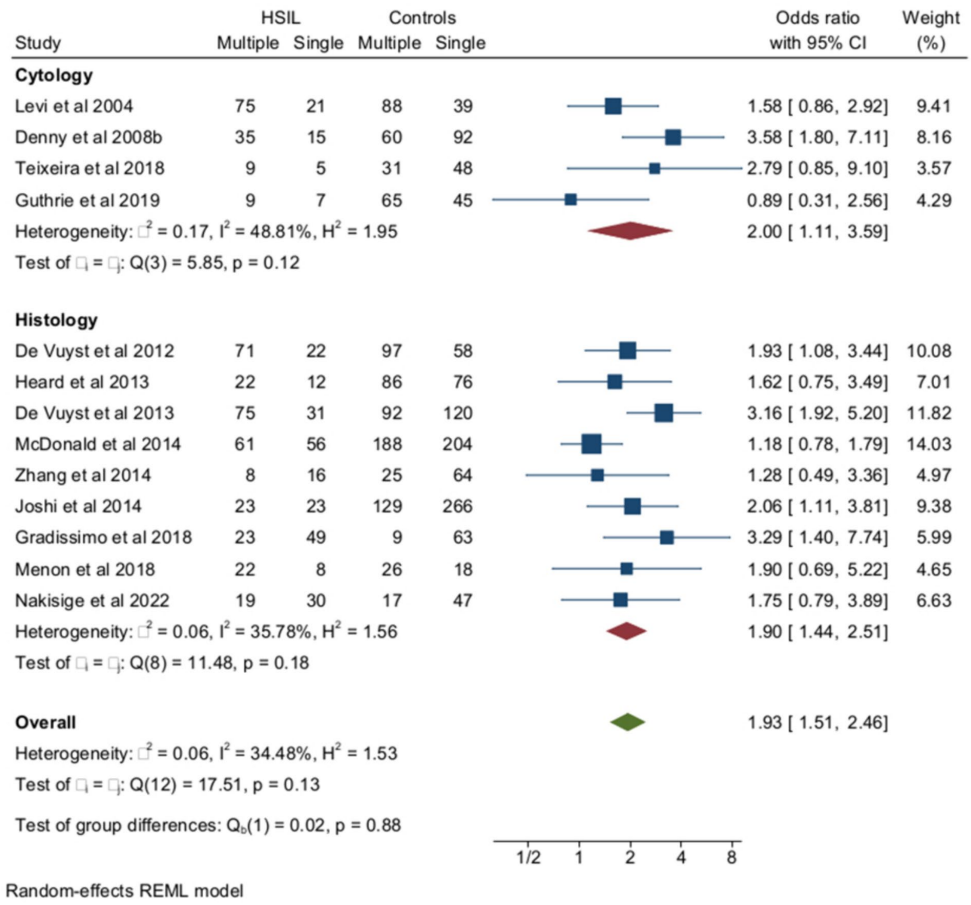

FIGURE 5
Prevalence and odds ratio (OR) of multiple human papillomavirus (HPV) infections in squamous intraepithelial (SIL) cervical lesions in human immunodeficiency virus (HIV)-positive women compared to HIV-negative women.

Biologic basis and clinical implications

Mixed low- and high-risk HPV infections are well-known markers of increased sexual exposure to infection, and, at least in African studies, the association between HIV seropositivity and multiple HPV infections has been mainly attributed to an earlier sexual debut and increased sexual promiscuity in HIV+ subjects compared to HIV-negative controls (14, 15, 18, 19). However, comparative studies between HIV-positive and HIV-negative women with similar sexual exposure (e.g., sex workers and intravenous drug addicts) (17, 18, 20, 21) found that multiple HPV infections were more common among HIV-positive than HIV-negative women, suggesting that other factors play a role in this association. In particular, several authors have described an interaction between HIV and HPV viruses on the cellular mechanism of oncogenesis, increasing the progression of HPV-associated lesions (22). On the other hand, it is also possible that HPV cervical infection could increase the susceptibility to HIV acquisition in heterosexuals by increasing the number of local target cells, such as dendritic or CD4+ cells, which are typically increased during the local immune response to HPV infection (23).

Whatever the reason for the excess prevalence of multiple HPV infections among HIV+ subjects, this association could have important clinical and epidemiological consequences.

In the papers analyzed, there was a high variation in HPV genotypes between countries. Multiple HPV infections, at least in African countries, are often associated with non-vaccine HPV types (4, 5, 24), as demonstrated by a recent meta-analysis on the prevalence of various HR-HPV genotypes in sub-Saharan African countries, which found that most of the HPVs identified are not yet included in vaccines, especially those available in that part of the world (11, 25). Similarly, high variation of HPV genotypes and high rates of multiple HPV infections have also been reported in a meta-analysis of studies from Latin America (26). Overall, all these data suggest that the variation of HPV genotypes associated with multiple HPV infections could restrict the efficacy of current vaccines, especially in countries with limited resources (26–28).

Conclusion

The results of this meta-analysis suggest that, among women living with HIV, multiple HR-HPV infections are common and are associated with an increased prevalence of overall SIL and HSILs compared to HIV-negative controls. These associations were also confirmed in studies with a high rate of antiretroviral therapy and a low rate of immunodepression. Although the mechanism underlying

the association between HIV and HPV cervical lesions is still poorly understood, it is possible that the increase in the number of genotypes associated with multiple HPV cervical lesions could negatively impact the efficacy of current vaccines, especially in low-resource nations.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: the data that support the findings of this study are available from the corresponding author, (MD), upon reasonable request. Requests to access these datasets should be directed to MD, matti.domino@gmail.com.

Author contributions

CC: Writing – review & editing. MD: Writing – review & editing. MP: Formal analysis, Writing – original draft. BG: Methodology, Writing – original draft. AS: Writing – original draft.

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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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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1403548/full#supplementary-material

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Effects of romosozumab combined with routine therapy on pain relief, disease progression and adverse reactions in patients with postmenopausal osteoporosis: a systematic review and meta-analysis

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Background: Postmenopausal osteoporosis (PMOP) increases fracture risk in women. Though traditional treatments are slow to act, combining romosozumab with conventional therapy shows promise. Despite its growing use, studies on effectiveness are limited. This study aims to systematically evaluate the combined therapy's impact on pain relief, disease progression, and adverse reactions in PMOP patients.

Methods: Databases including PubMed, EMBASE, ScienceDirect, and the Cochrane Library were searched from their inception to September 2023 to identify randomized controlled trials (RCTs) evaluating the role of romosozumab in PMOP. Random or fixed effect models were employed for statistical analysis. Two reviewers independently assessed the quality of the included studies and extracted the data. The meta-analysis was conducted using RevMan 5.4 software.

Results: Six RCTs with a total sample size of 17,985 cases were included. The incidence of vertebral fractures was compared and analyzed after 12 and 24 months of treatment. Romosozumab significantly reduced the incidence of vertebral fractures at 24 months (OR = 0.36; 95% CI: 0.35–0.52) but not at 12 months (OR = 0.39; 95% CI: 0.14–1.05). It was also associated with a decreased incidence of nonvertebral fractures (OR = 0.79; 95% CI: 0.66–0.94) and clinical fractures at 24 months (OR = 0.70; 95% CI: 0.59–0.82) compared to standard therapy. Romosozumab demonstrated a significant improvement in percentage change in bone mineral density (BMD) [mean difference (MD) = 10.38; 95% CI: 4.62–16.14] and in hip joint BMD (MD = 4.24; 95% CI: 2.92–5.56). There was no notable difference in adverse reactions compared to standard care ($p > 0.05$). Funnel plots displayed a predominantly symmetrical pattern, suggesting no evidence of publication bias in the selected literature.

Conclusion: Combining romosozumab with conventional therapy effectively treats PMOP, significantly reducing vertebral, non-vertebral, and clinical fractures while increasing BMD in the hip, femoral neck, and lumbar spine. However, further high-quality studies are needed for validation.

KEYWORDS
romosozumab, menopause, osteoporosis, fracture, adverse reactions

1 Introduction

Postmenopausal osteoporosis (PMOP) is the most common form of primary osteoporosis, typically characterized by high bone turnover. PMOP is age-related and generally occurs within 5–10 years after menopause. The cumulative bone loss rate during early menopause is higher than that during late menopause. The occurrence of PMOP is mainly affected by the sharp decrease in estrogen levels in the postmenopausal body, which results in greater bone resorption than bone formation. This leads to reduced bone mass, changes in bone structure, bone pain, decreased height, brittle fractures, and other symptoms (1, 2). Osteoporosis (OP) is an asymptomatic or "silent" disease that represents a significant and growing economic burden on healthcare systems and societies worldwide. PMOM greatly increases the likelihood of fragility fractures in about 50% of women. These fractures can have severe and disabling effects, resulting in long-lasting discomfort and restrictions in physical abilities, ultimately leading to a reduced quality of life (3).

The China OP prevalence study revealed that the prevalence of OP among postmenopausal women was 32.1%, significantly higher than the prevalence among men (4). It is found that the prevalence level of OP in women over 50 years old in China is remarkably higher than that in the United States, Canada, and other countries (5, 6). OP patients experience varying degrees of decline in BMD and bone mass, decreased bone strength, and an increased risk of brittle fractures. According to relevant epidemiological data from the United States, the risk of fractures in female OP patients is even higher than the combined risk of breast, ovarian, and uterine cancers (7). Furthermore, osteoporotic fracture patients are more likely to experience recurrent fractures. Studies have shown that patients who have suffered hip fractures are at 2.5 times higher risk of recurrent fractures, while patients with vertebral fractures have a 4 times higher risk. Additionally, patients who have suffered other types of fractures also face a higher risk of recurrent fractures, estimated to be approximately 2–3 times higher (8, 9). Preventing, diagnosing, and treating OP is crucial as it has a remarkable impact on the life quality of patients and leads to a high incidence of osteoporotic fractures.

In addition to vitamin D and calcium as basic treatments, drugs to treat OP are classified into two main categories based on their mechanism of action. The first category includes drugs that inhibit bone resorption, such as calcitonin, estrogen receptor modulators, bisphosphonates, and receptor activator of NF-κB (RANKL) inhibitors. The second category includes drugs that promote bone formation, such as parathyroid hormone analogues and parathyroid hormone-related peptide analogues (10). In January 2018, the European Medicines Agency (EMA) approved the listing of romosozumab (EVENITY™), which was jointly developed by Amgen and UCB. The US Food and Drug Administration (FDA) approved the product for marketing in April 2019. Romosozumab is a monoclonal antibody that has been humanized, and it functions by inhibiting the activity of sclerostin, a protein that negatively regulates bone metabolism. This inhibition can promote both bone formation and bone resorption. The treatment is accessible to postmenopausal women at high risk of fractures, as well as patients who cannot tolerate other medications. Romosozumab holds the distinction of being the world's first sclerostin inhibitor approved for marketing, and it is currently the sole OP drug with dual effects (11, 12).

Several clinical controlled studies have been conducted to explore the therapeutic effects of romosozumab on patients with PMOP. However, the conclusions of these studies vary, and significant differences exist in their designs, leading to poor applicability (13). The current literature on the clinical efficacy of romosozumab in treating PMOP provides inconclusive results. Therefore, romosozumab's efficacy in treating PMOP should be evaluated through high-quality research. Additional research is needed to establish the efficacy of romosozumab in combination with conventional therapies. More high-quality scientific studies are necessary to provide reliable evidence on the feasibility of this approach. Hence, this study aims to conduct a meta-analysis to analyze the effectiveness of romosozumab in combination with conventional therapy for postmenopausal patients with OP. The study seeks to offer new insights for clinical advancements.

2 Methods

This systematic review and meta-analysis were performed in compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

2.1 Search strategy

We conducted a comprehensive search for relevant studies on PMOP across various databases, including PubMed, EMBASE, ScienceDirect, and the Cochrane Library. Relevant information regarding the treatment of PMOP with romosozumab was collected. A literature search was conducted using the combination of the following medical subject headings with the Boolean operators: romosozumab, menopause, OP, disease progression, and clinical prognosis.

2.2 Eligibility criteria

2.2.1 Literature inclusion criteria

Population/participants: Patients diagnosed with OP using dual-energy X-ray absorptiometry (DXA) measurements of bone mineral density (BMD) in one of three ways:

(a) BMD *T*-score of ≤ -2.5 at the L1-4 lumbar spine, femoral neck, total hip, or distal radius 1/3.
(b) History of brittle fracture occurring in the vertebral body or hip.

(c) *T*-score between −2.5 and −1.0 (indicating low bone mass) accompanied by a history of brittle fracture in the proximal humerus, pelvis, or distal forearm.

Intervention: Romosozumab based routine treatment.

Comparison: Placebo.

Outcome: Studies that reported multiple outcomes, including vertebral fracture rate, non-vertebral fracture rate, clinical fracture rate, lumbar BMD, hip joint BMD, femoral neck BMD, and the incidence of adverse reactions.

Study design: Randomized controlled trials (RCT) evaluating the efficacy of romosozumab in combination with standard treatment for PMOP.

2.2.2 Exclusion criteria

Retrospective cohort studies, case-control studies, case series, reviews, case reports, meta-analyses, as well as *in vitro* and animal studies were not considered for inclusion.

2.3 Quality assessment and data extraction

The study included an evaluation of bias risk, which was performed using the bias risk assessment tool recommended by the Cochrane Systematic Review Manual 5.3.2. Two researchers independently screened the literature and extracted data, while also assessing the quality of the extracted data and cross-checking it. Any discrepancies were resolved through discussion or by consulting a third researcher. Express document management software and Excel office software were used to manage and extract research data. If the study provided incomplete data, we contacted the authors of articles. The extracted data included author name, publication date, number of cases, study methods, and outcome indicators such as vertebral fracture rate, non-vertebral fracture rate, clinical fracture rate, lumbar BMD, hip BMD, femoral neck BMD, and incidence of adverse events.

2.4 Data synthesis and statistical analysis

Meta-analysis was conducted using RevMan 5.4 software from the Cochrane Collaboration Network. A two-tailed $p < 0.05$ was considered statistically significant. Relative risk (RR) was employed as the effect index. The average and standard deviation values of lumbar BMD, hip joint BMD, and femoral neck BMD were entered into RevMan 5.4, with weighted mean difference (WMD) used as the effect index. A 95% confidence interval (CI) was calculated for all analyses. To assess the heterogeneity among studies, the χ^2 test was performed initially. Studies with *p*-values greater than 0.05 and I^2 values less than 50% were deemed homogeneous, prompting the adoption of a fixed-effect model for the meta-analysis. In cases where the *p*-value was less than 0.05 and the I^2 value equaled or exceeded 50%, indicating a significant level of heterogeneity among studies, the random-effects model was utilized to ascertain the combined effect and evaluate the study's homogeneity. When the *p*-value was less than 0.05 and the source of heterogeneity remained unclear, a descriptive analysis was employed instead of a meta-analysis.

3 Results

3.1 Literature search

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a literature study was conducted. The database search yielded 1,034 articles, and after removing duplicates, 761 articles remained. Upon reviewing titles and abstracts, 543 articles were identified, with 387 articles being excluded due to their irrelevance, being reviews, case reports, or lacking controlled literature. Subsequently, the full texts of the remaining articles were carefully reviewed, and incomplete data were excluded. Six randomized controlled trials (RCTs) were ultimately included, comprising a total of 17,985 participants for meta-analysis (14–19). The flowchart illustrating the literature screening process is displayed in Figure 1. Table 1 presents the characteristics of the included studies.

3.2 Quality assessment

In this meta-analysis, three out of the six studies reported detailed patient baseline characteristics. All literature included in this study provided comprehensive descriptions of the observational indicators and research methods employed, along with specific grouping methods. Additionally, they reported on the implementation of blinding, including the number and reasons for its use, as well as any loss of follow-up or withdrawal during the study period. Based on the analysis of the Jadad scale, studies with a score of ≥3 was considered high-quality, while that with a score of ≤2 was considered low-quality. Supplementary Figures S2, S3 display the risk bias analysis.

3.3 Meta analysis result

3.3.1 Bone fracture rate of vertebral body

Two studies reported vertebral fractures after 12 and 24 months of treatment. The pooled results indicated a significant decrease in the incidence of vertebral fractures at 24 months (OR = 0.36; 95% CI = 0.35–0.52, $p < 0.00001$; $I^2 = 87\%$) but not at 12 months (OR = 0.39; 95% CI: 0.14–1.05, $p = 0.06$; $I^2 = 90\%$) (Figure 2). According to the results of heterogeneity test, $Chi^2 = 17.87$, df = 3, $p = 0.0005$, $I^2 = 83\%$, indicating that heterogeneity was evident in the research data, which was analyzed by random effect model (Figure 2).

3.3.2 Non-vertebral bone fracture rate

Two studies reported the incidence of non-vertebral fractures in patients after treatment. The meta-analysis results showed that romosozumab was associated with a decreased incidence of nonvertebral fractures (OR = 0.79; 95% CI = 0.66–0.94, $p = 0.009$; $I^2 = 0\%$) (Figure 3). According to the results of the heterogeneity test, $Chi^2 = 0.14$, df = 1, $p = 0.71$, $I^2 = 0\%$, indicating that the included research data exhibited no significant heterogeneity (Figure 3).

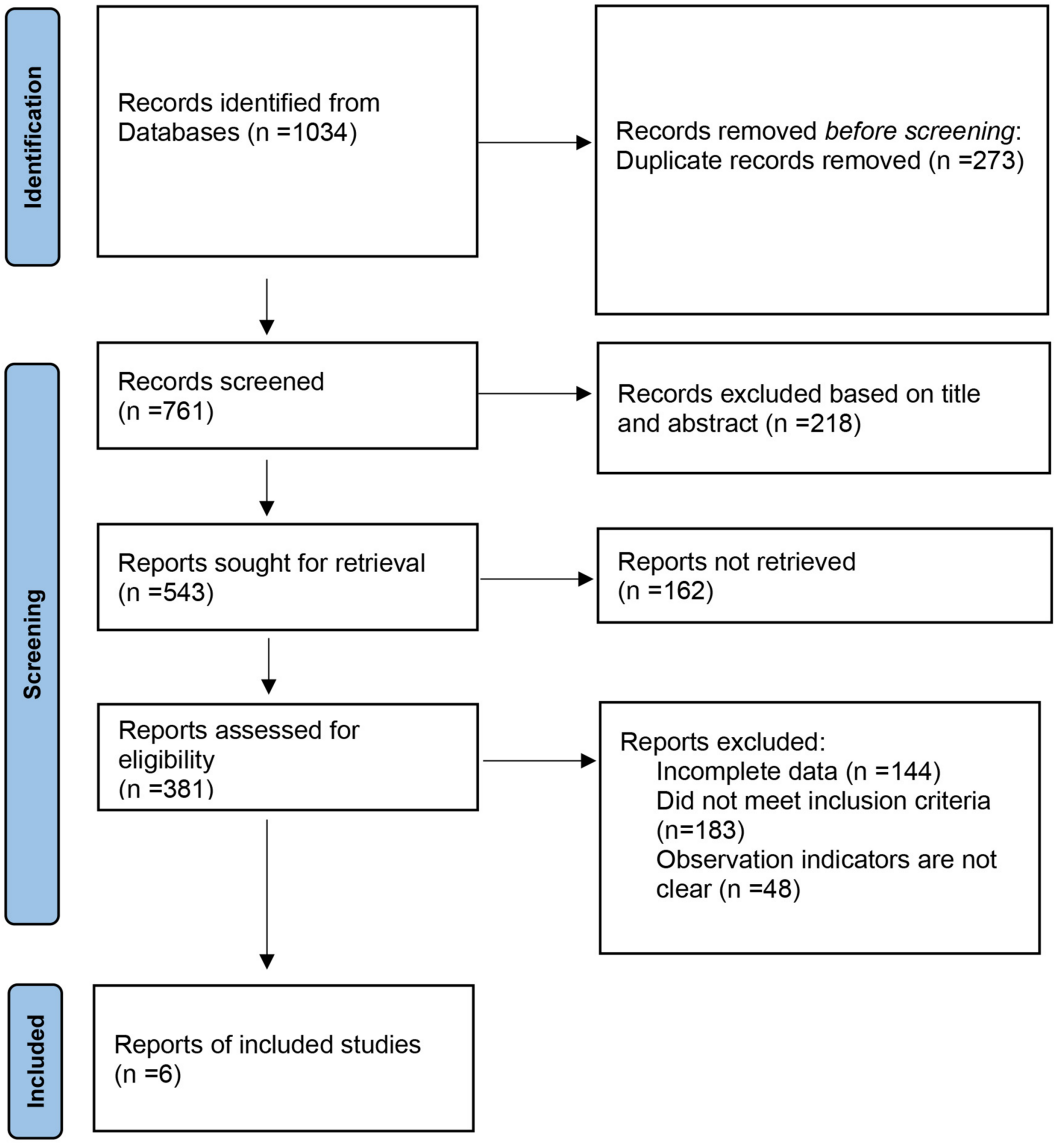

FIGURE 1
Flowchart of the literature screening process.

3.3.3 Clinical fracture scale

Two studies reported the incidence of clinical fractures in patients after treatment. Pooled results revealed that, compared to standard therapy, romosozumab decreased clinical fractures at 24 months (OR = 0.70; 95% CI = 0.59–0.82, $p < 0.00001$; $I^2 = 0\%$) (Figure 4). According to the results of the heterogeneity test, $Chi^2 = 0.34$, df = 1, $p = 0.56$, $I^2 = 0\%$, indicating that the included research data showed no significant heterogeneity.

3.3.4 Percentage change in BMD of lumbar vertebra

Percentage BMD change at the lumbar spine in the romosozumab versus control group at 12 months was analyzed in four studies. Four RCTs, comprising a total of 3,516 patients in the romosozumab group and 3,463 patients in the standard care group, demonstrated significant improvement in percentage change BMD with romosozumab [mean difference (MD) = 10.38; 95% CI = 4.62–16.14, $p = 0.0004$; $I^2 = 100\%$] (Figure 5). Heterogeneity test results showed significant heterogeneity among the included studies, with $Chi^2 = 44538.17$, df = 3, $p < 0.00001$, $I^2 = 100\%$. Therefore, a random-effects model was used for the analysis (Figure 5).

3.3.5 Percentage change in BMD of hip joint

Percentage BMD change in the romosozumab versus control group at 12 months was evaluated by four studies. The meta-analysis results showed a significant improvement in percentage change in hip joint BMD with romosozumab compared to standard care (MD = 4.46; 95% CI = 3.02–5.91, $p < 0.00001$; $I^2 = 97\%$) (Figure 6). The heterogeneity test showed that with $Chi^2 = 91.83$, df = 3, $p < 0.00001$, $I^2 = 97\%$, the results indicated that heterogeneity was evident in the research data (Figure 6).

TABLE 1 Basic characteristics of included studies.

Include the literature	Year of publication	Sample size		Intervention measures		Age (years)	*T*-score of hip joint or femoral neck	Outcome index
		Control group	Research group	Control group	Research group			
Cosman et al. (14)	2016	3,322	3,591	Placebo treatment	Romsozumab plus routine therapy	Unknown	−2.5 to 3.5	①②③
Langdahl et al. (15)	2017	209	206	Routine treatment	Romsozumab plus routine therapy	55–90	−2 ± 5	④⑤⑥
Inshibashi et al. (16)	2017	59	59	Placebo treatment	Romsozumab plus routine therapy	55–85	≤ −2.5	④⑤⑥
Saaga et al. (17)	2017	2,047	2,046	Routine treatment	Romsozumab plus routine therapy	Unknown	Unknown	①②③
McClung et al. (18)	2014	47	100	Routine treatment	Romsozumab plus routine therapy	55–85	≤ −2.0	④⑤⑥
Cosman et al. (19)	2018	3,148	3,151	Routine treatment	Romsozumab plus routine therapy	Unknown	Unknown	④⑤⑥

① Bone fracture rate of vertebral body. ② Non-vertebral bone fracture rate. ③ Clinical bone fracture rate. ④ Changes of bone mineral density of lumbar vertebrae. ⑤ Changes of bone mineral density of hip joint. ⑥ Density change of femoral neck.

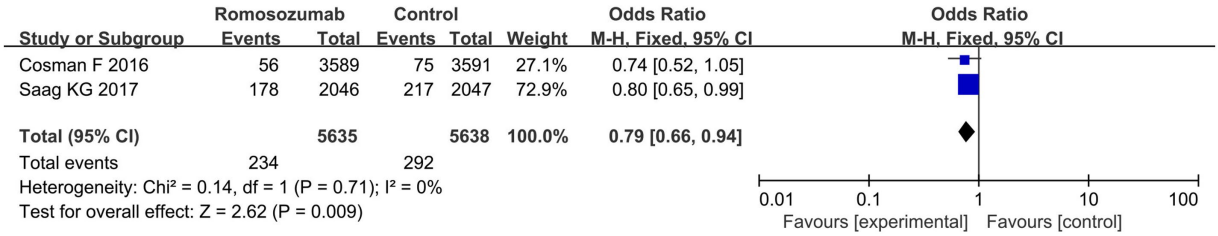

FIGURE 2
Comparison of vertebral fracture rate between the two groups after treatment.

3.3.6 Percentage change in BMD of femoral neck

After 12 months of treatment, four studies compared the percentage change in the BMD of the femoral neck. The pooled results showed a significant improvement in hip BMD with romosozumab (MD = 4.24; 95% CI = 2.92–5.56, $p < 0.00001$; $I^2 = 100\%$) (Figure 7). The heterogeneity test results indicated significant heterogeneity among the included studies ($Chi^2 = 3713.68$, df = 3, $p < 0.00001$, $I^2 = 100\%$).

3.3.7 Safety analysis

Five clinical controlled studies reported the incidence of adverse reactions (14–18). The study by Langdahl et al. (15) reported that nasopharyngitis (13% vs. 10%), hypercalcemia (1% vs. 10%), and arthralgia (10% vs. 6%) were common adverse reactions after treatment with romosozumab and standard care. In terms of adverse reactions, there was no notable difference ($p > 0.05$). Study by Ishibashi et al. (16) reported that patients treated with romosozumab had a higher risk of severe cardiovascular adverse reactions.

3.3.8 Publication bias analysis

Funnel plots were drawn based on vertebral fracture rate, non-vertebral fracture rate, and clinical fracture rate. Publication bias was analyzed (Supplementary Figures S3–S5). Upon analyzing the funnel plots, the majority showed symmetrical distribution.

4 Discussion

PMOP is a subtle disease that often presents no symptoms in the initial stages. It is characterized by a reduction in BMD and microstructural changes in the bone, which can result in decreased bone strength and a higher likelihood of fractures (20). The main factor influencing postmenopausal bone mass loss is estrogen deficiency. The

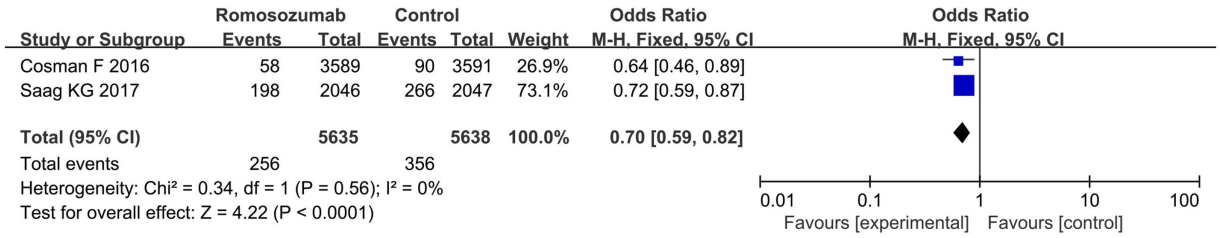

FIGURE 3
Comparison of non-vertebral bone fracture rate between the two groups after treatment.

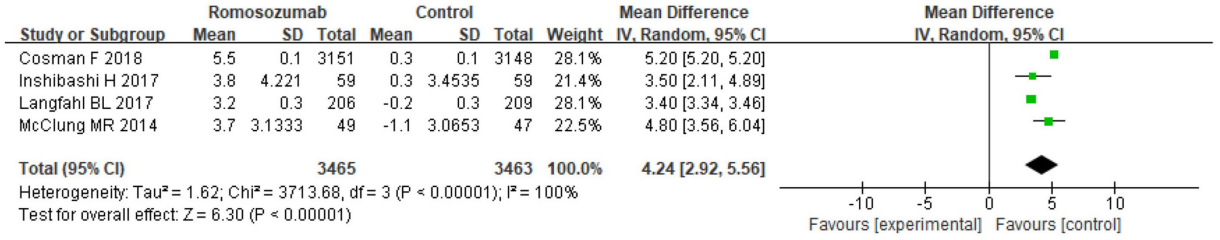

FIGURE 4
Comparison of clinical bone fracture rate between the two groups after treatment.

decrease in estrogen during menopause can induce an increase in RANK receptor expression on the osteoclast membrane via the RANKL pathway during osteoclast differentiation, as well as a decrease in the secretion of osteoprotegerin (OPG). Within the RANKL pathway, RANKL is expressed by osteoblasts and bone marrow stromal cells, which then bind to RANK receptors on the surface of osteoclast precursors. This binding promotes osteoclast differentiation and increases bone resorption. This imbalance directly leads to rapid bone loss and an increased risk of osteoporotic fractures. Because of the high incidence of OP and the severe consequences of osteoporotic fractures, the WHO defines OP as a major public health problem of concern (21). It is estimated that 50-year-old women have a 50% chance of experiencing osteoporotic fractures. OP can lead to a significant reduction in their quality of life. Treating osteoporotic fractures can also place a huge burden on the entire healthcare system, and this burden will increase as the elderly population grows each year (22).

The current study demonstrated a significant reduction in the incidence of vertebral fractures at 12 and 24 months, as well as a decrease in nonvertebral and clinical fractures, with romosozumab compared to standard therapy. Supporting our findings, a meta-analysis by Liu et al. (23) also found that romosozumab was associated with a significantly reduced risk of new vertebral fracture, nonvertebral fractures and hip fractures at 24 months. Studies on the population of Latin American countries show that the incidence of osteoporosis (OP) varies from 22.2 to 33.8% due to differences in sample size, sample screening criteria, and research methods. The incidence of osteoporotic brittle fractures caused by frequent falls is as high as 11 to 23.8% (24). Among them, the mortality rate also increased remarkably with the increase of physical activity disorder and life quality degeneration, ranging from 21.5 to 30% (25). In Latin American countries, each post-menopausal patient with OP spends approximately US$775 per year on OP treatment, and the average cost of an 11-day conservative hospital stay for hip fracture in a Latin American public hospital is approximately US$394,000, with a mortality rate of 23.3% after 6 months (26). Currently, the representative drug for promoting bone resorption is tropism, but its widespread clinical use is limited by the increased risk of osteosarcoma (27). As a monoclonal antibody, romosozumab exerts its anti-osteoporotic effect by antagonizing the activation of the Wnt signaling pathway by osteosclerotic proteins and binding to RANKL (28). According to incomplete statistics, within 1 year after the occurrence of hip fracture, about 1 to 5 patients will die of various complications, and the overall disability rate of hip fracture is as high as 50% (29). Vertebral fracture is the most common fracture type in PMOP, and the probability of recurrent fracture after a vertebral fracture is relatively high. Combined with our results, the incidences of vertebral, non-vertebral, and clinical fractures after treatment were compared and analyzed. Study participants had a remarkably lower incidence of vertebral fractures, non-vertebral fractures, and clinical fractures. Our findings on BMD improvement at the lumbar spine, total hip, and femoral neck with romosozumab at 12 months corroborate the positive effects reported by Liu's et al. (23) meta-analysis. Combining romosozumab therapy with conventional treatment can have a synergistic effect, significantly reducing the incidence of fractures and enhancing the clinical prognosis of patients with PMOP. Diagnostics of OP are based on BMD, which is the gold standard worldwide. This study compared and analyzed the changes in BMD of the lumbar spine, hip, and femoral neck bones after 12 months of treatment. Based on our analysis, the study group had higher BMD in the lumbar spine, hip, and femoral neck bones. It is revealed that the long-term effect of romosozumab combined with routine treatment is better and can successfully enhance the BMD of PMOP patients, promote bone strength, and significantly reduce the risk of fractures. The reason is that romosozumab, as a monoclonal antibody, can activate the Wnt pathway by antagonizing sclerostin, ensuring the normal transmission of the Wnt/β-catenin pathway, promoting bone formation, and inhibiting bone resorption (30, 31).

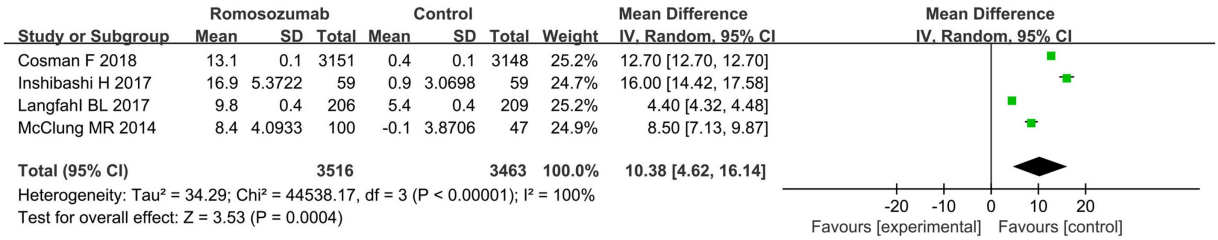

FIGURE 5
Forest plot comparing lumbar BMD between two groups after 12 months of treatment.

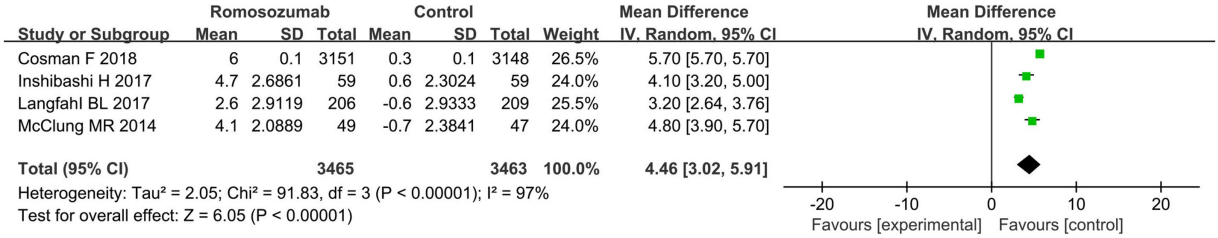

FIGURE 6
Forest plot comparing hip joint BMD between two groups after 12 months of treatment.

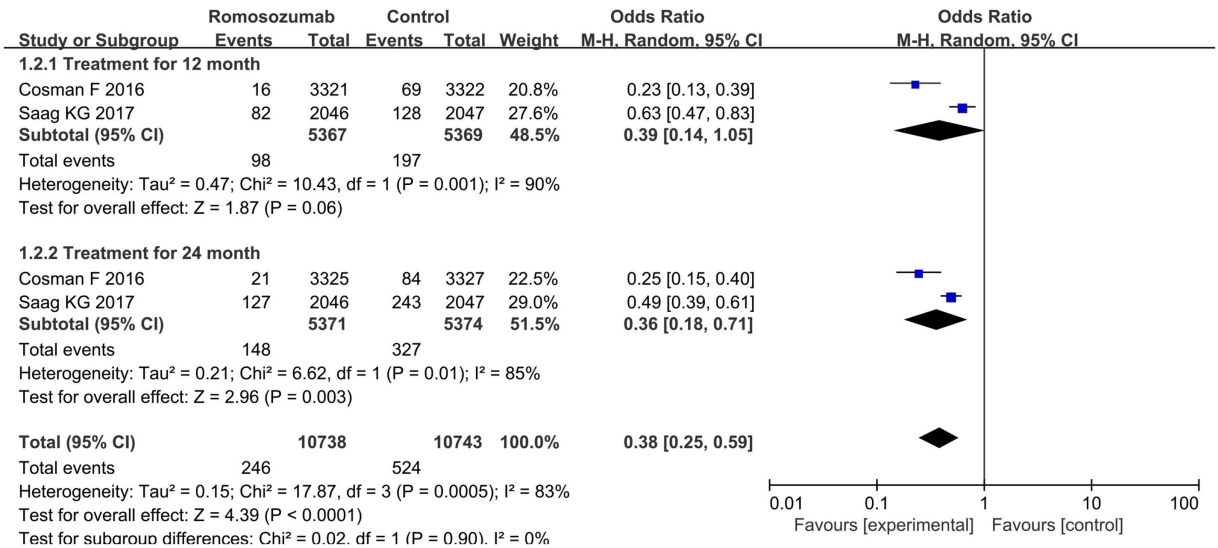

FIGURE 7
Forest plot comparing BMD of the femoral neck between two groups after 12 months of treatment.

Cardiovascular events have been the focus of various drug studies, and romosozumab is no exception. The cardiovascular effects of sclerostin, the target of romosozumab, are complex, and changes in this index alone cannot be used to explain cardiovascular events. Additionally, the Wnt signaling pathway has both advantages and disadvantages regarding cardiovascular disease, with more evidence suggesting that this pathway has a protective effect. A black box warning has been issued for romosozumab in patients with high risk factors for cardiovascular disease or stroke. A study by Saag et al. (17) indicated that the rate of serious cardiovascular events was higher with romosozumab than with alendronate. The incidence of adverse reactions to romosozumab was similar to that of the control group. The mean age of the patients contained by McClung et al. (18) was higher; on the one hand, older patients have a poorer cardiovascular base; on the other hand, the effect of romosozumab on osteosclerotic proteins and the Wnt pathway may be influenced by age. Alendronate

has a protective effect on the cardiovascular system, but this has not been confirmed by the meta-analysis. This study included a small number of studies and did not classify cardiovascular events. The number of one-off studies was low due to the lack of original reports. Additionally, there were ethnic and gender differences in the study's population, which did not facilitate the generalization of the findings. Most of the study cycles focused on 12 months, and the evaluation of efficacy and safety was limited due to the small number of original studies and the lack of stratified analysis for different treatment cycles and long-term outcomes. This study has several limitations. Firstly, a small number of studies were included, and most of these were conducted in Western countries, which limits the generalizability of the findings to other races and regions. Secondly, the meta-analysis was limited to studies in English, which may lead to publication bias. Finally, due to the limited number of studies, we did not perform a sensitivity analysis, which may influence the quality of the results. Therefore, validation will require more high-quality RCTs.

5 Conclusion

In conclusion, the combination of romosozumab and conventional therapy emerges as a viable clinical treatment option for postmenopausal patients with OP. Our results demonstrated a significant reduction in fracture risk and improvement in BMD among postmenopausal women with OP who received this treatment, with no notable increase in the incidence of adverse effects.

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

GG: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. JC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing – original draft, Writing – review & editing. YX: Conceptualization, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. JD: Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing.

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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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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1440948/full#supplementary-material

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A systematic review and meta-analysis of the globally reported International Classification of Diseases to Perinatal Mortality (ICD-PM)

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Introduction: Accurate recording and identification of perinatal mortality causes are crucial to reducing the global burden of perinatal mortality through targeted interventions. However, existing studies on the International Classifications of Diseases to Perinatal Mortality (ICD-PM) are limited by inconsistent results and variations by gestational age. Thus, this review aims to synthesize and document updated data on the causes of death using the ICD-PM classification.

Methods: Electronic databases such as the PubMed via MEDLINE, SCOPUS, Web of Sciences, EMBASE, Cochrane Library, and PROSPERO were searched to retrieve studies published from 2016 to February 2024. The Newcastle–Ottawa Scale (NOS) was used to assess the quality of the included studies, and heterogeneity between the studies was assessed using I^2 statistics. ICD-PM coded reported data were extracted to Microsoft Excel, and aggregate data of frequencies and percentages were reported.

Results: Out of the 23 included studies, 48,596 perinatal mortalities were reported, and approximately 96% (46,816 deaths) were classified according to the ICD-PM. The pooled rate of stillbirths in high-income countries was 23/1,000 births; in low-income countries, it was found to be approximately twice as in high-income countries. Regarding the category of deaths, 25,563 (54.6%) deaths were recorded in the antepartum period, and more than half, 14,887 (58.2%), were classified under unspecified causes (A6). Moreover, 6,148 (13.7%) and 14,835 (31.7%) deaths were coded with intrapartum and neonatal period causes, respectively. The leading causes of perinatal mortality during the intrapartum were acute intrapartum events (I3) 3,712 (57.8%). Furthermore, neonatal death was caused by low birth weight and prematurity (N9) 4,091 (27.6%), congenital malformations, and chromosomal abnormalities (N1) 2,512(16.9%).

Conclusion: Congenital malformations, and chromosomal abnormalities contribute to 1 in every 10 perinatal deaths and 1 in every 4 neonatal deaths. Other specified antepartum disorders are responsible for over half of antepartum deaths, while acute intrapartum events are the leading cause of intrapartum deaths, with a significant proportion remaining unexplained. Maternal complications related to the placenta, membranes, cord, labor, and delivery play a significant role in antepartum and intrapartum deaths. Targeted interventions and improved monitoring of high-risk pregnancies are crucial to reducing perinatal mortality rates. Further investigation is needed to enhance understanding and address unexplained perinatal deaths.

Systematic review registration: [https://clinicaltrials.gov/], identifier [CRD4202452549].

KEYWORDS

ICD-PM, stillbirth, neonatal death, perinatal mortality, meta-analysis

1 Introduction

Perinatal mortality is defined as the loss of fetuses at or beyond 20 weeks, deaths during labor and delivery, as well as early neonatal deaths (1). Globally, the stillbirth rate is estimated to be 13.9/1,000 births, resulting in approximately 2.6 million stillbirths annually (2, 3). Singapore and Finland have the lowest stillbirth rates, with only 2/1,000 births. In sub-Saharan Africa, the stillbirth rate is estimated at 21/1,000 births (3, 4). Notably, low-income countries account for approximately 98% of the reported stillbirths (5). Perinatal deaths have been insufficiently documented, and large variations exist across regions (4, 5).

Perinatal mortality can have far-reaching social, psychological, economic, and medical consequences (6). Consequently, perinatal death imposes a substantial burden on societies as it can have unforeseen negative consequences for families (6, 7). Additionally, the perinatal mortality rate is an important indicator of a country's development. Therefore, analyzing perinatal deaths is valuable for clinicians and policymakers, helping identify areas for improvement and shaping effective policies. However, many countries, specifically low- and middle-income countries, have no national registration for perinatal mortality (8, 9).

A narrative review showed that over 81 different classification systems were used to categorize perinatal deaths between 2009 and 2014 (10), such as ReCoDe, INCODE, and TULIP (11–13). These systems often require additional evidence, such as histological findings or post-mortem examinations, to support certain diagnoses (13). Furthermore, some of these classification systems were developed using specific, computerized systems and programs to record patient information, and the application of these systems may also require the use of similar technological tools (14, 15).

In 2016, the World Health Organization (WHO) introduced the International Classification of Diseases to Perinatal Mortality (ICD-PM), a standardized system designed to uniformly identify causes and harmonize for classifying stillbirths and early neonatal deaths (death of the neonate within 7 days) data globally (16). Additionally, the ICD-PM was developed to have minimal data requirements, be simple to use, and have fewer clinical details compared to some other recently developed classification systems for perinatal mortality. The ICD-PM code has three main categories: antepartum death (after fetal viability), intrapartum death (during labor and delivery), and early neonatal death (within the first week of birth). Each of these categories represents a distinct period, which helps healthcare professionals understand the timing and potential causes of perinatal mortality (16).

Furthermore, the ICD-PM categories include 6 antepartum causes of death (designated by "A"), 7 intrapartum causes of death (designated by "I"), and 11 neonatal causes of death (designated by "N"). For each cause, the maternal condition contributing to perinatal death is recorded. The existing ICD-10 groups have been reordered and expanded to more accurately represent the spectrum of possible conditions, including a new category for cases where no maternal condition is identified (17). Fetal abnormalities, infection, antepartum hypoxia, fetal growth disorder, placental insufficiency, maternal health conditions, or other complications during pregnancy are the major potential causes of perinatal death during the antepartum period. Intrapartum deaths, which occur during labor and delivery, primarily result from birth asphyxia, birth trauma, low birth weight and prematurity, umbilical cord accidents, or maternal emergencies. Early neonatal deaths are associated with prematurity, congenital anomalies, infections, or other medical conditions (18).

Accurate recording of the cause of death and identification of preventable causes is essential to reducing the global burden of perinatal mortality. Additionally, this helps guide the allocation of limited resources to have the greatest impact on reducing perinatal mortality rates. However, studies using the ICD-PM classification for stillbirths have shown inconsistent results, as highlighted in a previous systematic review that only provided descriptive measures, such as ranges and median values (19). Additionally, discrepancies existed across economic regions, and there are challenges in categorizing a high proportion of antepartum deaths as unspecified causes. Nevertheless, subsequent studies have been published since the review.

In contrast, our review extracted all refined articles on perinatal mortality into Microsoft Excel and organized them accordingly, reporting the data in the form of frequency and percentage for each category of the ICD-PM classification. The data were then tabulated alongside the maternal complications. Furthermore, findings were extracted based on the gestational age used to define perinatal mortality and presented in table format. Additionally, the pooled rates of stillbirth and perinatal mortality were estimated based on the reports of the ICD-PM classification.

2 Methods

2.1 Data sources and search strategy

This systematic review was reported in accordance with the 2010 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (20). We reviewed the literature for articles, established eligibility criteria, selected relevant studies, critically appraised the included studies, and conducted data analysis and synthesis. The study was registered in Prospero with the number CRD4202452549.

Abbreviations: CI, Confidence interval; ICD-PM, International Classification of Disease-Perinatal Mortality; SB, stillbirth rate; PMR, perinatal mortality rate; WHO, World Health Organization.

The following electronic databases were systematically searched from 1 January 2016 to 14 March 2024: PubMed via MEDLINE, SCOPUS, Web of Sciences, EMBASE, Cochrane Library, and PROSPERO. We developed a search strategy using Medical Subject Heading (MeSH) terms and keywords. The terms/keywords include "International Classification of Diseases Perinatal Mortality" OR "ICD-PM" AND "mortality, perinatal" OR "perinatal mortality," OR "perinatal death" OR "stillbirth." The search strategy is provided in Supplementary File (search strategy). Additionally, manual searching of references of retrieved articles and previous systematic reviews were conducted to include studies missed in database searching.

2.2 Eligibility criteria and screening

All original studies or literature published in the English language were included. Articles that used prospective or retrospective cross-sectional, case–control, cohort, and randomized controlled trial designs were eligible. The criteria followed for the inclusion of the studies were causes reported using ICD-10 and studies focused on stillbirth (from 20 weeks of gestation until delivery) and early/late neonatal deaths (deaths during the first 7/28 days of life from birth). Perinatal mortality assessed with other ICD codes or in combination with earlier versions of ICD were not considered in this review. Case reports, case series, and commentaries were also excluded.

After excluding duplicates in EndNote software, all articles searched from the databases were exported to Covidence, a web-based tool for article screening. Two investigators (HK, MMR and NBY) independently screened articles based on their titles and abstracts. Subsequently, the same investigators conducted full-text screening of the articles retained in the first phase. Disagreements between the two were resolved through a discussion between three investigators (HK, NBY, and EM).

2.3 Data extraction and quality appraisal

We developed a data extraction form in Microsoft Excel, the first Microsoft Excel, consisting of the author name, year of publication, country, design, sample size, outcome, estimates, ICD-PM causes, and other relevant study population characteristics. The second Microsoft Excel file consists of the author names listed in the columns and rows containing the number of perinatal mortalities tabulated by maternal causes during the antepartum, intrapartum, and neonatal periods. Finally, after all the data were extracted for the antepartum, intrapartum, and neonatal periods, the maternal and fetal factors for each period were aggregated, and data of frequencies and percentages were presented. Data extraction was conducted independently by two investigators (HK and NBY). In cases of inconsistencies, the issues were resolved through discussion and by involving additional third investigators (EM or MMR).

We assessed the quality of the included studies using appropriate tools for the study designs. The NOS for assessing the quality of non-randomized studies in meta-analyses (21) was used to appraise observational studies. A NOS of 7–9 was considered high quality, 5–6 was moderate, and below 5 was low. Studies that scored low quality were not included in the analysis. Similarly, two investigators (HK and EM) assessed the quality of the included studies, and the disagreement between them was resolved through consensus and the involvement of additional authors. The full quality assessment result of the included studies is provided in Supplementary Table S1.

2.4 Analysis

The findings of the review were summarized and synthesized qualitatively and quantitatively. The causes and timing of deaths were described qualitatively and using relevant summary measures of frequency and percentage. The stillbirth rate and perinatal mortality rate were calculated per 1,000 births. Tables were used to summarize ICD-PM mortality using frequencies and percentages. We conducted a meta-analysis of the combined estimates using a random-effects (DerSimonian and Laird) method with an inverse-variance approach, adjusting to the study weights (22). Forest plots were used to present the findings graphically. Statistical heterogeneity between the studies was assessed using I^2 statistic. The findings of the I^2-test were classified as having low (25%), moderate (50%), and high (75%) heterogeneity (23). When there was evidence of heterogeneity, subgroup analysis was performed to check effects across different groups. We used Egger's test and funnel plots to assess publication bias. If bias existed, we used a trim-and-fill analysis. Sensitivity analysis was conducted to check the robustness of the findings. All analyses were performed in STATA version 17.0.

3 Results

This systematic review and meta-analysis was focused on the ICD-PM classification reports across the globe. A thorough search of electronic databases resulted in the retrieval of 21,644 records. From these records, a careful screening process led to the inclusion of only 23 articles in the ICD-PM classification, and 14 studies were used to estimate the pooled rate of stillbirth and perinatal mortality (Figure 1).

3.1 Characteristics of the included studies

This review included 23 studies from various regions around the world. Out of the 23 studies, 17 were conducted in low- and middle-income countries: Zambia (24), Nepal (25), Solomon Island (26), Suriname (27), India (28), Nigeria (29), Pakistan (30), Sri Lanka (31), China (32), Jordan (33), Tanzania (34), Turkey (35, 36), North Macedonia (37), Thailand (38), South Africa (39), and Colombia (40), and one study was conducted at the sub-regional level, which includes four sub-Saharan African countries (Malawi, Zimbabwe, Kenya, and Sierra Leone) (41). The remaining four studies were conducted in high-income countries, particularly in Italy (42, 43) and Hong Kong (44, 45). Additionally, one study was conducted in the United Kingdom and South Africa (46).

The studies were published between 2016 and 2022, with the majority of articles published in 2020. Approximately half of the study designs were retrospective and prospective cohort studies. Regarding the method of assessing perinatal mortality, eight studies have not reported the method of certification of death. The remaining studies stated the certificate of death or reported by ICD-PM-trained professionals. The details are available in Supplementary Table S2.

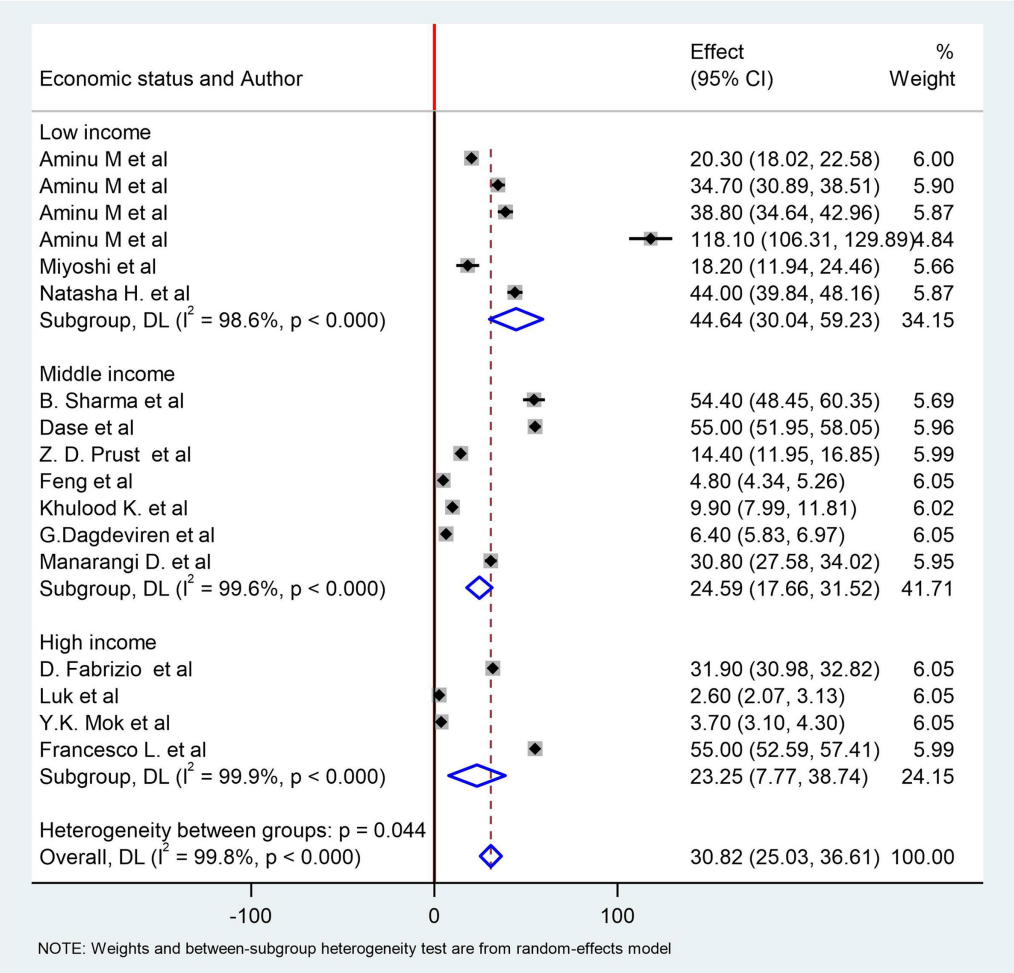

FIGURE 1
Flow chart of study selection for systematic review and meta-analysis of the global report of ICD-PM classification.

A total of 48,596 perinatal deaths were reported across the 23 articles reviewed, with approximately 96% (46,816 deaths) classified according to the ICD-PM. Among these deaths, 25,563 (54.6%) were antepartum fetal deaths, reported by all 23 articles, and classified accordingly. Intrapartum deaths were reported by 22 studies, with 6,418 (13.7%) fetal deaths classified based on the ICD-PM system. Additionally, 11 studies included deaths during the neonatal period, with 14,835 (31.7%) neonatal deaths classified according to the ICD-PM coding. A summary of the included articles is available in Table 1 and Supplementary Table S2.

3.2 Stillbirth and perinatal mortality rate

Out of the 23 studies included in the analysis, only 14 reported the total number of births during the study period, which amounted to a total of 514,989 births. These studies reported stillbirth rates from 17 countries (one sub-regional study that included four Sub-Saharan African countries) (24, 26–29, 32–35, 41–45). From the included studies, nine articles used a gestational age of 28 weeks and above cutoff or a birth weight of more than 1,000 g to define stillbirth (24, 25, 27, 29–31, 34, 39, 41). A study conducted in the United Kingdom and South Africa (46) used a cutoff of 24 and 28 weeks for the two countries, respectively. The remaining 13 studies defined stillbirth as a fetal death starting between 20 and 28 weeks of gestation or weighing 350/500 g and above (26, 28, 32, 33, 35–38, 40, 42–45).

The highest stillbirth rate was reported in a study from Sierra Leone, with a rate of 118/1,000 births (41), while the lowest rate was reported from Hong Kong at 2.6/1,000 births (44). The pooled rate of stillbirth from 14 studies in the global report of ICD-PM classification is 31/1,000 births (95%CI: 25.03, 36.61). We stratified the studies based on the economic classification of countries. The pooled rate of stillbirths in high-income countries using four studies (42–45) was 23/1,000 births (95%CI: 7.77, 38.74). The level of heterogeneity was high, as evidenced by an I^2 value of 97.9% ($p < 0.0001$).

Moreover, the pooled rate of stillbirth in middle-income countries using seven studies (26–29, 32, 33, 35) was 25/1,000 births (95% CI: 17.66, 31.52) with a high level of heterogeneity. In low-income countries, the pooled rate of stillbirth (24, 34, 41) was found to be 45/1,000 births (95%CI: 30.04, 59.23) (Figure 2). Similarly, the level of heterogeneity was high. We conducted Egger's test to examine the presence of publication bias and obtained a *p*-value of 1. This result indicates that there is no statistically significant evidence of publication bias in the included studies. Egger's test result is available in

TABLE 1 Characteristics of the included studies.

Author	Publication year	Country	Study design	Sample size	SB rate	PMR	Total death reported	In ICD-PM included
Allanson et al.	2016	UK and SA	Retrospective	NA	NA		9,756	9,748
Priyani AAH et al.	2017	Sri Lanka	Retrospective	NA	NA		291	291
Tina Lavin et al.	2018	South Africa	Not reported	NA	NA		26,810	26,810
Aminu M et al.	2019	Sub-Saharan Malawi Zimbabwe Kenya Sierra Leone	Prospective	14,729 8,847 8,273 2,879	20.3 34.7 38.8 118.1		1,267	968
Miyoshi et al.	2019	Zambia	Retrospective	1754	18.2	42	75	75
Mary S.	2019	Colombia	Cross-sectional	NA	NA		3,901	3,361
B. Sharma et al.	2020	India	Prospective	5,574	54.4		314	314
D. Fabrizio et al.	2020	Italy	Prospective	141,013	31.9		443	432
Dase et al.	2020	Nigeria	Retrospective	21,462	55		1,177	760
T. Wasim et al.	2020	Pakistan	Prospective	11,850	NA	58.2	690	690
Z. D. Prust et al.	2020	Suriname	Cross-sectional	9,089	14.4		113	107
Luk et al.	2020	Hong Kong	Retrospective	34,920	2.6	3.4	119	119
Y.K. Mok et al.	2020	Hong Kong	Retrospective	39,625	3.7		145	135
Khulood K. et al.	2020	Jordan	Prospective	10,328	9.9		102	95
Natasha H. et al.	2021	Tanzania	Prospective	9,333	44	71	744	459
G.Dagdeviren et al.	2021	Turkey	Cross-sectional	74,102	6.4		475	458
Shrestha J et al.	2021	Nepal	Retrospective	NA			461	461
WHO	2021	North Macedonia	Prospective	NA			202	169
Taweevisit et al.	2022	Thailand	Retrospective	NA			330	330
Francesco L. et al.	2022	Italy	Retrospective	34,417	55		191	191
Salih Metin et al.	2022	Turkey	Retrospective	NA	NA		229	229
Manarangi De Silva	2022	Solomon Island	Retrospective	11,056	30.8		341	194
Feng et al.	2024	China	Retrospective	87,588	4.8		420	420
Total							48,596	46,816

NA, not applicable or only included prenatal death reports; SB, stillbirth; SA, South Africa; PMR, perinatal mortality rate; UK, United Kingdom.

Supplementary File under the subtitle of Egger's test. The funnel plots are also available in Supplementary Figure S1.

Four studies (24, 30, 34, 44) reported perinatal deaths, with one study by Wasim et al. in Pakistan (30) including deaths up to 7 days or early neonatal deaths only, while the other three studies reported deaths within the neonatal period (28 days). The highest perinatal death rate was reported in Tanzania at 71/1,000 live births (34), and the lowest rate was reported in Hong Kong at 3.4/1,000 births (44). Further details of the studies' reports are found in Table 1 and Supplementary Table S2.

The pooled rate of perinatal mortality from four studies (24, 30, 34, 44) was 44/1,000 births. The level of heterogeneity was high ($p < 0.0001$). When we exclude the study by Luk et al., which was conducted in a high-income country (44), the pooled perinatal mortality rate is approximately 58/1,000 live births (Figure 3). Egger's test was conducted and the result revealed the absence of publication bias. The result is available in Supplementary File in Egger's test subsection. The funnel plots are available in Supplementary Figure S2.

3.3 ICD-PM classification

A total of 23 studies were included in this review, which reported on stillbirth or perinatal mortality. However, three of Priyani et al. (31), Shattnawi et al. (33), and Lupariello et al. (43) these studies did not provide tabulation with maternal conditions (details of maternal conditions (M1–M5) are available in Supplementary Table S3). From these, Francesco et al. (43) reported maternal complications, including antepartum and intrapartum maternal complications. We excluded the maternal complications for this review (43). Khulood et al. (33) reported the fetal and maternal causes separately. Priyani et al. (31) reported the fetal and neonatal causes of death but did not tabulate the maternal causes, including the antepartum, intrapartum, and neonatal classifications.

For a detailed understanding of the causes of death, the reviewed studies were classified into three categories. The first category, which comprised all deaths regardless of gestational age, was used to define stillbirth or PM. The second category includes 14 studies that used to define stillbirth or PM, after 20 weeks of gestation. Within this

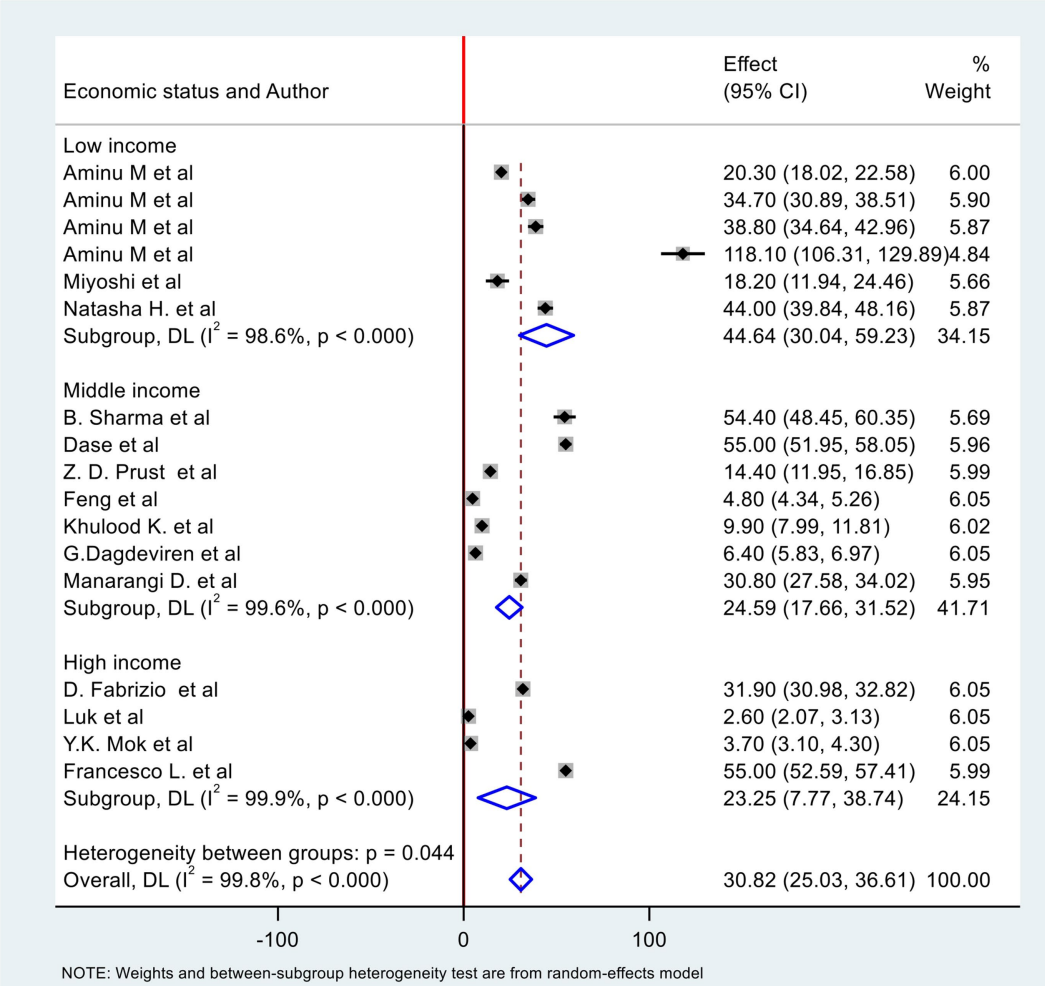

FIGURE 2
Forest plot of stillbirth rate from studies used ICD-PM classification.

category, three studies that reported on pregnancies after 20 weeks are from the Solomon Islands (26), China (32), and Jordan (33). Six studies that reported on pregnancies after 22 weeks were from India (28), North Macedonia (37), Thailand (38), Colombia (40), and Italy (42, 43). Additionally, four studies reported on pregnancies after 24 weeks of gestation were from Turkey (35, 36), the United Kingdom (46), and Hong Kong (44, 45). Two studies from Thailand (38) and Colombia (40) had two categories: 22–28 and 28 and above. The third category consisted of 10 studies, all of which were conducted in low- and middle-income countries and defined perinatal mortality after 28 weeks and above gestation.

3.4 Antepartum death for all studies

Table 2 presents the results of the included studies in the review, along with the classification of antenatal deaths and maternal tabulation. Antepartum deaths were reported in all (24–46) articles, with a total of 25,563 recorded deaths. The most common cause for antepartum stillbirths was unspecified antepartum death 14,8,872 (58.2%), and more than half of these deaths were accompanied by M5 (no maternal condition/healthy mother), followed by other (A4) 3,362 (13.1%) and by fetal growth disorders 2,804 (11%).

3.5 Intrapartum death for all studies

Except for the study from China (32), the remaining 22 studies (24–31, 33–46) reported a total of 6,418 intrapartum deaths classified according to the ICD-PM coding. The leading causes of perinatal mortality during the intrapartum period were acute intrapartum events (I3), accounting for 3,712 cases (58.1%), and unspecified causes, with 1,156 cases (17.9%). Among these, maternal tabulation was also available in 6,400 cases. The leading maternal causes of perinatal mortality were complications of the placenta, cord, and membranes (M1) and complications of labor and delivery (M3) (Table 2).

3.6 Neonatal deaths for all studies

Eleven studies (24, 25, 30, 31, 34, 36, 37, 39, 40, 44, 46) reported 14,835 neonatal deaths according to ICD-PM coding. However, there

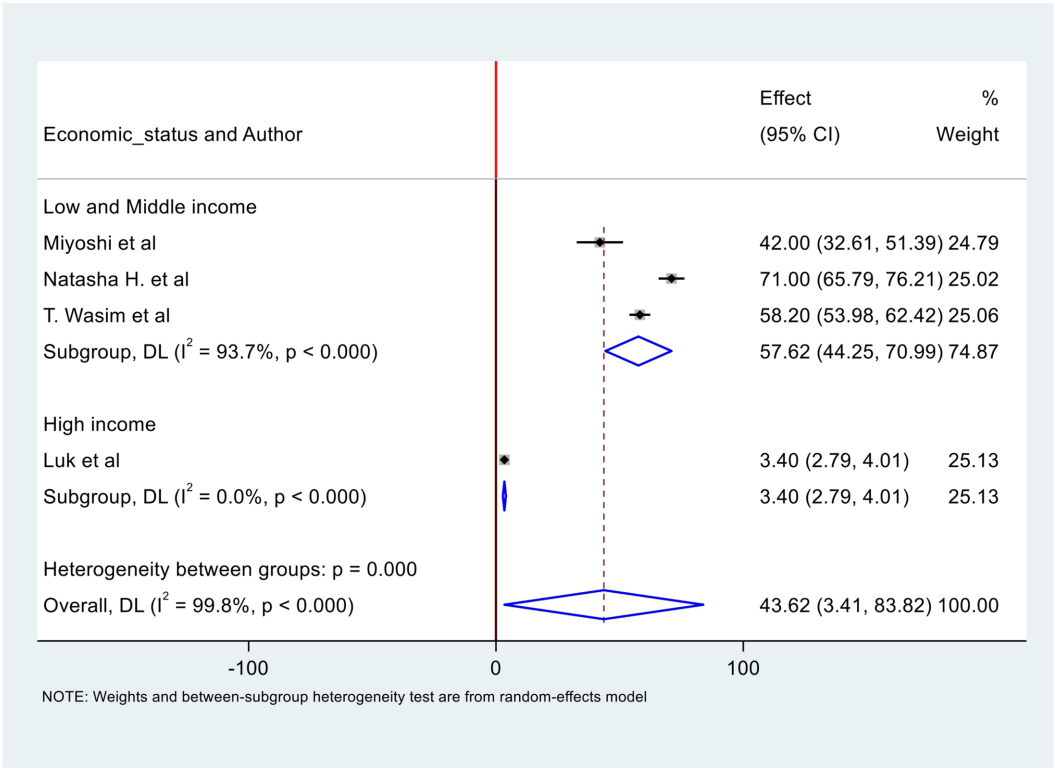

FIGURE 3
Forest plot of perinatal mortality rate from studies used ICD-PM classification.

are discrepancies in the reporting of perinatal mortality. Six studies (24, 34, 36, 40, 44, 46) that reported neonatal deaths include the first 28 days of life, and five studies (25, 30, 31, 37, 39) considered only early neonatal deaths. The most common cause of neonatal death was N9, preterm, or low birth weight (57.6%), followed by N4, complications of an intrapartum event (17%); all of these conditions were associated with maternal complications of labor and delivery. The third cause of death was congenital malformations (16.9%) (Table 2).

3.7 Perinatal mortality defined after 20 weeks

Table 3 shows findings based on studies that defined perinatal mortality after 20 weeks of gestation or (350/500 g and above for unknown gestational age) until 7/28 days of the postpartum period. However, studies that defined perinatal mortality after 28 weeks of gestation were excluded. Fourteen studies were included and the studies were from Solomon Island (26), India (28), China (32), Jordan (33), Turkey (35, 36), North Macedonia (37), Thailand (38), Colombia (40), Italy (42, 43), Hong Kong (44, 45), and the United Kingdom (46). In two studies, the perinatal mortalities were not tabulated with maternal conditions and reported the antepartum and intrapartum causes of death (33, 43).

3.8 Antepartum death after 20 weeks of gestation

In this gestational age category, 8,094 antepartum deaths were classified according to ICD-PM classification from 14 studies (26, 28, 32, 33, 35–38, 40, 42–46). Congenital malformation and chromosomal abnormalities (A1) 1,448 (17.9%) and antepartum hypoxia (A3) 1,325 (16.4%) were the leading causes of perinatal mortality during the antepartum period. From these, 7,909 maternal complications were tabulated with perinatal mortality. The leading tabulated causes are complications of placenta, cord, and membrane (M1) 2,235 (28.2%) and no maternal condition (M5) 3717 (47%).

3.9 Intrapartum deaths after 20 weeks of gestation

Except for the study from China (32), the aforementioned 13 studies (26, 28, 32, 33, 35–38, 40, 42–46) reported a total of 1,278 intrapartum deaths, which were classified according to the ICD-PM. Among these deaths, acute intrapartum events (I3) accounted for 612 cases (47.9%), and congenital, malformations, and chromosomal abnormalities (I1) were responsible for 225 cases (17.6%). From 1,276 cases classified as intrapartum maternal causes, complications of placenta, cord, and membrane were identified as the cause for 357 deaths (28.2%), and no maternal conditions were identified as the cause for 442 deaths (34.9%).

3.10 Neonatal deaths after 20 weeks of gestation

In five studies (36, 37, 40, 44, 46), 1,914 neonatal deaths were reported using the ICD-PM classification. Except for a study conducted by the WHO in North Macedonia (37), which included

TABLE 2 Causes perinatal death according to ICD-PM of all studies.

Maternal condition	M1:Complication of placenta, cord, membrane	M2: Maternal complication of pregnancy	M3:Other complications of labor and delivery	M4:Maternal surgical and medical conditions	M5:No maternal conditions	Three studies (31, 33, 43) *	Total (%)
Antepartum death							25,563
A1: Congential malformations and chromosomal abnormalities	168	440	19	156	1,105	61	1949 (7.6)
A2: Infection	162	24	3	369	72	32	662 (2.5)
A3: Antepartum hypoxia	817	123	30	483	251	195	1899 (7.4)
A4: Other specified antepartum disorder	2,452	55	23	652	135	45	3,362 (13.1)
A5: Disorder related to fetal growth	559	637	29	739	813	27	2,804 (11)
A6: Antepartum death unspecified cause	1,148	252	43	5,102	8,241	101	14,887 (58.2)
Khulood K. et al.	19	9	2	4	44	–	–
Total (%) M1-M5 = 25,180	5,325 (21.1)	1,540(6.1)	149(25.4)	7,505(20.7)	10,661(16.8)		
Intrapartum death							6,418
I1: Congenital malformation and chromosomal abnormalities	9	27	114	41	287	9	487 (7.6)
I2: Birth trauma	2	0	6	8	4	0	20 (0.3)
I3: Acute intrapartum event	1,246	115	1,201	645	494	11	3,712 (57.8)
I4: Infection	28	8	7	51	6	0	100 (1.5)
I5: Other specified intrapartum disorder	352	57	26	87	24	4	550 (8.6)
I6: Disorder related to fetal growth	130	33	65	75	89	1	393 (6.1)
I7: Intrapartum unspecified cause	290	67	212	412	170	5	1,156 (18)
Khulood K. et al.	4				8		
Total (%) M1-M5 = 6,400	2061 (32.2)	307 (4.8)	1,631 (25.5)	1,329 (20.6)	1,082 (16.9)		
Neonatal Death							14,835
N1: Congenital malformations, deformations, and chromosomal abnormalities	94	271	10	196	1903	38	2,512 (16.9)
N2: Disordersrelatedtofetal growth	23	2	3	64	89	3	184 (1.2)
N3: Birth trauma	0	0	1	3	10	0	14 (0.09)
N4: Complications of intrapartum event	288	15	1707	360	151	11	2,532 (17)
N5: Convulsions and disorders of cerebral status	20	3	22	26	91	0	162 (1.1)
N6: Infections	99	39	42	212	425	1	818 (5.5)
N7: Respiratory and cardiovascular disorders	90	72	81	832	1,311	6	2,392 (16.1)

(Continued)

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TABLE 2 (Continued)

Maternal condition	M1:Complication of placenta, cord, membrane	M2: Maternal complication of pregnancy	M3:Other complications of labor and delivery	M4:Maternal surgical and medical conditions	M5:No maternal conditions	Three studies (31, 33, 43) *	Total (%)
N8: Otherneonatalconditions	358	14	7	94	245	2	720 (4.8)
N9: Low birth weight and prematurity	502	456	2,319	477	313	24	4,091 (27.6)
N10: Miscellaneous	14	8	0	97	124	0	243 (1.6)
N11: Neonataldeathof unspecified cause	293	71	19	113	670	1	1,167 (7.8)
Total (%) M1-M5 = 14,749	1,781 (12)	951 (6.4)	4,211 (28.5)	2,474(16.8)	5,332 (36.2)		

*Studies reported based on ICD-PM classification but do not tabulated with maternal condition.

early neonatal death, the remaining studies focussed on the first 28 days of life. The leading causes of neonatal deaths were congenital malformations, and chromosomal abnormalities (N1) with 1,682 cases (27.3%), respiratory and cardiovascular disorders (N7) with 713 cases (11.6%), and low birth weight and prematurity (N9) with 1,597 cases (26%).

3.11 Perinatal mortality after 28 weeks

Twelve studies (24, 25, 27, 29–31, 34, 38–41, 46) defined perinatal mortality as the death of a fetus after 28 weeks of gestation and until 7/28 days of postpartum day. However, studies from Thailand (38) define perinatal mortality (PM) after 22 weeks of gestation. The results were categorized into two groups: 22–28 weeks (less than 1,000 g) and 28 weeks or more (1,000 g and above). These findings were presented separately, and the results for gestational age of 28 weeks or more, or birth weight of 1,000 g and above, were included in this category (Table 4).

3.12 Antepartum death after 28 weeks

Twelve studies (24, 25, 27, 29–31, 34, 38–41, 46) included 18,343 antepartum deaths in ICD-PM. The leading cause of antepartum death was categorized under antepartum death, unspecified cause (A6) 11,387 (62%), which is frequently associated with maternal surgical and medical conditions. The maternal tabulation revealed that three-fourths of the causes of antepartum death were no maternal conditions (M5) and maternal surgical and medical conditions (M4) (Table 4).

3.13 Intrapartum death after 28 weeks

Twelve studies (24, 25, 27, 29–31, 34, 38–41, 46) reported and classified 5,462 intrapartum deaths according to the ICD-PM classification. The leading cause of death was an acute intrapartum event (I3), 3,222 (59%). Furthermore, nearly 60% of maternal causes of death were complications of the placenta, cord, membrane (M1), and other complications of labor and delivery (M3) (Table 4).

3.14 Neonatal death after 28 weeks

Eight studies (24, 30, 31, 33, 34, 40, 46, 47) reported 9,901 neonatal deaths according to ICD-PM coding. Four studies (24, 34, 40, 46) included both early and late neonatal death, and three studies (30, 33, 47) reported only early neonatal death. Half of the neonatal deaths were caused by complications of the intrapartum event (N4) 2422 (24.5) and low birth weight and prematurity (N9) 2528(25.5%) (Table 4).

3.15 Sensitivity analysis

To assess the influence of individual studies on the overall stillbirth rate, a leave-one-out sensitivity analysis was conducted. The results of the sensitivity analysis indicated that the pooled rates were

TABLE 3 Causes perinatal death according to ICD-PM for perinatal mortality define gestational age after 20 weeks.

Maternal condition	M1:Complication of placenta, cord, membrane	M2: Maternal complication of pregnancy	M3:Other complications of labor and delivery	M4:Maternal surgical and medical conditions	M5:No maternal conditions	Two authors (33, 43)*	Total (%)
Antepartum death							8,094
A1: Congential malformations and chromosomal abnormalities	161	427	19	72	736	33	1,448 (17.9)
A2: Infection	75	21	2	34	20	24	176 (2.2)
A3: Antepartum hypoxia	673	89	25	207	219	112	1,325 (16.4)
A4: Other specified antepartum disorder	102	39	23	53	129	10	365 (4.4)
A5: Disorder related to fetal growth	407	92	29	275	410	17	1,230 (15.2)
A6: Antepartum death unspecified cause	798	154	42	339	2,159	67	3,559 (44)
Khulood K. et al.	19	9	2	4	44		
Total (%) M1-M5 = 7,909	2,235 (28.2)	831 (10.5)	142 (1.7)	984 (12.4)	3,717 (47)		
Intrapartum death							1,267
I1: Congenital malformation and chromosomal abnormalities	6	16	92	8	99	4	225 (17.6)
I2: Birth trauma	2	0	6	8	4	0	20 (1.6)
I3: Acute intrapartum event	244	47	74	42	195	10	612 (47.9)
I4: Infection	16	3	0	5	5	0	29 (5.3)
I5: Other specified intrapartum disorder	2	5	26	9	23	4	69 (5.3)
I6: Disorder related to fetal growth	27	22	38	23	55	0	165 (12.9)
I7: Intrapartum unspecified cause	56	12	14	18	53	5	158 (12.4)
Khulood K. et al.	4				8		
Total (%) M1-M5 = 1,276	357 (28.2)	105 (8.3)	250 (19.7)	113 (8.9)	442 (34.9)		
Neonatal death							6,147
N1: Congenital malformations, deformations, and chromosomal abnormalities	85	259	7	55	1,276		1,682 (27.3)
N2: Disordersrelatedtofetal growth	4	2	3	4	10		23 (0.37)
N3: Birth trauma	0	0	1	3	10		14 (0.2)
N4: Complications of intrapartum event	60	8	12	8	97		185 (3)
N5: Convulsions and disorders of cerebral status	9	0	4	1	40		54 (0.9)
N6: Infections	28	8	3	15	331		385 (6.2)
N7: Respiratoryand cardiovascular disorders	50	45	15	39	564		713 (11.6)

(Continued)

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TABLE 3 (Continued)

Maternal condition	M1:Complication of placenta, cord, membrane	M2: Maternal complication of pregnancy	M3:Other complications of labor and delivery	M4:Maternal surgical and medical conditions	M5:No maternal conditions	Two authors (33, 43)*	Total (%)
N8: Other neonatal conditions	21	10	4	10	241		286 (4.6)
N9: Lowbirthweight and prematurity	409	153	730	74	231		1,597 (26)
N10: Miscellaneous	8	3	0	0	22		33 (0.05)
N11: Neonataldeathof unspecified cause	294	72	17	110	682		1,175 (19.1)
Total (%) M1-M5 = 6,147	968 (15.7)	560 (9.1)	796 (12.9)	319 (5.2)	3,504 (57)		

*Studies reported based on ICD-PM classification but do not tabulated with maternal condition.

not influenced by any single study. The detailed results of this analysis are found in Supplementary Figure S3 and Supplementary Table S4 in the section titled Sensitivity Analysis.

4 Discussion

4.1 Main findings

This review was conducted to determine the rate of perinatal mortality and identify causes of perinatal mortality according to ICD-PM based on existing global reports. More than half a million births were reported from 14 studies and the pooled stillbirth rate was 31/1,000 births globally. However, the pooled stillbirth rate in low-income countries is unacceptably high. From 23 studies, 46,816 perinatal mortalities were classified according to ICD-PM. The most commonly identified causes for antepartum deaths coding on other specified antepartum disorders (A4: Vasa previa, ruptured cord, twin-twin transfusion etc.) (13%). Moreover, regardless of gestational age used to define stillbirth or PM this review revealed 17.9% of neonatal deaths were caused by congenital malformations and chromosomal abnormalities.

Acute intrapartum events (I3) accounted for the largest proportion of intrapartum deaths for all classifications applied in this review. Deaths without specific fetal cause occur in 2 out of 10 intrapartum deaths among studies that defined perinatal mortality above 28 weeks of gestation. Whereas, studies considered above 20 weeks or conducted in high- or middle-income countries reported 1 out of 20 perinatal mortalities during the intrapartum period. The leading cause of perinatal mortality during the neonatal period for gestational age 20 weeks and above was congenital malformation, deformation, and chromosomal abnormalities (27.3%). However, low birth weight and prematurity (25.5%) were reported as common causes of perinatal death defined after 28 weeks.

For associated maternal conditions, the complications of placenta, cord, and membranes (M1) (28.2%) and maternal surgical and medical conditions (M4) (31.1%) categories were the most common category assigned for antepartum deaths for perinatal death defined above 20 and 28 weeks, respectively. Complications of labor and delivery (M3) (27.5) accounted for the highest proportion of intrapartum deaths for gestational age above 28 weeks categories. In the studies defining perinatal mortality as the death of a fetus after 20 weeks of gestation, 57% of neonatal deaths were not associated with maternal conditions, however, neonatal deaths were commonly associated with congenital malformation and chromosomal abnormalities.

4.2 Comparison with existing literature

This review revealed a pooled stillbirth rate of 45/1,000 births using ICD-PM classification reports from low-income countries. A meta-analysis study conducted using demographic and health survey data in Sub-Saharan Africa showed a stillbirth rate of 34/1,000 births (4), which is lower than the present finding. This difference might be explained by the relatively better reporting systems in hospital-based registries compared to a population-based survey (48). The stillbirth rate in low-income countries remains quite high, and the countries in the region are unlikely to achieve the Sustainable Development Goal target of 12 stillbirths per 1,000 births by 2030 (8, 49).

TABLE 4 Causes perinatal death according to ICD-PM for perinatal mortality define gestational age after 28 weeks.

Maternal condition	M1:Complication of placenta, cord, membrane	M2: Maternal complication of pregnancy	M3:Other complications of labor and delivery	M4:Maternal surgical and medical conditions	M5:No maternal conditions	One author (31)*	Total (%)
Antepartum death							18,343
A1: Congential malformations and chromosomal abnormalities	19	17	5	86	483	28	638 (3.5)
A2: Infection	101	7	2	346	57	8	521 (2.8)
A3: Antepartum hypoxia	386	59	20	334	175	83	1,057 (5.8)
A4: Other specified antepartum disorder	2,363	20	13	612	30	35	3,073 (16.7)
A5: Disorder related to fetal growth	182	552	5	480	438	10	1,667 (9.1)
A6: Antepartum death unspecified cause	358	106	22	4,770	6,097	34	11,387(62.1)
Total (%) M1-M5 = 18,145	3,409 (20.1)	761 (5.6)	67 (0.3)	6,628 (31.1)	7,280 (42.9)		
Intrapartum death							5,462
I1: Congenital malformation and chromosomal abnormalities	3	16	84	33	245	5	386 (7.1)
I2: Birth trauma	0	0	1	0	0	0	6 (0.002)
I3: Acute intrapartum event	1,042	81	1,146	611	341	1	3,222 (59)
I4: Infection	18	6	7	48	4	0	83 (1.5)
I5: Other specified intrapartum disorder	350	54	23	84	6	0	517 (9.4)
I6: Disorder related to fetal growth	107	12	32	53	37	1	242 (4.4)
I7: Intrapartum unspecified cause	234	56	207	394	120	0	1,011 (18.5)
Total (%) M1-M5 = 5,455	1754 (32.2)	225 (4.1)	1,500 (27.5)	1,223 (22.4)	753 (13.8)	–	–
Neonatal death							9,901
N1: Congenital malformations, deformations, and chromosomal abnormalities	13	18	5	144	1,080	38	1,298 (13.1)
N2: Disorders related to fetal growth	19	0	0	60	82	3	164 (1.6)
N3: Birth trauma	0	0	0	0	2	0	2 (0.02)
N4: Complications of intrapartum event	250	11	1701	356	93	11	2,422 (24.5)
N5: Convulsions and disorders of cerebral status	13	3	20	25	71	0	132 (1.3)
N6: Infections	82	37	40	206	300	1	666 (5.2)
N7: Respiratoryand cardiovascular disorders	44	34	72	797	969	6	1,922 (19.4)
N8: Other neonatal conditions	341	4	5	85	102	2	539 (5.4)

(Continued)

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TABLE 4 (Continued)

Maternal condition	M1:Complication of placenta, cord, membrane	M2: Maternal complication of pregnancy	M3:Other complications of labor and delivery	M4:Maternal surgical and medical conditions	M5:No maternal conditions	One author (31)*	Total (%)
N9: Low birth weight and prematurity	100	307	1,591	408	98	24	2,528 (25.5)
N10: Miscellaneous	5	3	0	96	75	0	179 (1.8)
N11: Neonatal death of unspecified cause	0	1	3	5	39	1	49 (0.5)
Total (%) M1-M5 = 9,815	867 (8.8)	418 (4.2)	3,437 (35)	2,182 (22.2)	2,911 (29.6)	--	--

*Studies reported based on ICD-PM classification but do not tabulated with maternal condition.

The stillbirth rate reflects the quality of healthcare that women receive during the perinatal period (50). According to the WHO, deficiencies in antenatal care contribute to increased stillbirth rates (51). Furthermore, research showed that high-quality antenatal care and the active involvement of healthcare providers in educating mothers about pregnancy danger signs can reduce stillbirths (52). Investing in the healthcare system and providing good-quality and timely maternal services may prevent significant rates of stillbirths (53). Therefore, to achieve the Sustainable Development Goal target 2030, an evaluation of perinatal mortality policies and strategies might be needed in countries with a high level of stillbirth or perinatal mortality.

Our review using the ICD-PM coding system on a global report revealed that the majority of perinatal mortality occurs during the antepartum period. Nearly half of the antepartum deaths were reported to be associated with maternal complications of the placenta, cord, surgical, or medical conditions. Additionally, the majority of antepartum deaths were coded under A6, which is death with an unspecified cause but mainly associated with the complication of cord, placenta, and membrane, as well as surgical and medical conditions of the women. Likewise, a systematic review and meta-analysis study conducted in South Asia and Sub-Saharan Africa revealed stillbirth is associated with premature rupture of the membrane, diabetes mellitus, hypertension, advanced maternal age, antepartum hemorrhage, and anemia (54, 55).

Acute intrapartum events, or intrauterine hypoxia, were the leading causes of intrapartum death and were commonly associated with the maternal condition of placenta, cord, and membrane complications. A systematic review conducted in low-income countries also revealed similar findings: placental causes (7.4–42%), asphyxia and birth trauma (3.1–25%), umbilical problems (2.9–33.3%), and amniotic and uterine factors (6.5–10.7%) were leading causes of perinatal mortality (56). Additionally, a systematic review revealed that uterine rupture after prior myomectomy (surgical removal of uterine fibroids) occurred mainly earlier than 36 weeks of gestation and the onset of labor (57).

Our review of ICD-PM coding and different studies highlights the already-established importance of investment in antenatal care to reduce perinatal mortality (4). However, the effect of existing implementation programs in perinatal care services might need to be evaluated on perinatal mortality reduction. For instance, in 2016, the WHO recommended increased antenatal care contacts in the third trimester (58). In response to these recommendations, countries such as Ethiopia and South Africa incorporated their national guidelines (47, 58).

Additionally, various interventions have a clear benefit in reducing stillbirth rates. These include nutritional interventions, midwife-led models of care, trained traditional birth attendants (reducing stillbirths by 31% in low- and middle-income countries), insecticide-treated anti-malarial nets (reducing fetal loss by 33%), smoking cessation, support for women at risk of low birth weight, carrying personal case notes, diuretics, nitric oxide, progesterone, antioxidants for preventing preeclampsia, altered dietary salt, screening for gestational diabetes and thyroid dysfunction, diet and exercise for preventing gestational diabetes, ultrasound for fetal assessment in early and late pregnancy, fetal movement counting, fetal and umbilical Doppler ultrasound, uteroplacental Doppler ultrasound, antenatal cardiotocography, and symphysial fundal height measurement for detecting abnormal fetal growth (59).

A commonly cited cause of perinatal mortality is prematurity and prematurity-related (54, 60, 61). However, simply identifying that prematurity is an important contributor to deaths gives no information

regarding the optimal timing for interventions (62). From the ICD-PM classification, we see that approximately 16% of the total perinatal mortality (A5, I6, and N9) was due to prematurity, and 63.1% (29,254/46,329) of these deaths were also related to a maternal complication. This information is vital to public health experts and policymakers in targeting interventions; a heightened awareness of the causes of such deaths allows a focus on preterm-related issues, underscoring that both obstetric and neonatal interventions are required.

Nearly 11% of the overall causes of perinatal mortality were due to congenital deformations, malformations, and chromosomal abnormalities. These causes were more commonly noted in perinatal deaths occurring after 20 weeks of gestation (21.6%) or in studies conducted in high- or middle-upper-income countries, compared to deaths occurring at 28 weeks and above or in low-income countries (6.8% 6). This might be due to the detection of chromosomal abnormalities using fetal autopsy and genetic evaluation in studies conducted in high-income countries (44). Likewise, a systematic review conducted in low-income countries showed congenital anomalies accounted for 2.1–33.3% of stillbirths (56). Furthermore, a meta-analysis study conducted in Africa also revealed anencephaly alone constitutes 694,857 from 4,963,266 births (63).

Additionally, a meta-analysis study conducted in Denmark also showed congenital malformations were the leading causes of stillbirth (64). The national screening program for congenital malformation detected many severe malformations using ultrasonography (64). This implies the healthcare system might be delayed in addressing preventable stillbirth causes with nutritional supplementation of folic acid. Therefore, the integration of early detection of congenital abnormalities and folic supplementation into routine antenatal care is essential in the reduction of perinatal mortality.

The implementation of ICD-PM coding with simplified training can greatly facilitate its adoption in low-resource settings, enabling better tracking and analysis of maternal and perinatal outcomes. This approach aligns to achieve sustainable development targets (47). Therefore, we strongly recommend that low-resource settings utilize the ICD-PM classification system. By adopting this coding system on an international scale, a consistent and globally recognized classification of perinatal deaths can be established, enabling policymakers, clinicians, and researchers to access comparable data and make informed decisions.

This review represents the first global report in the ICD-PM classification, categorizing ICD-PM reports based on gestational age definitions used in the studies. Furthermore, the rates of stillbirth and perinatal death were pooled from available hospital-based reports using ICD-PM coding, which is considered reliable and reflective of the actual scope of the issue. However, a limitation of this study is that we did not assess the challenges associated with implementing ICD-PM coding. Additionally, this review included studies that used retrospective data, which opens the possibility of biases and potentially limits the generalizability of the findings. Therefore, future studies should focus on addressing these issues to enhance the accuracy of the ICD-PM classification.

5 Conclusion and recommendations

In conclusion, this review highlights the high global stillbirth rate, particularly in low-income countries, and antepartum deaths, which identify the leading causes of perinatal mortality based on the ICD-PM classification. Antepartum deaths are commonly attributed to disorders related to fetal growth and other antepartum-unspecified causes. Furthermore, the analysis suggests that a substantial number of deaths are classified as antepartum death (58%), intrapartum death (18%), and neonatal deaths (7.8%) without a specific fetal/neonatal cause. The number increased when studies were only conducted in low- or middle-income countries. In every 10 antepartum deaths, 6 were categorized under antepartum death with unspecified cause. Thus emphasizing the importance of further investigation to enhance understanding and reduce unexplained perianal mortalities.

Intrapartum deaths are predominantly categorized as acute intrapartum events, while neonatal deaths are caused by respiratory and cardiovascular disorders, as well as low birth weight and prematurity. Congenital malformations and chromosomal abnormalities also significantly contribute to perinatal mortalities. Therefore, it is vital to implement a comprehensive approach to address fetal growth disorders, including enhanced prenatal screening, targeted interventions for placental and maternal conditions, improved detection and management of congenital anomalies, strengthened maternal-fetal medicine expertise, and addressing social determinants of health. These measures aim to prevent preterm birth and ensure access to specialized neonatal intensive care services, ultimately optimizing fetal development and preventing perinatal death.

Accurate classification and reporting of perinatal mortality according to the ICD-PM system are crucial for understanding the patterns and addressing the causes of perinatal deaths, ultimately leading to improved maternal and perinatal outcomes worldwide. International organizations can promote the adoption of the ICD-PM classification system globally, enabling standardized reporting and data comparability for monitoring perinatal mortality trends. Further research should be conducted to evaluate the existing policies on perinatal care and the effectiveness of interventions in low-income countries.

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

HK: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. EM: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – review & editing. NY: Conceptualization, Investigation, Methodology, Project administration, Visualization, Writing – review & editing.

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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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Supplementary material

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Registration and characteristics of clinical trials on traditional Chinese medicine and natural medicines for endometriosis: a comprehensive analysis

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Objective: To investigate the characteristics of clinical trials on traditional Chinese medicine (TCM) or natural medicines for treating endometriosis, aiming to inform future clinical practice and the development of new effective drugs.

Method: The global clinical trial registration platform was searched to identify clinical trials investigating the efficacy of TCM/natural medicine in treating endometriosis. Relevant trials were selected based on stringent inclusion and exclusion criteria. Data entry was performed using Microsoft Excel, while data analysis was conducted using SPSS version 23.

Results: The study encompassed 57 trials, of which ClinicalTrials.gov accounted for 18, ChiCTR for 3, ICRP for 15, and ChiDTR for 21 trials. The number of registrations showed a significant positive correlation with the years. Of the 57 clinical trials, 87.7% were randomized, 63.2% were blinded, 78.9% followed a parallel intervention model, and 56.1% had a sample size below 100. Regarding trial phases, 45.6% of clinical trials did not specify a phase, while Phase 3 and Phase 4 clinical trials accounted for 17.5%. Nine clinical trials involved drugs that are already on the market, including six Chinese patent medicines: Sanjie Zhentong Capsules, Honghua Ruyi Pills, Huayu Sanjie Enema Liquid, Kuntai Capsules, Wenjing Tang, and Xuefu Zhuyu Capsules. Outside China, Iran has the highest number of registrations for natural medicine treatments for endometriosis, with curcumin being the most registered natural medicine.

Conclusion: The analysis reveals that clinical trials on TCM and natural remedies for endometriosis often utilize randomization; however, substantial deficiencies remain in blinding and sample size adequacy. These findings suggest that, despite growing interest in TCM and natural remedies, further methodological improvements are necessary to enhance the credibility of future studies. This research highlights the importance of rigorously designed clinical trials in verifying the safety and efficacy of these alternative therapies, which may influence future therapeutic approaches for managing endometriosis.

KEYWORDS

traditional Chinese medicine, natural products, natural medicine, clinical trials, registration, endometriosis

Introduction

Endometriosis is a common chronic gynecological disorder, with an incidence rate of approximately 5 to 15% among women of reproductive age (1, 2). This condition characterized by the presence and proliferation of uterine lining tissue (glands and stroma) outside the uterine cavity, leads to recurrent bleeding, pain, infertility, and the formation of nodules or masses (3, 4). It significantly impacts patients' quality of life and is a primary cause of female infertility. Currently, traditional treatments for endometriosis primarily consist of drug interventions (both non-hormonal and hormonal) and surgical procedures (which can be conservative or radical) (5). Combined hormonal contraceptives and progestogens are considered the first-line treatment regimen (6). However, long-term use of hormonal therapy can result in various side effects, including headaches, weight gain, and breast pain, as well as potential risks such as osteoporosis (7, 8). Therefore, it is crucial to identify safe and effective alternative therapies.

According to the theory of Traditional Chinese Medicine (TCM), the etiology of endometriosis is attributed to "Blood stasis" (9, 10). TCM boasts a long history of treating endometriosis and continues to be a significant component of modern therapies. Over time, TCM has evolved into a distinctive, personalized, and precise treatment approach that provides promising and unique scientific insights into human health (11, 12). Many renowned TCM gynecologists have developed unique treatment methods and theories based on their extensive clinical experience (13). Moreover, research grounded in Western medical theories has explored the pathological mechanisms underlying TCM treatment of endometriosis, providing preliminary validation of TCM potential mechanisms of action and clinical efficacy (14, 15).

Clinical trials are the standard method for evaluating the efficacy of pharmacological interventions for particular diseases (16, 17) and play a critical role in the development of new drugs (18). Therefore, analyzing registered clinical trial data is essential for guiding clinical practice and advancing future research. Since its launch by the National Institutes of Health (NIH) in 2000, ClinicalTrials.gov has emerged as one of the most significant clinical trial registration platforms globally, accounting for approximately two-thirds of all registered clinical trials (19). Subsequently, various countries have established their own clinical trial registration platforms. In 2005, the China Clinical Trial Registry (ChiCTR) was established and recognized as a primary registration agency by the World Health Organization's International Clinical Trials Registry Platform (ICTRP) (20). The ICTRP in 2006, integrating 18 international clinical trial registration centers and providing data on over 200,000 clinical trials (21, 22). On September 6, 2013, the China Food and Drug Administration (CFDA) issued Notice No. 28, requiring all drug clinical trials to be registered and publicly disclosed on the "Traditional Chinese Medicine Clinical Trial Registration and Information Disclosure Platform (ChiDTR)" (23). Thus, ClinicalTrials.gov, ChiCTR, ICTRP, and ChiDTR serve as valuable data sources for the clinical registration characteristics of studies on Traditional Chinese Medicine or natural medicines for the treatment of endometriosis worldwide.

Analyzing registered trials for newly developed drugs provides valuable insights into their design, development, and potential shortcomings. In the design and implementation of new drug trials, ethical obligations require consideration of potential risks alongside anticipated benefits (24). To our knowledge, no published papers currently discuss the characteristics of clinical trials on TCM and Natural Medicines for Endometriosis. Furthermore, analyzing registered clinical trials can help identify key drugs and formulations, offering clinicians and researchers important perspectives on TCM and Natural Medicines for Endometriosis. This study aims to analyze the methodological characteristics and key drugs of clinical trials involving TCM and Natural Medicines for Endometriosis registered on ClinicalTrials.gov, ChiCTR, ICTRP, and ChiDTR. The results of this analysis may guide clinical practice and future research directions, particularly in developing new effective therapies.

Materials and methods

Search strategy and selection criteria

In the ChiCTR database, the search was conducted using "endometriosis" as the keyword for the "Research Disease Name." For the ChiDTR database, "Traditional Chinese Medicine/Natural Medicine" was specified under "Drug Type," with the same indication identified through the keyword "endometriosis" Within the ICRP database, we employed the term "endometriosis" for our search criteria. The search in the clinicaltrials.gov database focused on "endometriosis" under the "condition" field, applying specific filters to exclude trials labeled as "withdrawn," those including "male" participants, and "patient registries."

Inclusion criteria included: (1) participants must be adult females; (2) the indication for inclusion was endometriosis; (3) interventions involved the use of natural medicines. Exclusion criteria included: (1) The exclusion criterion was failure to meet any one of the inclusion criteria; (2) incomplete registration, indicated by the platform's display of missing ethics approval documentation or erroneous uploaded files; (3) studies that were diagnostic, foundational in science, etiological, epidemiological, or survey-based; (4) interventions that utilized synthetic drugs or proprietary Chinese medicines; (5) lack of disclosed specific medications, for example, when the intervention was simply listed as TCM or a combination of Chinese and Western medicine.

This study defines Traditional Chinese Medicine (TCM) or natural medicines used for treating endometriosis as those explicitly stated in the clinical trial protocol, including prescriptions of herbal medicines, herbal extracts, or active ingredients derived through extraction and isolation from herbal medicines.

Data screening, extraction and analysis

The data screening was executed in four distinct phases. Initially, two researchers independently managed the first three stages; subsequently, they collaboratively reviewed the data during the fourth stage. Disagreements were resolved through consensus or by consultation with a third author. In the first phase, the data, sourced from four clinical trial databases—ClinicalTrials.gov, ChiCTR, ICTRP, and ChiDTR—as delineated

in the "Search strategy" section of "Materials and methods," were imported into an Excel document, with duplicates eliminated based on the clinical trial registration numbers. During the second phase, the data were sifted according to the predefined inclusion and exclusion criteria outlined in the "Materials and methods" section. In the third phase, the removal of redundant trials was carried out by matching the applicant (sponsor) and other IDs across the databases. In the fourth phase, the researchers collaboratively reviewed the data. Disagreements were resolved through consensus or by consultation with a third author. Additionally, this phase entailed cataloging the registration number, study type, registration date, applicant (sponsor), traditional/natural medicine name, and trial design parameters (allocation method, intervention model, blinding, trial phase, and sample size). Data were processed and analyzed using SPSS statistical software version 22.0. Excel 2016 was used for graphing in this study.

Results

Search results

The detailed retrieval process was shown in flow diagram (Figure 1). Following the aforementioned retrieval method, this study obtained 110, 3, 635, and 1,163 results from the ChiCTR, ChiDTR, ClinicalTrials.gov, and ICTRP platforms, respectively. As the ICTRP platform encompasses clinical trials registered on ClinicalTrials.gov and ChiCTR, trials duplicating these records were excluded during the selection phase. In compliance with the established inclusion and exclusion criteria, the ClinicalTrials.gov, ChiCTR, ICTRP, and ChiDTR platforms yielded 18, 3, 15, and 21 clinical trials concerning herbal/natural medicine treatments for endometriosis, respectively, resulting in a total of 57 trials included in this study.

General characteristics of the included clinical trials

Of the 57 clinical trials encompassed by the research, the greatest number were registered in 2022, accounting for 12 trials, with 2023 trailing at 9 trials. Figure 2A elaborates on the registration details across different years. Linear regression analysis indicated significant differences between the years and the number of registrations. The registration count for clinical trials addressing endometriosis with TCM/natural remedies has markedly risen in recent years ($F = 17.088$, $p = 0.002$). The applicant institutions for these clinical trials were divided among universities (45.6%), hospitals (42.1%), and industry (12.3%), with specific proportions shown in Figure 2B. The majority of the applying institutions were from Asia (84.2%), with China having the highest proportion (45.6%), followed by Iran (24.6%), as shown in the distribution in Figure 2C.

Design characteristics of the included clinical trials

Of the 57 clinical trials included, the majority (87.7%) employed a randomized design, 63.2% of the trials used blinding, with 36.8% adopting a double-blind design, and 78.9% chose a parallel design as the intervention model. Regarding the phases of clinical trials, 45.6% did not specify the phase, while Phase 3 and Phase 4 clinical trials constituted 17.5% of the total. As for sample size, more than half (56.1%) of the clinical trials had fewer than 100 participants. Based on the above, we believe that clinical trials for herbal/natural medicine treatments for endometriosis should increasingly adopt blinding designs and expand sample sizes, in order to achieve higher quality clinical research and to increase their credibility. For detailed characteristics of the clinical trial designs, please refer to Figure 3.

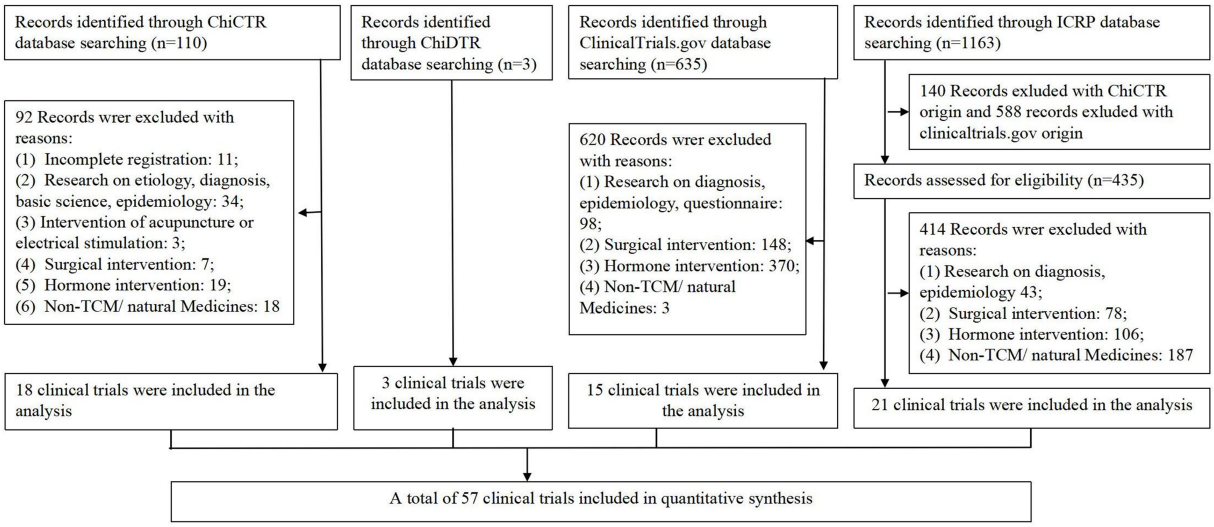

FIGURE 1
Flow diagram of the study selection process. TCM, Traditional Chinese Medicine; ChiCTR, Chinese Clinical Trial Register; ICTRP, Chinese Drug Clinical Trial Registration and Information Publicity Platform (ChiDTRInternational Clinical Trials Registry Platform).

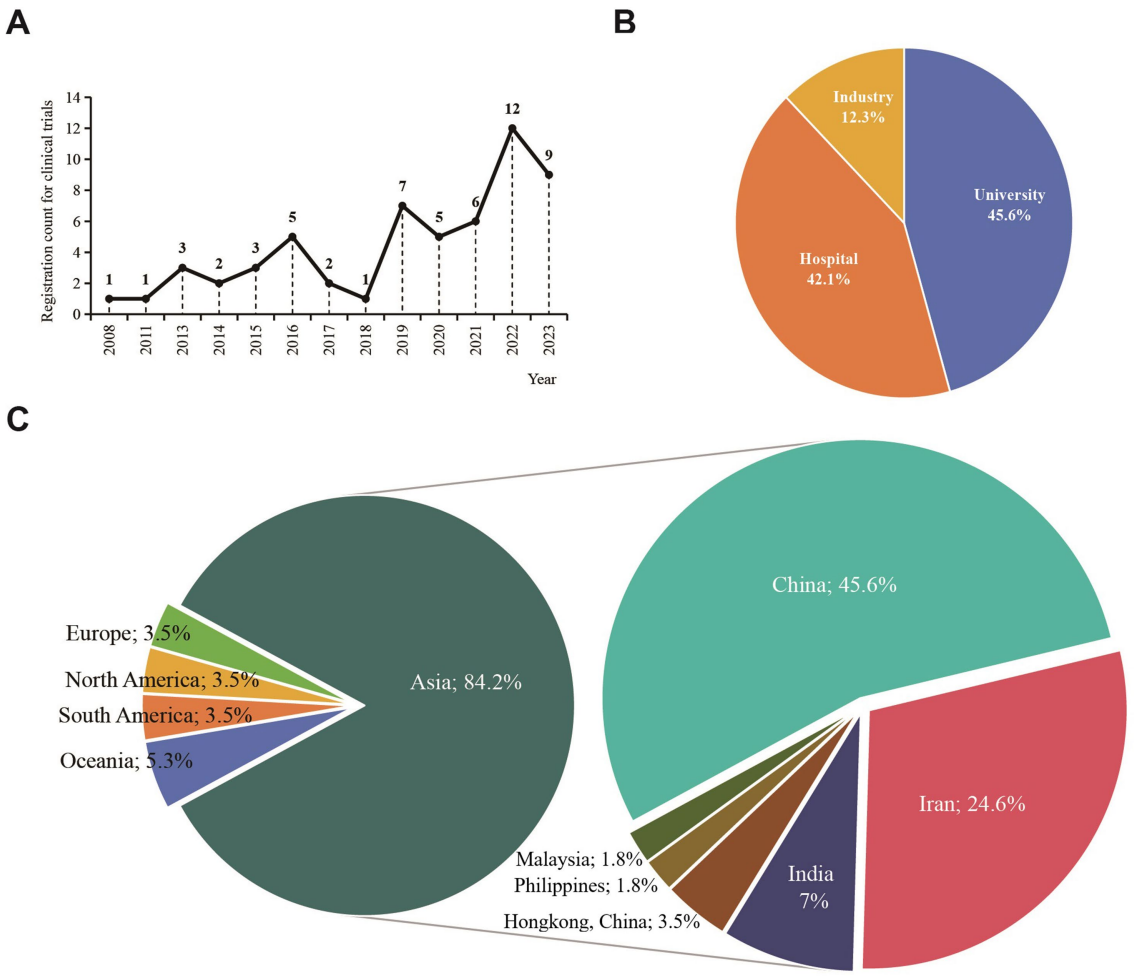

FIGURE 2
General characteristics of the included clinical trials encompassing TCM/natural medicine as interventions for endometriosis. (A) the relationship of time and number of registration; (B) Distribution of applicant institutions among different industries; (C) Distribution of applicant institutions' region.

TCM or natural medicine was used to treat endometriosis in the included clinical trials

A total of 26 clinical trials, focusing on the application of TCM/natural medicine for the treatment of endometriosis, have been registered across the aforementioned four platforms. Notably, all of these trials were conducted exclusively by applicants from China. It is worth mentioning that 50% (13/26) of these trials failed to specify the clinical stage, with the exception of a single trial registered on the ChiCTR platform. Of these 26 clinical trials, 18 (69.2%) trials were from ChiCTR, 3 (11.6%) were from ChiDTR, and 5 (19.2%) were from Clinicaltrials.gov. This indicates a preference among Chinese researchers to register with ChiCTR. The main reason for this preference is that ChiDTR is primarily a clinical trial registration platform for marketing purposes, requiring strict approval by the CFDA. On the other hand, Clinicaltrials.gov is a clinical trial registration platform in the United States. Among the 26 trials, 9 of them involve drugs that have already been approved and put on the market. These drugs include 6 TCM: Sanjie Zhentong Capsules, Honghua Ruyi Pills, Huayu Sanjie Enema Liquid, Kuntai Capsules, Wenjing Tang, and Xuefu Zhuyu Capsules (refer to Table 1 for more details).

Apart from China, Iran has the highest number of registrations of natural medicines for the treatment of endometriosis, with a total of 14 related clinical trials. Among these trials, curcumin is the most commonly registered natural drug (refer to Table 2 for more information).

Discussion

This study found that most applicants for clinical trials on TCM and natural medicines for endometriosis are primarily from institutions in China and Iran. While this geographic concentration is significant, it must be viewed in light of the region's rich cultural heritage. The prevalence of these studies may be heavily influenced by longstanding cultural traditions, rather than solely by robust scientific evidence. This is particularly important when considering the historical significance of traditional medicine in Asia, which includes systems like TCM, Ayurveda, and Iranian Traditional Medicine (25). These systems, rooted in natural medicinal substances and herbal

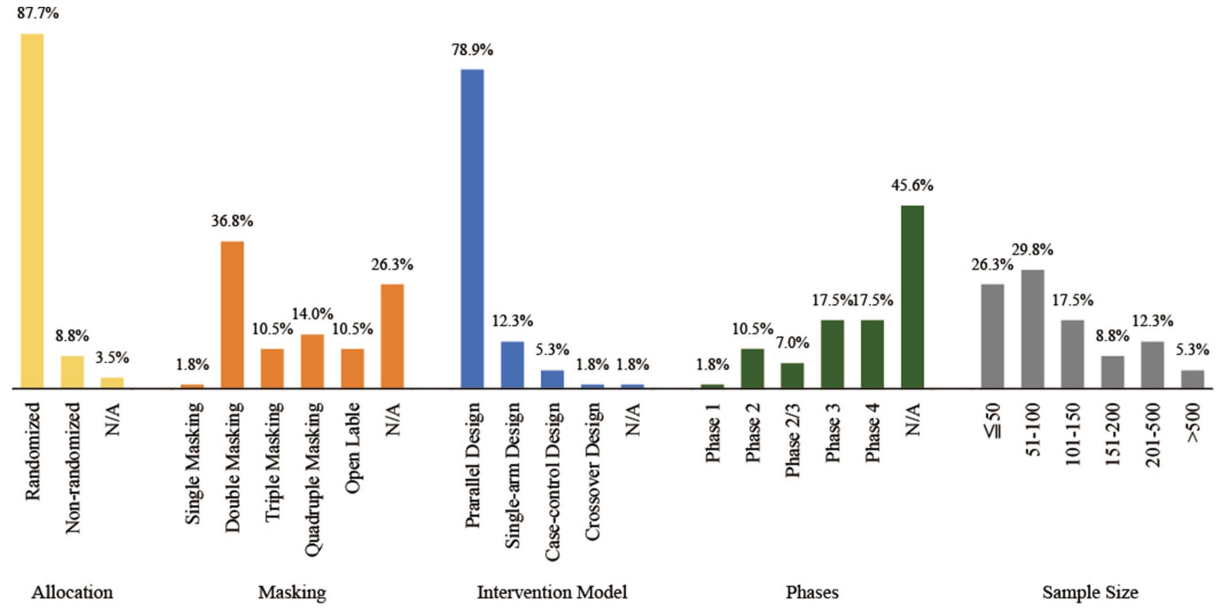

FIGURE 3
Design characteristics of the included clinical trials. N/A represent not available.

remedies, have developed over millennia (26). The longevity and evolution of these practices, such as TCM's origins in ancient China and its continuous development over thousands of years, highlight the profound impact of cultural factors on their use (27). Therefore, interpreting the geographical distribution of trials requires caution, as cultural influences likely play a significant role in shaping the research landscape.

This investigation identified merely three clinical trials focused on the commercialization of TCM for endometriosis treatment, all of which have yet to receive market approval. This implies that in the span of nearly 10 years since 2013, no new pharmaceutical products of TCM for treating endometriosis have been granted market approval. The primary reason may be that the complex composition of TCM, shaped by factors such as production region, climatic conditions, and harvesting periods, poses significant challenges to quality control (28, 29), which has contributed to the historically low number of registered clinical trials for new TCMs (30). However, advancements in modern science and the refinement of China's pharmaceutical regulatory policies have partially alleviated these challenges. Consequently, since 2020, there has been a notable increase in registration applications for new TCMs, accompanied by a substantial rise in clinical trial registrations (31). These findings correspond with the upward trend observed in this study, indicating that the number of registered clinical trials focused on treating endometriosis with TCM/natural remedies has significantly increased, particularly after 2019.

The defining characteristics of high-quality clinical trials include randomization, blinding, parallel structuring, and the selection of an appropriate sample size (32–34). The results of this study reveal that although most clinical trials on TCM and natural medicines for endometriosis utilize a randomized design, some trials still lack key methodological components, such as a control group, randomization, or blinding. Among the trials analyzed, a significant 36.8% were not blinded, which could potentially compromise the objectivity of the results. Blinding is a crucial criterion for high-quality clinical trials, as it ensures that findings remain free from the subjective preferences or biases of participants, investigators, or assessors (35). A detailed review of the ChiCTR platform suggests that placing the blinding option separately from the main design features, at the end, may cause researchers to easily overlook it during trial registration. This survey also revealed that over half of the clinical trials on Traditional Chinese Medicine and natural medicines for endometriosis enrolled fewer than 100 participants, and the majority of the trial protocols omitted the method for estimating sample sizes. A sample size that is too small, coupled with the absence of strict sample size estimates, can lead to the generation of false negative results, hindering the detection of true differences between different interventions (36). Therefore, future clinical trials should enhance their quality and confidence by adopting reasonable sample size estimation, implementing randomized control, and employing blinded design.

Of the clinical trials included in this research, drugs involved in nine trials are commercially available, including six Chinese patent medicines: Sanjie Zhentong Capsules, Honghua Ruyi Pills, Huayu Sanjie Enema Liquid, Kuntai Capsules, Wenjing Tang, and Xuefu Zhuyu Capsules. Four of these TCM—Sanjie Zhentong Capsules, Huayu Sanjie Enema Liquid, Kuntai Capsules, and Xuefu Zhuyu Capsules—are included in the "Integrated Chinese and Western Medicine Clinical Guidelines for endometriosis" issued by the Gynecology Committee of the Chinese Association of Integrative Medicine (10). This further indicates that the results of high-quality clinical trials have been widely recognized by professionals. The Honghua Ruyi Pill is a refined Tibetan medicine derived from the classical formula "Twenty-Five Flavor Gelsemium Pills" (37). Wenjing Tang is derived from the Southern Song dynasty's esteemed medical practitioner Chen Ziming's collection "Fu-Ren Da Quan Liang Fang (38, 39)."

TCM and natural therapies for endometriosis have emerged as a research hotspot, with studies showing their potential to alleviate

TABLE 1 The clinical trials conducted by Chinese applicants on the use of TCM/natural medicines for treating endometriosis.

Trial ID	Database	Phase	Drug name (Chinese name)	Marketed*
ChiCTR2300070047	ChiCTR	N/A	Neiyifang Decoction	No
ChiCTR2300069698	ChiCTR	N/A	Yiqi Xiaozheng Granules	No
ChiCTR2300069429	ChiCTR	N/A	Gengnian Zishen Oral Liquid	No
ChiCTR2200066946	ChiCTR	N/A	Guiqiong Xiaoyi Fang	No
ChiCTR2200066925	ChiCTR	N/A	Guiqiong Xiaoyi Fang	No
ChiCTR2200058583	ChiCTR	N/A	Wenjing Tang	Yes[#]
ChiCTR2200057987	ChiCTR	Phase 1	Zishen Quyu Jiedu Granules	No
ChiCTR2200056830	ChiCTR	N/A	Neiyifang Granules	No
ChiCTR2100045119	ChiCTR	N/A	Xiaoliu Fang	No
ChiCTR2100042830	ChiCTR	N/A	Yangjing Zhongyu Tang	No
ChiCTR2000040639	ChiCTR	N/A	Yangjing Zhongyu Tang	No
ChiCTR2000036735	ChiCTR	N/A	Gegensu Tablets	No
ChiCTR1900028624	ChiCTR	Phase 4	Kuntai Capsules	Yes
ChiCTR1900027665	ChiCTR	N/A	Yishen Xiaozheng Granules	No
ChiCTR1900027189	ChiCTR	Phase 4	Sanjie Zhentong Capsules	Yes
ChiCTR-IPR-17013692	ChiCTR	Phase 4	Sanjie Zhentong Capsules	Yes
ChiCTR-IPC-16008214	ChiCTR	Phase 4	Huayu Sanjie Enema Liquid	Yes
ChiCTR-TRC-13003283	ChiCTR	Phase 4	Sanjie Zhentong Capsules	Yes
CTR20140292	ChiDTR	Phase 2	Zhidan Huayu Capsules	No
CTR20132622	ChiDTR	Phase 3	Neiyi Tongjing Granule	No
CTR20140107	ChiDTR	N/A	Zhenggong Capsules	No
NCT04218487	Clinicaltrials.gov	Phase 4	Xuefu Zhuyu Capsules	Yes
NCT02676713	Clinicaltrials.gov	Phase 2	Fufang Zhongcaoyao	No
NCT02031523	Clinicaltrials.gov	Phase 4	Sanjie Zhentong Capsules	Yes
NCT04942015	Clinicaltrials.gov	Phase 4	Honghua Ruyi Pills	Yes
NCT02832271	Clinicaltrials.gov	Phase 2	Epigallocatechin Gallate	No

N/A represent not available; [#]marketed as Wenjing pills; *Data from the official website of the Chinese State Food and Drug Administration (https://www.nmpa.gov.cn/datasearch/home-index.html).

symptoms such as dysmenorrhea and reduce adnexal masses (40). However, several key issues persist that require further investigation to establish the effectiveness and safety of these treatments. The underlying mechanisms by which TCM and natural therapies exert their effects, particularly when combined with hormonal or pain-relief medications, are not yet fully elucidated. This underscores the need for future research to carefully evaluate the safety and efficacy of such combinations. Furthermore, existing studies are generally small in scale, which highlights the need for larger, high-quality clinical trials designed with rigorous methodologies to confirm the therapeutic potential of TCM and natural therapies for endometriosis (40, 41). Additionally, the potential side effects and long-term safety of these treatments, especially in combination with conventional therapies, have not been adequately investigated. To strengthen the evidence base, future studies should focus on multicenter, randomized controlled trials with blinding, along with long-term follow-up studies to assess sustained outcomes and safety profiles. Furthermore, collaboration between researchers in Western medicine and TCM may facilitate the development of integrative treatment models and enhance the overall understanding of endometriosis management.

This study has inherent limitations that necessitate cautious interpretation of its findings. While our analysis included four major clinical trial registration platforms—ClinicalTrials.gov, ChiCTR, ICTRP, and ChiDTR—we recognize that it is impossible to encompass all registries, particularly those within a single country, such as China's two primary platforms: ChiCTR, recognized as a principal registry by ICTRP, and ChiDTR, established by the CFDA for new drug applications. The ICTRP's periodic updates of data from 18 international clinical trial registries may experience temporal delays, and trials registered by non-English-speaking researchers could introduce biases during language translation. Furthermore, cultural differences in medical practices, including the significant role of traditional medicine in Asia, and the differential regulation of herbal remedies—classified as drugs in Asia but as food or dietary supplements in Western countries—may affect the interpretation of our findings. Additionally, only a small proportion of the clinical trials included in this study have published their results on clinical trial registration platforms, limiting further investigation into the efficacy and adverse reactions of these trials.

TABLE 2 The clinical trials conducted by Iran applicants on the use of natural medicines for treating endometriosis.

Trial ID	Phase	Drug name	Plant source
IRCT20220115053713N4	Phase 2/3	Ziziphus jujube, Ginseng, and Punica	*Ziziphus abyssinica* Hochst. ex A.Rich.; *Ginseng quinquefolium* (L.) Alph.Wood; *Punica granatum* L.
IRCT20200925048836N4	Phase 3	*Silybum marianum*	*Silybum eburneum* Coss. & Durieu
IRCT20221111056469N1	N/A	Curcumin	*Curcuma aeruginosa* Roxb.
IRCT20220408054455N1	Phase 3	Achillea Cretica	*Achillea cretica* L.
IRCT20170923036334N4	N/A	Curcumin	*Curcuma aeruginosa* Roxb.
IRCT20191207045636N1	Phase 2	*Cymbopogon citratus* oil	*Cymbopogon citratus* (DC.) Stapf
IRCT20201121049457N1	Phase 3	Curcumin	*Curcuma aeruginosa* Roxb.
IRCT20190625044004N1	Phase 3	Chamomile and flaxseed oil	*Matricaria recutita* L.
IRCT20120718010324N66	Phase 3	Curcumin	*Curcuma aeruginosa* Roxb.
IRCT20200701047981N1	Phase 3	Ayurveda	Fennel root and seeds, chicory root and seeds, celery seed, cucumber seed, badrang cucumber seeds, melon seed, vinegar, Water, red sugar
IRCT2015101724569N1	Phase 2	Resveratrol	*Polygonum cuspidatum* Siebold & Zucc. or *Vitis acerifolia* Raf.
IRCT201501059463N34	N/A	Garlic tablets	*Allium sativum* L.
IRCT201501059463N35	N/A	Garlic tablets	*Allium sativum* L.
NCT05983224	N/A	Quercetin	Various food sources like apples, berries, cabbage, and onions

N/A represent not available.

Conclusion

This study analyzed 57 clinical trials on TCM and natural remedies for endometriosis. These trials, predominantly conducted in China and Iran, often reflect cultural practices as much as scientific rigor. Despite the frequent use of randomization, many trials lack key methodological elements, such as blinding and adequate sample sizes, which seriously undermines their reliability. The study underscores the necessity for more rigorously designed and larger-scale trials to thoroughly evaluate the efficacy and safety of these treatments, particularly when used in conjunction with conventional therapies.

Author contributions

YZ: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. YiW: Writing – original draft, Writing – review & editing, Conceptualization, Investigation, Methodology, Visualization. ZX: Writing – original draft, Writing – review & editing. YuW: Investigation, Methodology, Writing – original draft, Writing – review & editing, Data curation. CX: Investigation, Methodology, Writing – original draft, Writing – review & editing, Conceptualization. JL: Investigation, Writing – original draft, Writing – review & editing, Methodology. MJ: Conceptualization, Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing.

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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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Prediction and prevention of late-onset pre-eclampsia: a systematic review

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Background: Pre-eclampsia is a major cause of perinatal morbidity and mortality worldwide. Late-onset pre-eclampsia (LOP), which results in delivery ≥34 weeks gestation, is the most common type. However, there is a lack of knowledge in its prediction and prevention. Improving our understanding in this area will allow us to have better surveillance of high-risk patients and thus improve clinical outcomes.

Methods: A systematic review was performed using a search of articles on PubMed. The search terms were ((late-onset) AND (pre-eclampsia)) AND ((risk factor) OR (risk) OR (prediction) OR (management) OR (prevention)). Primary literature published between 1 January 2013 and 31 December 2023 was included. Human studies assessing the prediction or prevention of late-onset pre-eclampsia were eligible for inclusion.

Results: Sixteen articles were included in the final review. The key risk factors identified were Body Mass Index (BMI), chronic hypertension, elevated mean arterial pressures (MAPs), nulliparity, and maternal age. No clinically useful predictive model for LOP was found. Initiating low dose aspirin before 17 weeks gestation in high-risk patients may help reduce the risk of LOP.

Conclusion: While aspirin is a promising preventor of LOP, preventative measures for women not deemed to be at high-risk or measures that can be implemented at a later gestation are required. Biomarkers for LOP need to be identified, and examining large cohorts during the second or third trimester may yield useful results, as this is when the pathogenesis is hypothesized to occur. Biomarkers that identify high-risk LOP patients may also help find preventative measures.

KEYWORDS

late-onset pre-eclampsia, prediction, prevention, risk factor, management

1 Introduction

Pre-eclampsia is a multi-system disorder of pregnancy, defined as new-onset hypertension (>140/90 mmHg), after 20 weeks gestation, with evidence of maternal systemic involvement such as proteinuria, liver transaminitis, neurological dysfunction, and hematological changes. It affects approximately 4.6% of pregnancies (1) and is associated with 10–15% of maternal deaths worldwide (2). Preeclampsia is generally classified as early-onset (EOP, delivery at <34 weeks gestation) and late-onset (LOP, delivery at ≥34 weeks gestation) (3, 4). It may present with headaches, abdominal pain, foetal growth restriction and oedema, or less commonly with visual disturbances, seizures and oliguria (5, 6).

Current research suggests that EOP and LOP have different aetiologies (3, 7). EOP likely arises from altered decidual spiral artery remodeling during placentation, leading to deficient blood flow to the placenta, placental hypoxia, and syncytiotrophoblast dysfunction, which causes disturbed production of angiogenic and pro-inflammatory factors (8, 9). EOP is also often associated with fetal growth restriction (7). Like EOP, LOP is associated with syncytiotrophoblast dysfunction, causing disturbed production of angiogenic and pro-inflammatory factors, but this occurs later in pregnancy (9, 10). Further in LOP there is no histopathological evidence for altered decidual spiral artery remodeling during placentation (9, 10). An imbalance of angiogenic factors/anti-angiogenic factors, particularly low levels of PlGF, may contribute to hypo-perfused placental lesions in LOP (9). As gestation increases, synciotrophoblast stress increases as well as endothelial cell dysfunction (11, 12). This has led to thoughts about pre-existing maternal conditions such as obesity, hypertension and diabetes contributing to LOP (11). The different pathologies for EOP and LOP may explain why biomarkers used for the prediction of EOP are not effective for LOP.

While there are predictive biomarkers and a preventative treatment for EOP, there remains a significant knowledge gap in the prediction and prevention of LOP. This is concerning as LOP is seven times more common than EOP (13) and is associated with severe birth outcomes, perinatal death, and cardiovascular disease (13, 14). Having predictors in place for LOP will allow for better surveillance of these patients, and improved clinical outcomes. There is currently no screening tool or preventative measures for LOP specifically.

To the best of our knowledge, there are no systematic reviews summarizing the current literature on the prediction and prevention of LOP. This systematic review evaluates primary literature on LOP published since 2013. It aims to enhance understanding of the risk factors, predictive models, and prevention strategies for LOP.

2 Materials and methods

2.1 Search strategy

This systematic review was conducted through a search of articles on PubMed published on or before 31 December 2023. The key words used were ((late-onset) AND (pre-eclampsia)) AND ((risk factor) OR (risk) OR (prediction) OR (management) OR (prevention)). The search was limited to articles published from 2013 onwards, including case reports, clinical studies, comparative studies, evaluation studies, multicentre studies, observational studies, and randomized control trials.

2.2 Inclusion criteria

Human studies assessing the prediction or prevention of LOP were eligible for inclusion. Articles that examined both LOP and EOP were included if these phenotypes were divided in the study's results.

2.3 Exclusion criteria

Exclusion criteria included manuscripts which did not investigate LOP prediction or prevention, did not define LOP as delivery >34 weeks, lacked a specific focus on LOP, were not available in English, or were based on animal models. Narrative reviews, systematic reviews, meta-analysis and validation studies were also excluded.

2.4 Article selection

Articles identified in the search were reviewed by two independent authors (AB and WZ). If there was disagreement, a third reviewer (ED) was consulted. Articles that did not meet the inclusion criteria were identified by reading through the titles and abstracts and subsequently removed. The remaining articles were carefully read-through, and those not meeting the inclusion criteria were removed.

3 Results

A total of 82 articles were identified from the search strategy (Figure 1), but 52 were excluded during the title and abstract screening. Subsequently, 30 full-text articles were reviewed, with 14 further removed based on the criteria listed in Figure 1. Thus, a total of 16 articles were ultimately included in the review.

3.1 Risk factors

The results of the studies included that looked at prediction and risk factors of LOP are summarized in Table 1. They covered a broad range of predictors, including maternal characteristics, serum biomarkers and small nucleotide polymorphisms.

Maternal characteristics such as BMI, age, nulliparity and hypertension were identified as risk factors for LOP. Incremental increases in BMI had a positive linear correlation with LOP in an observational study in Reunion Island among a cohort of 72,920 women (15). Obesity and LOP rates both increased by 11 and 12%, respectively, over the 18-year period (15). Among the same cohort, the significant risk factors for LOP were chronic hypertension, increasing BMI, nulliparity and increasing maternal age (15). In agreement, a recent study from Denmark found that women who developed LOP were mostly nulliparous and had significantly higher BMIs and blood pressure (16). A questionnaire survey of 112 women with LOP in Doula, Cameroon, found that LOP was associated with new paternity and nulliparity (17). Another cohort study in Reunion Island found that IVF, renal disease, gestational diabetes mellitus (GDM) and hypercholesterolaemia were significantly associated with LOP (18). Maternal ABO blood type has been investigated for its association with LOP (19). After excluding for individuals with gestational diabetes, chronic hypertension, and diabetes, the association between AB blood type and LOP development was not significant (19).

3.2 Biomarkers

3.2.1 Prediction

A range of serum biomarkers were evaluated for their role in predicting LOP. One study found an association between lower percentages of hyper-glycosylated human chorionic gonadotrophin

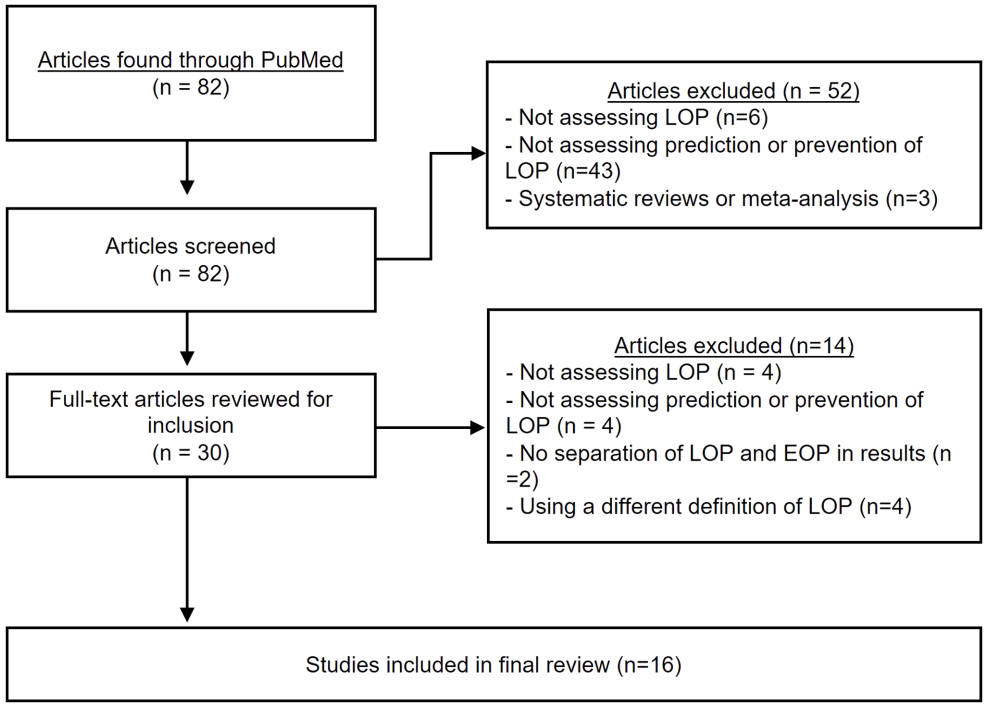

FIGURE 1
PRISMA flowchart. The above chart shows the different steps taken during the systematic review process.

(HCG-h) in the first trimester and the development of LOP (20). The addition of the biomarkers HCG-h, free b-HCG, PIGF and UtA-PI MoM, improved the sensitivity of their predictive model from 10 to 32% (20). First trimester serum apolipoproteins were not found to be significantly different between LOP and controls (16). Women with LOP were significantly associated with low first-trimester relaxin hormone levels, below the 10th centile (21).

Another study investigated the levels of butyrate-producing bacteria in the gut of women with LOP and obesity at 28 weeks gestation (22). They demonstrated that these women with LOP had significantly lower levels of butyrate-producing bacteria in their gut and lower serum butyrate compared to BMI-matched controls who did not go on to develop LOP (22). Low levels of butyrate in the LOP group was also associated with significantly higher serum triglyceride and VLDL levels at 28 weeks gestation compared to controls (22).

3.2.2 Diagnosis

Plasma fetuin A (FA) levels were significantly higher in 36 patients with LOP compared to 31 gestational-age-matched controls (23). However, plasma FA levels were not useful in discriminating between LOP and controls (23). Another study found complement factor levels, specifically C1q, Bb, C3a, C5a and MAC were significantly elevated in serum in LOP compared to controls even after correcting for BMI (24).

3.3 Placental characteristics

A number of studies investigated placental characteristics in predicting LOP. One prospective observational cohort study used a combination of maternal characteristics (ethnicity, chronic hypertension, smoking status, parity, family history, BMI), biomarkers (PIGF, PAPP-A, MAP, MSAFP, UtA-PI), and estimated placental volumes to determine if a first-trimester screening tool for pre-eclampsia could be developed (25). The first trimester screening performance of LOP was low, with detection rates of 15 and 48% for 5 and 10% false positive rates, respectively, whereas the detection rate for EOP was 85% (25). Elevated or reduced uterine artery resistance index at 18 to 23 + 6 weeks gestation was not associated with LOP in a retrospective observational study (26). However, LOP patients had a high prevalence of small for gestation age (SGA) and large for gestational age (LGA) births (26). LGA neonates born to LOP patients, were not associated with a low uterine artery mean resistance index (26). Using the sFlt-1/PIGF serum ratio to predict the onset of pre-eclampsia was found to be less accurate for LOP than EOP (27). The optimal ratio threshold for predicting both LOP and EOP within 1 to 4 weeks was found to be 66, and this had a high negative predictive value for LOP of 86–93% (27).

3.4 Single nucleotide polymorphisms

Single nucleotide polymorphisms (SNP)s have been investigated in mothers in association with pre-eclampsia. SNPs in IL-22 and IL-22 receptor alpha 1 (IL-22RA1) have been found to be associated with LOP in Chinese Han women (28). Significant differences in the distributions have been found for the SNP IL-22 rs2227485 between LOP women and controls (28). There were also significant differences for genotypic and allelic frequencies of the SNP IL-22RA1 RS3795299 between the LOP and controls (28).

TABLE 1 Summary of studies on prediction and risk factors of late-onset pre-eclampsia.

Author, year	Sample size	Study type	Relevant results
Robillard et al., 2019 (15)	LOP $n = 1,162$ Controls $n = 71,078$	18-year retrospective observational study	Incremental increases in BMI are associated with increasing incidence of LOP. Significant risk factors identified for LOP were advanced age OR 1.03 [1.02–1.04], chronic hypertension OR 4.95 [3.6–6.3], BMI OR 1.05 [1.04–1.06] and nulliparity OR 2.44 [2.1–2.8]. Chronic hypertension was the greatest independent risk factor for LOP $p < 0.001$.
Bendix et al., 2023 (16)	LOP $n = 27$ Controls $n = 194$	Case control study	No significant differences in first-trimester serum alipoprotein levels were found between the LOP and control group. The best performing screening model combined parity, age, BMI, MAP, ApoD, ApoB-100 and gave an AUC value of 0.87, sensitivity of 55.5% with 95% CI [30.3;80.7] for a false positive rate of 10%. Women with LOP had higher BMIs, MAPs and were mostly nulliparous ($p < 0.05$).
Iacobelli et al., 2017 (18)	LOP $n = 933$ Controls $n = 59,665$	Retrospective observational cohort study	There was a significant association between LOP and pre-existing diabetes, GDM, BMI > 30, IVF, kidney disease, hypercholesterolaemia ($p < 0.05$).
Murtoniemi et al., 2018 (20)	Total $n = 257$ LOP $n = 34$	Prospective cohort study	Lower levels of first-trimester HCG-h and higher MAPs were associated with LOP. The model with the highest prediction rates used the variables: age, prior PE, prior SGA DM-type 1, MAP, prior fetus mortus, hCG, %hCG-h, free beta hCG, PIGF, Uta-PI with an AUC value 0.66 with 32% sensitivity at 90% specificity.
Nguefact et al., 2018 (17)	LOP $n = 112$ EOP $n = 58$	5-month prospective cross-sectional study	LOP was significantly associated with new paternity, and nulliparity ($p < 0.05$).
Sanhal et al., 2016 (23)	LOP $n = 36$ Controls $n = 31$	Comparative study	Plasma fetuin A levels were significantly higher in the LOP group compared to controls $p < 0.001$, measured at gestation >34 weeks. Plasma fetuin A levels gave an AUC of 0.196, 95% CI [0.085,0.306]
He et al., 2016 (24)	LOP n-30 Controls $n = 30$	Case–control study	Serum levels of complement factors C1q, Bb, C3a, C5a and MAC measured >34 weeks gestation, were significantly higher in LOP compared to control group $p < 0.05$. The LOP group was significantly associated with increased age and BMI ($p < 0.05$)
Uiterweer et al., 2020 (21)	Pittsburgh population: LOP $n = 33$ Controls $n = 25$ Dutch population: LOP $n = 95$ Controls $n = 469$	Case–control study	Women with LOP were significantly associated with having lower relaxin levels at 9–13 weeks gestation, below the 10th centile in the Pittsburgh group OR 5.29 [1.1–25.5] and the Dutch group OR 2,03 [1.06–3.88]. Relaxin levels improved the detection rate of LOP by 2.5% in a prediction model combining maternal characteristics (age, BMI, nulliparity) and MAP. Women who developed LOP were also associated with a significantly higher first-trimester MAP, BMI and nulliparity ($p < 0.05$).
Sonek et al., 2018 (25)	LOP $n = 33$ Control $n = 1,022$	Prospective observational cohort study	Frist trimester screening of LOP using maternal characteristics (ethnicity, chronic hypertension, smoking status, parity, family history, BMI) had a low detection rate of 15% for 5% false positive. This was not improved by the addition of biomarkers or placental characteristics. The only biomarker statistically significant in LOP compared to the control group was MAP $p < 0.001$.
Verlohren et al., 2014 (26)	LOP $n = 1802$ Total $n = 26,893$	Retrospective observational cohort study.	No association was found between uterine artery resistance index and LOP ($p > 0.05$). There was a high prevalence of SGA and LGA neonates for the LOP group.
Burgess et al., 2019 (19)	LOP $n = 126$ Controls $n = 259$	Retrospective observational study	After controlling for GDM, CHTN, and DM, LOP was no longer significantly associated with having blood type AB OR 2.53 95% CI [0.7–9.2].
Andersen et al., 2019 (27)	Total $n = 501$	Retrospective observational study	The predictive performance of sFlt-PIGF ratio with a threshold of 66 was AUC 0.85 with 95% CI [0.8–0.9] within 4 weeks of developing LOP.
Altemani et al., 2021 (22)	LOP $n = 11$ Matched controls $n = 22$ Total controls $n = 202$	Case–control study	Obese LOP women had significantly lower levels of butyrate-producing gut bacteria and serum butyrate at 28 weeks gestation compared to age, parity and BMI-matched controls. The LOP group had significantly higher serum triglyceride and VLDL levels ($p < 0.05$).
Niu et al., 2017 (28)	LOP $n = 584$ Controls $n = 1,263$	Case–control study	Significant differences were found in distributions for SNP IL-22 rs2227485 between the LOP and control group $p = 0.002$, OR 1.125 [0.977–1.295]. Significant differences were found between LOP and controls in genotypic and allelic frequencies of SNP IL-22RA1 rs3795299 $p < 0.001$, OR 1.355 [1.165–1.576].

LOP, late-onset pre-eclampsia; PE, pre-eclampsia; MAC, membrane attack complex; MAP, mean arterial pressure; HCG-h, hyperglycosylated human chorionic gonadotrophin; AUC, area under the receiver operating characteristic curve; CI, confidence interval; SGA, small for gestational age; LGA, large for gestational age; GDM, gestational diabetes mellitus; CHTN, chronic hypertension, DM, diabetes mellitus; sFlt, soluble fms-like tyrosine kinase; PIGF, placental growth factor; BMI, body mass index; VLDL, very low-density lipoprotein; SNP, small nucleotide polymorphism; IL, interleukin.

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TABLE 2 Summary of studies on prevention of late-onset pre-eclampsia.

Author, year	Sample size	Study type	Relevant results
Moore et al., 2015 (29)	Total $n = 523$ Aspirin group $n = 265$ Placebo $n = 258$	Randomised control trial: secondary analysis	Daily aspirin given to high-risk pregnant women significantly reduced the rate of LOP compared to the placebo with $p = 0.047$.
Shanmugalingham et al., 2020 (30)	Total $n = 187$	Prospective observational cohort study	44% of high-risk women had inadequate adherence to aspirin. Women <90% adherent had significantly higher incidence of LOP with OR 4.2, 95% CI [1.4, 19.8]. Adequate adherence to aspirin reduced the incidence of LOP with $p < 0.001$.

3.5 Aspirin for prevention

The results of the studies on prevention of LOP are summarized in Table 2. Initiation of low-dose aspirin prior to 17 weeks gestation in high-risk pregnant women has been found to be protective against the development of LOP in a secondary analysis of a randomized control trial (29). The rate of LOP was significantly reduced in the low-dose aspirin group versus the placebo: 17.36% vs. 24.42% with $p = 0.047$ (29). There was also a significant reduction of LOP in women with chronic hypertension who took low-dose aspirin (29). Another study found that proper adherence to aspirin leads to a decreased incidence of LOP in women with pre-existing DM, chronic hypertension, systemic lupus erythematosus, or a history of pre-eclampsia (30). It was found that 44% of women had inadequate adherence to taking aspirin (30). Within this low-adherence group, 41% developed LOP, while only 5% developed LOP in the adequate-adherence group (30).

3.6 Quality assessment

The quality assessment of this systematic review reveals risks primarily associated with limitations in the search strategy, study selection, and potential publication bias. Despite efforts to mitigate bias by including articles with diverse findings, inherent publication bias may persist, especially including studies with significant results. Restricting the search to PubMed articles may also overlook relevant studies from other databases. Variation in late-onset pre-eclampsia definitions among included studies could impact result generalizability. Inclusion of studies with small sample sizes and conflicting results may introduce bias, reducing certainty in conclusions. Although attempts were made to reduce bias, study selection and potential publication bias should be considered when interpreting results.

3.7 Limitations of present review

This review had several limitations. The search terms identified few recent studies. Inconsistent definitions of LOP among studies led to their exclusion, limiting result scope. Some studies may not have used the term "late-onset," potentially causing missed articles. Most of the included studies had small sample sizes, likely reducing their statistical power, while conflicting results hampered drawing definitive conclusions. Variations in methods and timing of predictor assessment across studies additionally complicated result comparison.

4 Discussion

The present review analysed primary literature on the prediction and prevention of LOP. While several risk factors have been found, there is no clear clinical model for predicting or preventing LOP.

4.1 Prediction

The research demonstrates it is difficult to predict LOP in the first trimester. Among the studies included, no first trimester screening model could reliably predict LOP (16, 20, 25). This is consistent with the proposed mechanism, that the pathogenesis of LOP occurs later in pregnancy (31), suggesting that many of the biomarkers may not be observable until the second or third trimester. While first trimester serum apolipoproteins were not significantly different between LOP and controls, they may be useful for first-trimester screening but the study sample size of 27 patients was small (16). Furthermore, this study only assessed serum apolipoproteins once throughout pregnancy, and did not specify the gestation week (16), limiting its utility. It would benefit from a larger sample size and more precise gestational age definitions. Women with LOP were significantly associated with low first trimester serum relaxin levels, which may serve as a promising predictive biomarker (21). However, the first trimester serum relaxin hormone levels improved the detection rate of LOP by only 2.5% when combined with maternal characteristics (age, BMI, and nulliparity) and MAP (21). The sample size of 120 patients was also small (21). It would be beneficial to see if there are any changes in the serum apolipoproteins and relaxin levels for LOP patients later in pregnancy as this is when the pathogenesis of LOP is hypothesized to occur (31). Similarly, two other studies were unable to find a useful first trimester predictive model for LOP (20, 25). However, one study found that LOP patients ($n = 34$) had a significantly lower first trimester percentage of hyperglycosylated (h) HCG than women who did not develop LOP ($n = 223$) (20). This suggests that percentage h-HCG may be able to serve as a predictive biomarker for LOP or play a part in predictive models. However, the study only included women deemed to be at high risk of PE and did not specify how they determined this. These studies are limited with their small sample sizes which reflects a greater problem with prospective studies on LOP; the relatively uncommon condition means it is difficult to gather large sample sizes. A previous study which was used to inform current aspirin guidelines for the prevention of pre-eclampsia determined that a sample size of >1,600 participants would be required to give adequate power to show effects (32). Hence

these studies looking at the prediction of LOP should aim to use sample sizes of a similar scale.

Many inflammatory biomarkers are elevated during the manifestation of LOP. Both classical and alternative complement pathways were found to be activated during LOP (24). These findings corroborate the hypothesis that pre-eclampsia is a disease of pathological inflammation (33), as the complement system which activates inflammation in the body, has long been associated with inflammatory diseases (34). Detection of complement factors before LOP needs evaluation to decipher if complement factors can serve as predictive biomarkers. The downregulation of inflammation, including that of the complement system may be helpful in the prevention or treatment of LOP but requires further research. One study reported that plasma FA levels were significantly elevated in women with LOP (23) and indicated inflammation is repressed in these women. However, higher levels of FA are seen in other inflammatory diseases like metabolic syndrome, type 2 diabetes and fatty liver disease (35–38). It is unclear if plasma FA is always high in these patients who develop LOP, or if its upregulation is a part of the pathophysiology of LOP. Further research is necessary to assess the role of plasma FA levels in patients prior to the development of LOP, and to evaluate if it can serve as a predictive biomarker of LOP.

According to the studies included, the only predictors of LOP that would be useful in the first trimester are maternal characteristics. A high BMI, nulliparity, new paternity, advanced maternal age, chronic hypertension and high MAP (15–18, 25) were significantly associated with the development of LOP. This is in line with a meta-analysis (39) which also found systemic lupus erythematosus and chronic kidney disease to be risk factors for pre-eclampsia, noting that they did not look at LOP specifically. However, another study is conflicting as they demonstrated that primiparous women are four-times more likely to have EOP than LOP, but later contend that nulliparous women are at higher risk of LOP (17). Furthermore, they do not have a control group, and miss key predictors in their analysis such as BMI. Overall, the studies that used these maternal characteristics to predict LOP, still had low detection rates, and were thus not applicable clinically (16, 20, 25). These maternal characteristics may be used to identify patients at higher risk but are unable to accurately predict those who will develop LOP. Similarly, women with chronic hypertension are more likely to develop LOP due to the underlying vascular dysfunction, which can exacerbate abnormal placental development. However, a previous study has shown that the correlation between chronic hypertension and pre-eclampsia is more pronounced in EOP than in LOP (15).

The finding from the Reunion Island cohort that increasing BMI is a risk factor for LOP (15) is well supported by other literature which shows that pre-eclampsia is associated with pre-pregnancy BMI (39, 40). The Reunion Island study found that as BMI increased, so did the incidence of LOP but not EOP (15), which is of concern as obesity rates are rising world-wide. Interestingly, when controlling for maternal BMI and age, there was no association found between either LOP or EOP and gestational diabetes (15). This contrasts with another study on Reunion Island which found both GDM and pre-existing diabetes to be risk factors for LOP, however they did not control for maternal BMI and age (18). Altogether, this suggests that pre-pregnancy BMI and maternal age may be confounding factors in studies that identify GDM as a risk factor for pre-eclampsia (41–43). A recent study using the SPRING cohort in Australia found that obese patients who developed LOP had significantly higher serum triglyceride and VLDL levels at 28-weeks gestation compared to BMI matched controls (22). This is supported by the Reunion Island study, which also found that hypercholesterolaemia was associated with LOP (18). Measuring lipoproteins may therefore serve to identify which obese patients are at higher risk of developing LOP. By contrast a Danish study which did not separate between EOP and LOP found no differences in BMI between pre-eclampsia and non-pre-eclampsia women (27). This may be because they did not separate the data between EOP and LOP, as the previous study from Reunion Island found that BMI was more closely correlated with LOP than EOP (15). The Reunion Island cohort study is advantageous as it has a large sample size of >71,000 patients including 1,162 with LOP, and its 18-year duration, which allows for the identification of trends over time (15).

Gut microbiota has been shown to be altered in obese patients with LOP in the SPRING study. Lower butyrate producing gut bacteria and serum butyrate levels were significantly associated with LOP in obese patients (22). This indicates that a deficiency in serum butyrate may contribute to the development of LOP. Certain butyrate-producing gut bacteria have been associated with better glycaemic control (44) and serum butyrate supplementation reduces childhood obesity levels (45). This association in children indicates that butyrate supplementation may reduce the risk or help prevent LOP however this requires further investigation. The SPRING study is limited with a sample size of only 11 LOP patients, all of whom were clinically obese (22). The findings should be further explored, through monitoring of butyrate levels at different gestations throughout pregnancy with a greater sample size including obese and non-obese patients.

Many biomarkers that are predictive for EOP are not useful for LOP. By contrast to EOP (25), there was no association found between LOP and uterine artery resistance index or pulsatility index (16, 25, 26). This is in line with a meta-analysis on the utility of uterine artery doppler for predicting pre-eclampsia which found UtA-PI was a better predictor for EOP (46). Additionally, the sFlt/PIGF ratio was found to be a better predictor for EOP than LOP (27). Yet their results have high negative predictive values of 90 and 86% for EOP and LOP, respectively. These findings support the use of the sFlt/PIGF ratio in clinical practice for ruling out pre-eclampsia in women at high risk or with suspicion for developing pre-eclampsia. However, a key limitation in their study was that they only included women who were suspected of developing pre-eclampsia, some of whom were already symptomatic, which may have skewed the results. These findings align with a previous study that found the sFlt-1/PIGF ratio to be more efficient for predicting EOP (47). The limited clinical utility of these markers demonstrates the continuing challenges of predicting LOP.

The Type I vs. Type II model of pre-eclampsia may explain many of the differences in the prediction between EOP and LOP. This way of characterizing pre-eclampsia is based on the phenotypes, and organ dysfunction from a molecular level (48). Type I pre-eclampsia which is generally early-onset, is associated with significant placental dysfunction and this has a greater imbalance of sflt1 and PlGF (48). This may explain why placental characteristics like UTA-PI and sflt/PlGF ratio are better predictors for EOP (16, 25–27) as Type I pre-eclampsia is instigated by placental pathology (48). In contrast Type II pre-eclampsia which is generally late-onset, is suggested to

arise from maternal maladaptation to pregnancy arising from the cardiovascular system from underlying endothelial damage (48). This aligns with the studies finding that BMI, hypercholesterolaemia and chronic hypertension are better predictors of LOP (15, 18, 22) as these risk factors may predispose patients to endothelial damage. Overall, this Type I and Type II pre-eclampsia model may be used to form distinct predictive methods for EOP and LOP, based on the pathophysiologies and using this to guide interventions. For example, aspirin administration and placental monitoring may be crucial in preventing and managing Type I. In contrast, lifestyle changes, cardiovascular health management, and vigilant prenatal care are more relevant for Type II.

Heritable markers like blood type and SNPs have been associated with LOP. Significant differences in the SNPs IL-22 rs2227485 and IL-22RA1 rs3795299 between the LOP and controls have been demonstrated (28). However, they do not go into any further detail about the nature of these differences, which makes their findings difficult to interpret. Additionally, their study focuses on the Chinese Han population and further studies could be done to evaluate if these differences are also relevant to other groups. Various studies have found other SNPs to be associated with pre-eclampsia (49–51), but little progress has been made in using these SNPs for predicting LOP. Another study contends that interactions between SNPs and environmental factors will form the genetic basis of pre-eclampsia (52). There is still a long way to go in determining the function of these SNPs and whether they can be used to help predict this disease. Interestingly, while the blood type AB was also associated with LOP (19), after controlling for GDM, chronic hypertension and DM there was no association. Another similar sized study ($n = 185$) found no significant association between any ABO blood type and LOP (53) suggesting blood type is unlikely to predict LOP. It would be beneficial to confirm this by repeating these studies with larger cohorts.

4.2 Prevention

Aspirin may be useful in the prevention of LOP. Initiating low-dose aspirin in high-risk women before 17 weeks gestation significantly reduced the rate of LOP (29). Interestingly this study found no significant reduction in EOP (29). Other studies and meta-analyses (32, 54–56) that demonstrate the benefit of aspirin to prevent pre-eclampsia either do not separate pre-eclampsia into subtypes or define it as preterm (<37 weeks) vs. term (≥37 weeks). In particular, prior research demonstrates that aspirin is more effective in preventing preterm pre-eclampsia than term pre-eclampsia (32). Furthermore, this study (29) found that women with chronic hypertension benefitted the most from low-dose aspirin also contradicting the literature (57). Due to the contrasting results, it may be necessary to repeat their study with a larger sample size, and in a prospective nature to ensure adequate control and validity. However, adherence to aspirin in pregnancy is proven problematic with one study finding only 56% of women adherent to the prescribed aspirin (30). Low adherence to aspirin, different dosing and timing may explain why some studies have not found aspirin to be preventative of LOP. Further reviews and meta-analyses have also found aspirin to be preventative of pre-eclampsia among high-risk patients (55, 56). Yet this data does not focus on LOP specifically. It is necessary to explore these findings for LOP with randomized control trials among high-risk cohorts.

4.3 Conclusion and future directions

This review finds that key risk factors for LOP are BMI, chronic hypertension, high MAPs, nulliparity, and maternal age. The strongest predictors for LOP are chronic hypertension and an elevated first-trimester MAP. Chronic hypertension gave the highest odds ratio for LOP and an elevated MAP was the most common significant predictor identified across all studies.

Further studies should aim to use the identified risk factors in combination with other markers to form a clinically useful predictive model for LOP. Biomarkers for LOP need to be found, and perhaps looking additionally in the second or third trimester among large cohorts would yield useful results as this is when the pathogenesis is hypothesized to occur.

The present review demonstrates that aspirin may be a promising preventor for LOP among these women at high-risk. Further preventative measures are needed for patients not deemed to be at high risk, or which can be implemented at a later gestation. It is likely that the biomarkers which will identify patients at high risk of LOP would also aid in finding preventative measures.

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

AB: Data curation, Investigation, Writing – original draft. WZ: Investigation, Writing – review & editing. EM: Writing – review & editing. ED: Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

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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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Efficacy and safety of misoprostol compared with dinoprostone for labor induction at term: an updated systematic review and meta-analysis of randomized controlled trials

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Background: Labor induction is a common obstetric intervention, increasingly performed worldwide, often using prostaglandins like misoprostol and dinoprostone.

Objective: This study aims to compare the effectiveness and safety of intravaginal misoprostol versus dinoprostone for inducing labor, examining their impact on various maternal and neonatal outcomes.

Methods: A systematic review and meta-analysis were conducted using four databases—PubMed, Google Scholar, EBSCO, and the Cochrane Library—from January 2000 to April 2023. We included randomized controlled trials (RCTs) involving singleton pregnancies at term (37–42 weeks) with unfavorable cervices, where intravaginal misoprostol was compared to dinoprostone. Key outcomes evaluated for effectiveness included vaginal delivery within 24 h, overall vaginal delivery rate, and need for oxytocin augmentation. Safety outcomes assessed were tachysystole, uterine hyperstimulation, abnormal cardiotocography, NICU admissions, cesarean delivery, and APGAR scores. Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated using a random-effects model in Review Manager (RevMan) version 5.4.1.

Results: Eight RCTs with a total of 1,801 participants (937 in the misoprostol group and 864 in the dinoprostone group) met the inclusion criteria. Misoprostol required a significantly less oxytocin augmentation than dinoprostone [RR = 0.83; 95% CI (0.71, 0.97), $p = 0.02$]. Other outcomes, including rates of cesarean delivery, uterine tachysystole, hyperstimulation, and NICU admissions, showed no significant differences between the two groups, indicating comparable safety and efficacy profiles.

Conclusion: This meta-analysis demonstrates that intravaginal misoprostol is an effective and safe alternative to dinoprostone for labor induction at term. Misoprostol achieved comparable efficacy and safety outcomes while requiring

less oxytocin augmentation, supporting its potential as a practical induction agent in clinical settings.

KEYWORDS

misoprostol, dinoprostone, intravaginally, labor induction, term

Introduction

The delivery of a fetus can be induced by initiating intrauterine contractions using pharmacological or mechanical methods (1). Approximately 20% of all births are now intentionally induced through induction of labor (IOL), an increasingly common obstetric practice in modern obstetrics (2, 3), aimed at enhancing maternal and neonatal outcomes, especially when spontaneous labor may present risks. Common indications for labor induction include prolonged pregnancy (post-term), maternal conditions (e.g., hypertension, diabetes), and concerns about fetal well-being (e.g., intrauterine growth restriction) (4). Risks of stillbirth or neonatal death increase as gestation continues beyond term (around 40 weeks' gestation), making timely induction a preventive measure (5). Evidence suggests that elective induction at 41 weeks—or potentially earlier under specific conditions—may lower the risks associated with cesarean delivery and complications like meconium-stained amniotic fluid (6). Labor induction success is often defined as achieving vaginal delivery within 24–48 h (7).

In recent years, the use of labor induction (IOL) has significantly increased, growing from 9.0% of all births in 1989 to 23% in 2012 (8). A 2012 study analyzing data from numerous hospitals across the United States discovered that over two-fifths (42.9%) of nulliparous women and slightly more than a third (31.8%) of multiparous women underwent labor induction (9). Pharmacological therapies, such as oxytocin and prostaglandins, are administered orally, vaginally, or intravenously to mature the cervix for labor induction. While oxytocin is effective for labor augmentation in women with favorable cervices, a ripening agent may be used when induction of labor is performed on women with unfavorable cervices (10–12). Other treatments designed to aid the induction process in cases of unfavorable cervix, such as membrane rupture, have been associated with reduced efficiency and higher failure rates (13).

Dinoprostone, a prostaglandin E2 analog, has traditionally been used to induce labor using either an intracervical gel or a vaginal insert (14). However, its use in resource-constrained settings is hindered by challenges such as cost and the requirement for cold storage (15). Misoprostol, a prostaglandin E1 analog originally used in the 1980s to manage and cure peptic ulcer disease (16), has been extensively studied in randomized clinical trials for its efficacy in gynecologic and obstetric procedures. It is utilized for inducing uterine contractions and cervical ripening to facilitate labor induction (17–19). Unlike dinoprostone, misoprostol is significantly more affordable, easier to administer, does not require cold storage, and is readily available even in resource-constrained countries, giving it a distinct advantage over dinoprostone (20).

Many clinical trials have investigated the effectiveness and safety of intravaginal misoprostol versus dinoprostone (17–19, 21–25), finding that misoprostol is more effective in minimizing the requirement for oxytocin augmentation in labor induction (26, 27). The meta-analysis conducted by Wang et al. (19) found comparable outcomes between the misoprostol and dinoprostone groups, showing no significant differences. However, it should be noted that their study included Saxena et al. (28) and Chitrakar et al. (29), who administered dinoprostone intracervically instead of vaginally, which goes against the specified inclusion criteria.

Considering these concerns, we conducted an updated meta-analysis to explore whether there are significant differences in various outcomes between the misoprostol and dinoprostone groups, contrasting with the nonsignificant findings reported by Wang et al. (19).

Methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (30).

Literature search

A thorough search of PUBMED, Google Scholar, Ebsco, Cochrane Library, and CNKI was conducted from January 2000 to April 2023. The following combination of Medical Subject Heading (MeSH) terms and keywords were used in the database searches: "Misoprostol," "Dinoprostone," "Labor Induction," "Intravaginally," and "Term." A detailed search strategy is presented in the Supplementary Table S1. Two independent reviewers thoroughly reviewed the titles, abstracts, full texts, and bibliographies of all identified studies separately to identify potentially relevant research. The assessment included a detailed examination of references in the relevant literature to identify appropriate studies, with no restrictions based on geographical location, ethnicity, or publication language. In cases of discrepancy, a third author was consulted to reach a consensus. Additionally, gray literature sources were searched to identify potential publications relevant to this study. A detailed search strategy is presented in the Supplementary Table S1.

Data extraction

Initially, two reviewers independently examined the titles and abstracts of publications that met the inclusion criteria, followed by a comprehensive review of the full texts. Subsequently, they extracted data from the eligible studies and documented it in an information extraction table. Two researchers independently collected the following information from each study included in the analysis: (a) the name and year of the study, (b) study design, (c) study location, (d) the number of patients in each group (misoprostol vs. dinoprostone), (e) general characteristics of the patients (age, gestational weeks, dosage, and mean birth weight), and (f) all outcomes of interest. Any discrepancies in data extraction were resolved through discussion or by consulting a third reviewer.

Inclusion and exclusion criteria

This study included only RCTs and adhered to strict eligibility criteria for research inclusion, with no restrictions on intervention dosage. The specific parameters are detailed below:

PICO

P: Population

Singleton pregnant women with live intrauterine gestations, unfavorable cervices, and a gestational period of 37 to 42 weeks.

I: Intervention

Intravaginal misoprostol.

C: Comparison

Intravaginal dinoprostone.

O: Outcome

Cesarean section rate, vaginal delivery rate, vaginal delivery within 24 h, incidences of uterine tachysystole (defined as at least six contractions in a 10-min period sustained over two consecutive 10-min intervals), hyperstimulation (defined as fetal heart rate abnormality associated with tachysystole), necessity for oxytocin augmentation, NICU admissions, abnormal cardiotocography readings, and APGAR scores below 7 at 5 min.

Studies were excluded for various reasons, including unsuitable design (such as non-randomization), lack of relevant data, involvement of animal models, or if they were case reports, editorials, reviews, conference abstracts, or duplicate publications.

Statistical analysis

Statistical analysis was conducted using Review Manager (RevMan) version 5.4.1, following The Cochrane Collaboration's (2020) guidelines. For pooling categorical outcomes, risk ratios (RRs) and their corresponding 95% confidence intervals (CIs) were calculated using a random-effects meta-analysis approach. A random-effects meta-analysis was also performed for continuous outcomes to determine mean differences (MDs) and their 95% confidence intervals (CIs). Sensitivity analysis was conducted to address outcomes with severe heterogeneity. Funnel plots were not generated due to the presence of fewer than 10 studies. Higgins' I^2 statistics were used to quantify heterogeneity: I^2 values of 25–50% indicated mild heterogeneity, 50–75% indicated moderate heterogeneity, and values greater than 75% indicated severe heterogeneity (31). To identify and address sources of heterogeneity, sensitivity analyses were planned to use the leave-one-out method. A p-value of 0.05 or less was considered statistically significant.

Risk of bias assessment

The risk of bias within individual studies was evaluated using the Cochrane Risk of Bias Tool, which examines potential sources of bias across multiple domains, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. The risk of bias in each category was systematically classified as low, high, or unclear (32).

Results

Study selection, baseline, and characteristics overview

From an initial 7,658 search results across PubMed, Google Scholar, Cochrane Library, and EBSCO, we removed 4,264 duplicates, leaving 3,394 studies for screening. After excluding irrelevant studies, 26 full-text articles were reviewed. A full-text review of 26 studies followed, leading to the exclusion of 10 cohort studies (25, 33–41) and 14 studies due to non-relevant data, gestational age under 37 weeks, or inappropriate comparisons (21, 22, 42–53). Ultimately, eight RCTs were included in the analysis—six from Wang et al.'s meta-analysis (19) and two newly identified RCTs meeting our criteria (Figure 1).

Table 1 details the baseline and study characteristics of the included trials. This analysis encompasses eight RCTs with a total of 1,801 participants. Of these, 937 received misoprostol, while 864 were in the dinoprostone group. The dosage and administration regimens for both drugs varied among the trials. In three studies (17, 54, 55), the misoprostol group received 25 micrograms (μg) every 4 h for a total of six doses. One trial administered up to five doses of 50 μg every 4 h (56), two trials gave up to two doses of 25 μg every 6 h (18, 57), two trials administered up to three doses of 50 μg every 6 h (58, 59), and another trial administered up to two doses of 50 μg every 6 h (57).

For the dinoprostone groups, two trials administered 1–2 milligrams (mg) every 6 h for 24 h (18, 54), one trial administered 2 mg for a maximum of four doses every 6 h (55), two trials administered a 10 mg vaginal insert for up to 12 h (17, 56), one trial administered 3 mg into the posterior vaginal fornix for up to two doses every 6 h (57), and two trials administered 3 mg into the posterior vaginal fornix for up to three doses every 6 h (58, 59).

Quality assessment

We evaluated the validity of the eight RCTs using the Cochrane Risk of Bias Tool. Overall, these studies were determined to be of excellent quality and exhibited a low risk of bias across all seven assessment categories, thereby enhancing the credibility of our findings. A comprehensive assessment is illustrated in Figures 2, 3.

Maternal outcomes

Vaginal delivery within 24 h

Four studies (17, 18, 54, 56) involving 922 patients reported on vaginal delivery within 24 h. Using a random-effects model to pool the results, no significant difference was found between misoprostol and dinoprostone in achieving vaginal delivery within 24 h [RR = 1.08; 95% CI (0.97, 1.20) $p = 0.15$]. Additionally, no statistically significant heterogeneity was observed among the studies ($p = 0.76$, $I^2 = 0\%$; Figure 4).

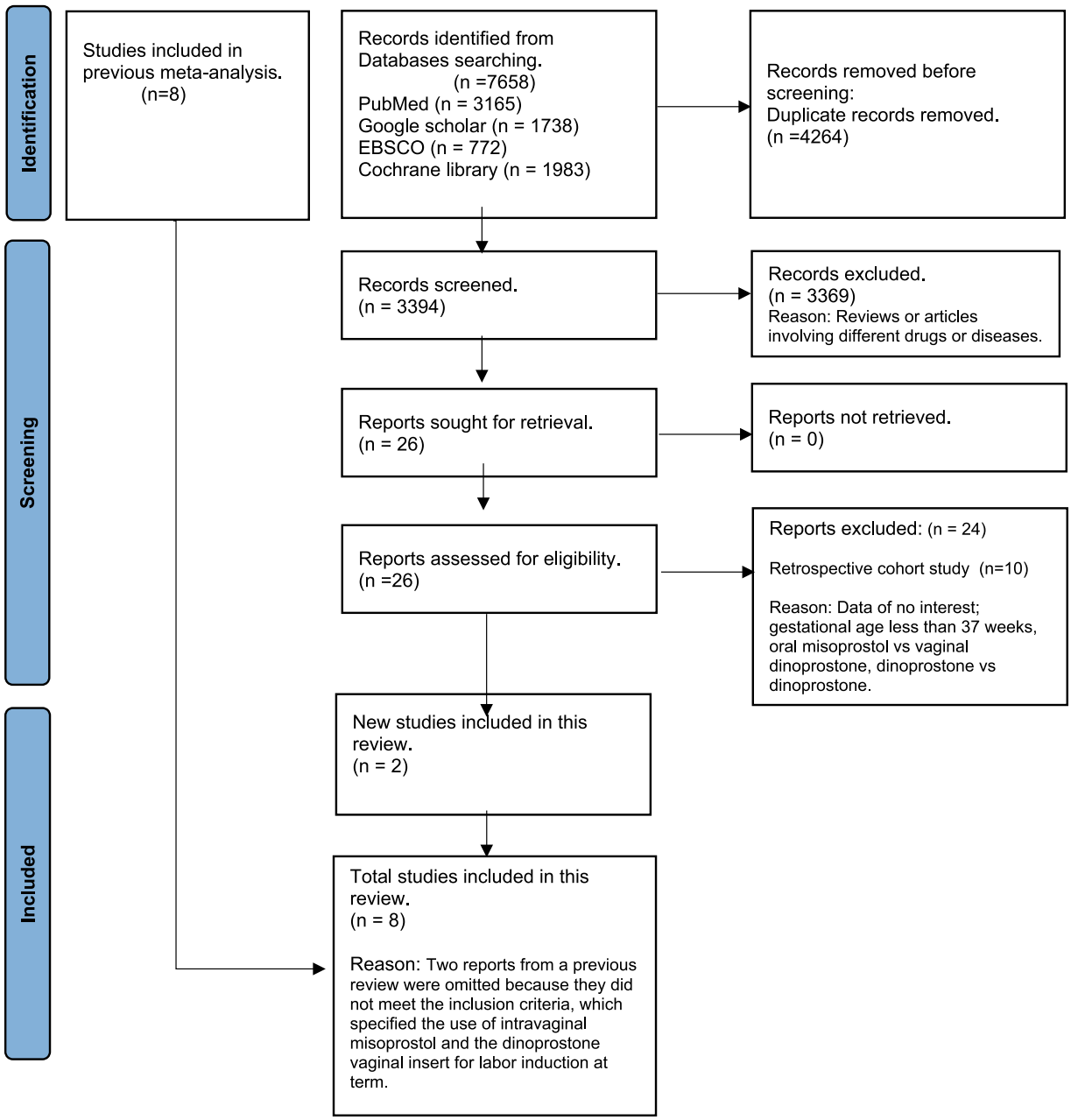

FIGURE 1
PRISMA flow chart.

Cesarean delivery

Eight studies (17, 18, 54–59), encompassing 1,858 patients, reported on cesarean delivery. Using a random-effects model to pool the combined effects, the results indicated no significant difference between the misoprostol and dinoprostone groups [RR = 0.95; 95% CI (0.74, 1.21) $p = 0.68$]. Additionally, there was no significant heterogeneity among the studies ($p = 0.10$, $I^2 = 41\%$; Figure 5).

Oxytocin augmentation

Five studies (17, 18, 54, 56, 59) involving 1,088 patients reported on oxytocin augmentation. Using a random-effects model to pool the combined effect, the results showed that the misoprostol group required significantly less oxytocin compared to the dinoprostone group [RR = 0.83; 95% CI (0.71, 0.97) $p = 0.02$]. Additionally, there was no significant heterogeneity observed among the studies ($p = 0.26$, $I^2 = 24\%$; Figure 6).

Uterine tachysystole

Five studies (18, 54, 56–58) involving 1,070 patients reported on the incidence of tachysystole. Using a random-effects model to pool the combined effect, the results showed that misoprostol was not significantly associated with a higher incidence of tachysystole compared to dinoprostone [RR = 1.27; 95% CI (0.76, 2.13) $p = 0.36$]. Additionally, no significant heterogeneity was observed among the studies ($p = 0.13$, $I^2 = 42\%$; Figure 7).

TABLE 1 General and baseline characteristics of the studies.

Study	Patient population	Country	Year	Misoprostol	Dinoprostone	Mean age years ($m \pm$ SD)		Dosage		Mean period of gestational weeks (m $\pm$ SD)		Mean Bishop score at induction ($m \pm$ SD)		Mean birth weight (grams $\pm$ SD)	
						Misoprostol	Dinoprostone	Misoprostol	Dinoprostone	Misoprotol	Dinoprostone	Misoprostol	Dinoprostone	Misoprostol	Dinoprostone
Young et al. (18)	344	Canada	2020	172	172	28.8 (± 5.6)	29.1 (± 5.70)	25 μg every 6 h	1-2 mg every 6 h	39.4 (±1.4)	40.0(±1.5)	4.1 (±1.9)	4.2 (±2.1)	3,621 (±557)	3,598 (±530)
De Bonrostro Torralba et al. (17)	198	Spain	2019	99	99	33.52 (± 5.04)	33.49 (± 4.9)	25 μg every 4 h	10 mg	292 (291–292)	292 (292–292)	3 (2–3)	3 (2–4)	3482.92 (± 366.8)	3475.31 (± 359.0)
Gregson et al. (54)	268	United Kingdom	2005	139	129	28.73 (± 5.34)	29.57 (± 5.19)	25 μg every 4 h	1–2 mg every 6 h	289.02 (24.91)	290.31 (9.52)	NA	NA	3,720 (445)	3,819 (472)
Ozkan et al. (56)	112	Turkey	2009	56	56	NA	NA	50 μg in the posterior fornix every 4 h	10 mg vaginal insert for a maximum of 12 h	NA	NA	NA	NA	3,250 (± 519)	3,119 (± 622)
Prager et al. (55)	390	Sweden	2008	199	191	32.2	33.3	25 μg every 4 h	2 mg 6–8 h	40.3	40.2	NA	NA	3,702	3,693
Ayaz et al. (58)	120	Pakistan	2010	60	60	23	25	50 μg every 6 h	3 mg every 6 h	NA	NA	NA	NA	3,165 (± 430)	3,273 (± 390)
Tan et al. (57)	169	Singapore	2010	54	57	31.27 (± 5.38)	31.42 (± 5.19)	25 μg every 6 h	3 mg every 6 h	39.66 (±1.20)	39.38 (±1.35)	2.84 (±1.02)	2.70 (±0.96)	NA	NA
				58		29.95 (± 4.43)		50 μg every 6 h		39.65 (±1.26)		2.57 (±1.06)		NA	NA
Saeed et al. (59)	200	Pakistan	2009	100	100	26.22 (± 3.40)	26.22 (± 3.40)	50 μg every 6 h	3 mg every 6 h	40.11 (± 1.37)	40.11 (± 1.37)	3.12 (± 1.28)	NA	NA	NA

(m ± SD): mean and standard deviation; μg: microgram; mg: milligram.

Note: mentions of Torralba et al. in any figure in the article refer to De Bonrostro Torralba et al. (17).

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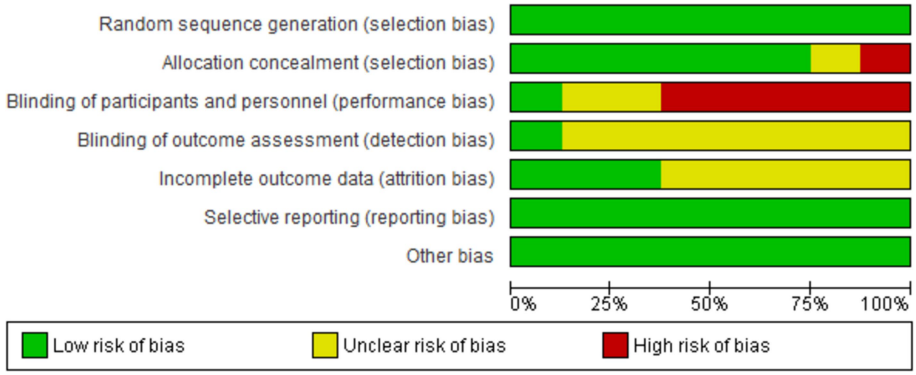

FIGURE 2
Risk of bias graph.

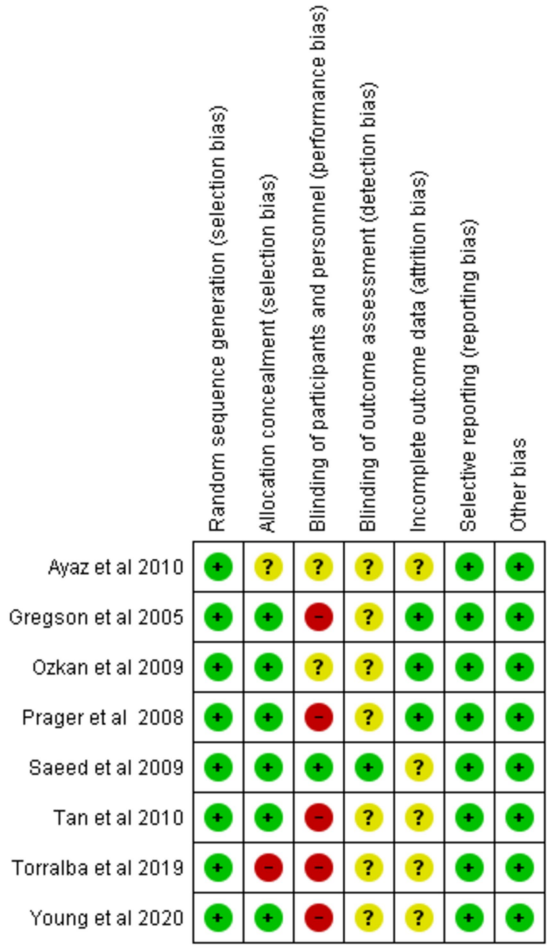

FIGURE 3
Risk of bias summary.

Vaginal delivery

Eight studies (17, 18, 54–59) involving 1,858 patients reported on vaginal delivery outcomes. Using a random-effects model to pool the combined effect, the results indicated no significant difference in vaginal delivery rates between misoprostol and dinoprostone [RR = 1.05; 95% CI (0.95, 1.16) $p = 0.37$]. Moderate heterogeneity was observed among the studies ($p = 0.02$, $I^2 = 55\%$; Figure 8).

Instrumental delivery

Five studies (14, 48, 49, 52, 53) involving 1,322 patients reported on instrumental delivery. A random-effects model was used to pool the combined effect, revealing no significant difference between the misoprostol and dinoprostone groups [RR = 1.01; 95% CI (0.79–1.29) $p = 0.96$]. Furthermore, no notable heterogeneity was detected among these studies ($I^2 = 5\%$; Figure 9).

Obstetrics outcomes

NICU admission

Six studies (17, 54–58), encompassing a total of 1,314 patients, reported on the incidence of NICU admissions. Employing a random-effects model to synthesize the data, the pooled results indicated no statistically significant difference between the two cohorts [RR = 0.76; 95% CI (0.42, 1.37) $p = 0.36$] (Figure 10). Furthermore, no notable heterogeneity was detected among these studies ($p = 0.90$, $I^2 = 0\%$; Figure 11).

APGAR score < 8 at 5 min

Four studies (17, 18, 54, 58), comprising a total of 774 patients, reported on APGAR scores below 8 in 5 min. No statistically significant heterogeneity was observed among these studies ($p = 0.79$, $I^2 = 0\%$). A random-effects model was employed to aggregate the combined effect, demonstrating no significant difference in the incidence of APGAR scores below 8 at 5 min between the two groups [RR = 1.18; 95% CI (0.38, 3.65) $p = 0.78$] (Figure 10).

Abnormal cardiotocograph

Five studies (17, 54–56, 59), encompassing 1,168 patients, reported on the incidence of abnormal cardiotocograph results. Using a random-effects model to pool the combined results, the analysis revealed no significant difference between misoprostol and dinoprostone [RR = 0.89; 95% CI (0.70), 1.14; $p = 0.36$]. No statistically significant heterogeneity was observed among the studies ($p = 0.21$, $I^2 = 32\%$; Figure 12).

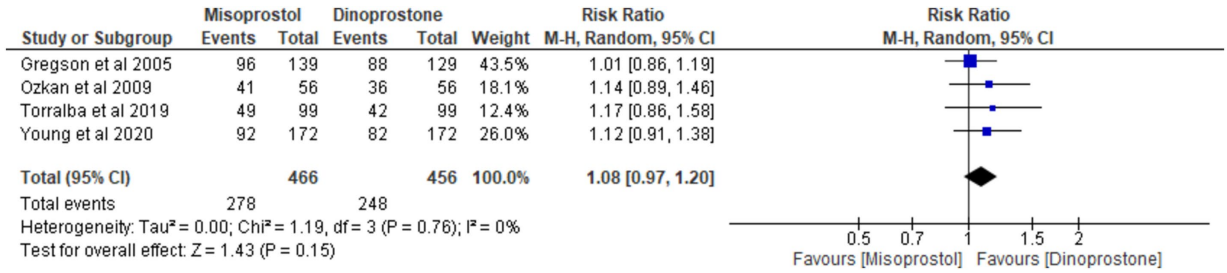

FIGURE 4
Forest plot of vaginal delivery at less than 24 h.

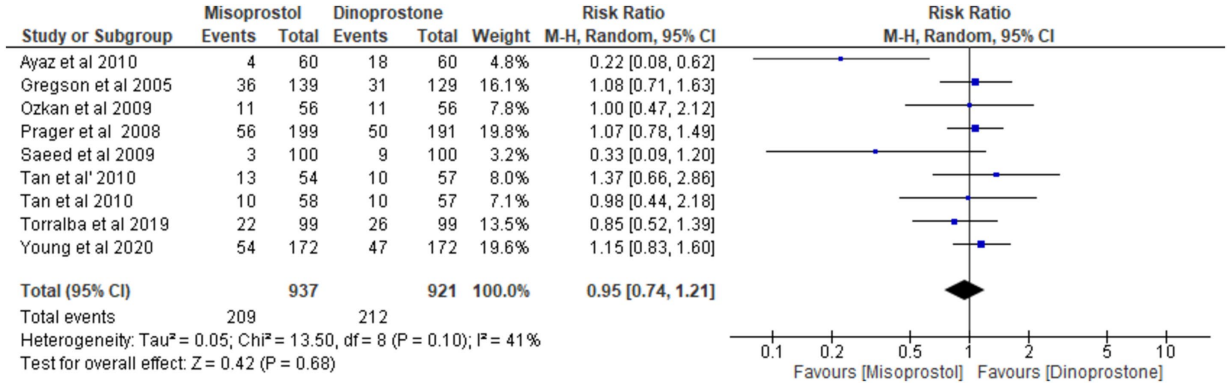

FIGURE 5
Forest plot of cesarean delivery.

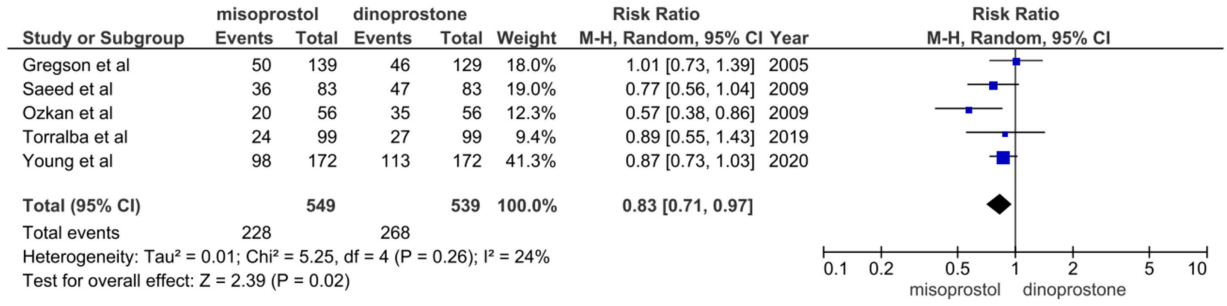

FIGURE 6
Forest plot of oxytocin augmentation.

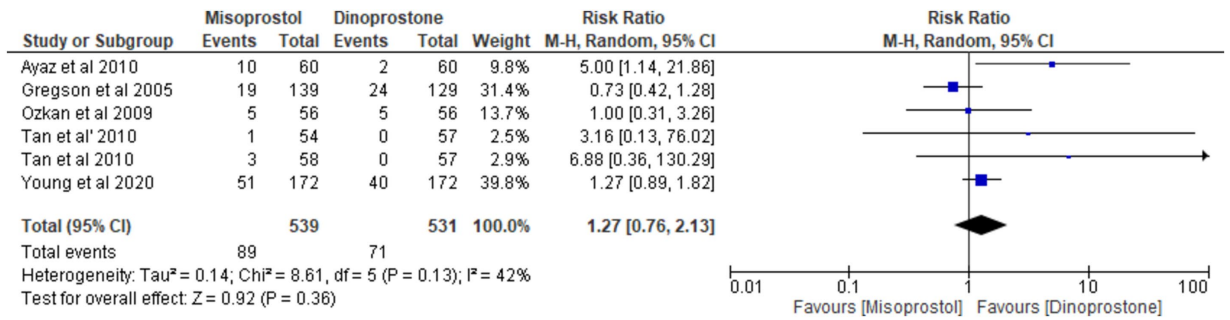

FIGURE 7
Forest plot of tachysystole.

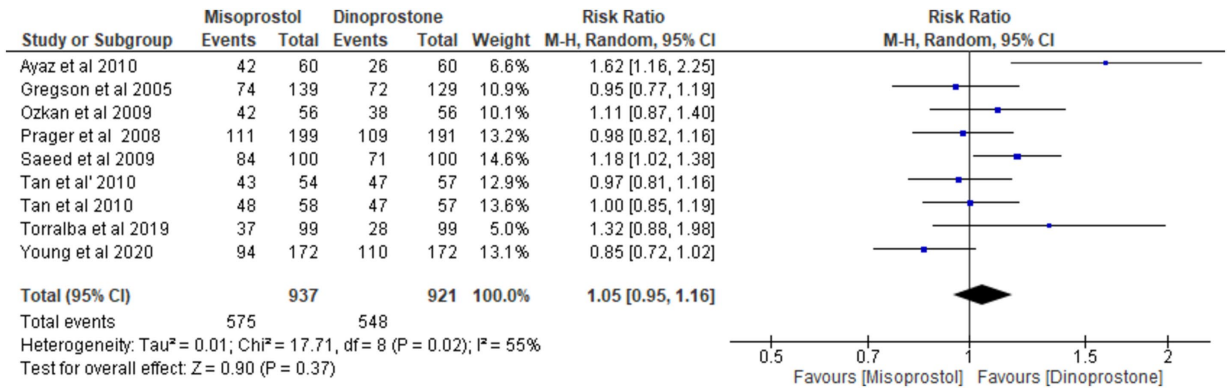

FIGURE 8
Forest plot of vaginal delivery.

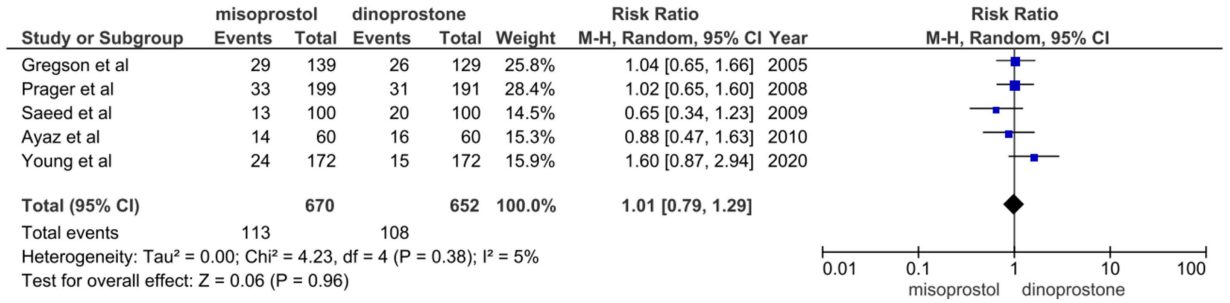

FIGURE 9
Forest plot of instrumental delivery.

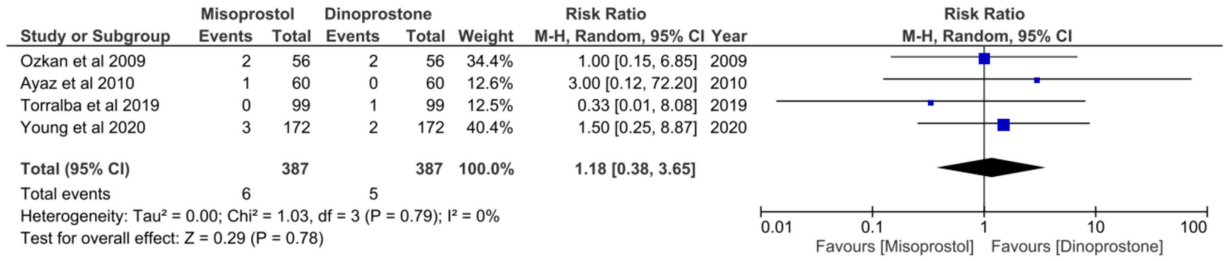

FIGURE 10
Forest plot of APGAR score < 8 at 5 min.

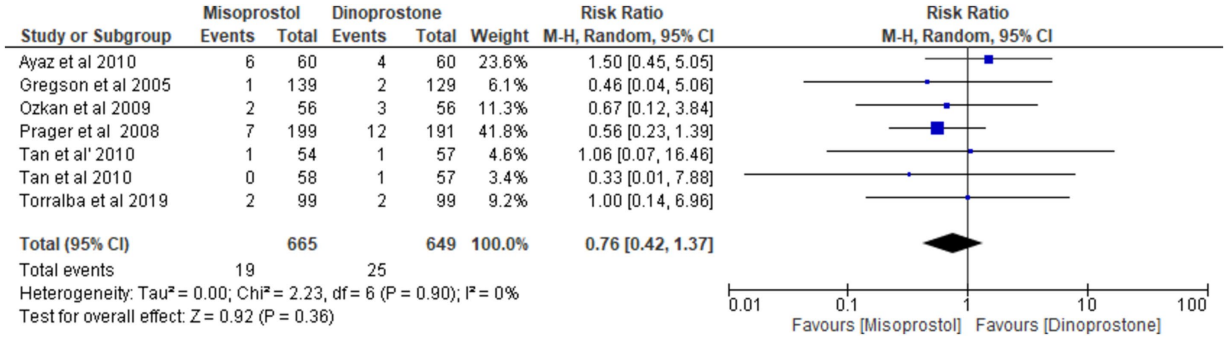

FIGURE 11
Forest plot of NICU admission.

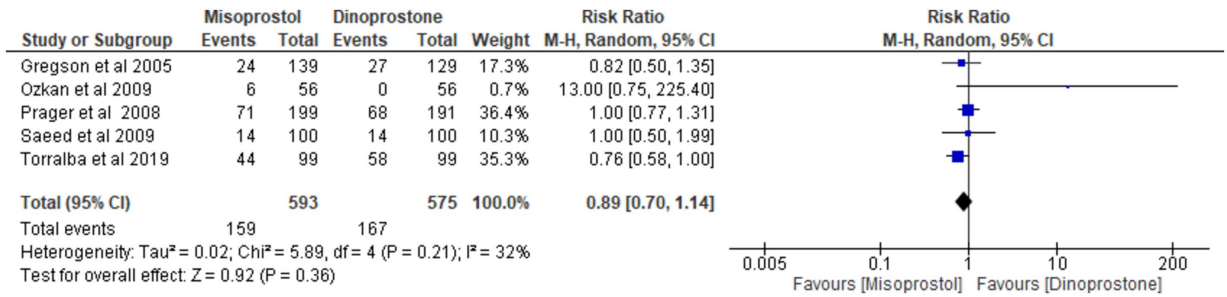

FIGURE 12
Forest plot of abnormal cardiotocograph.

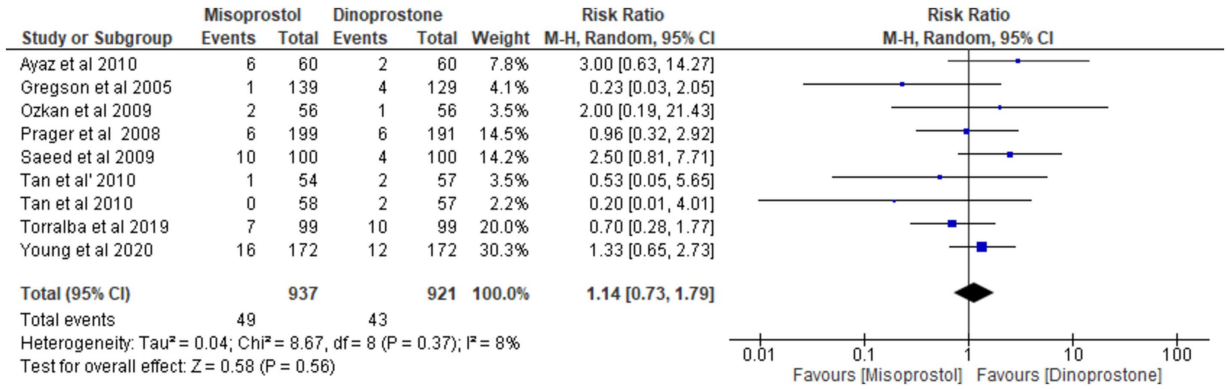

FIGURE 13
Forest plot of hyperstimulation.

Hyperstimulation

Eight studies (17, 18, 54–59), involving 1858 patients, reported the incidence of uterine hyperstimulation. A random-effects model was used to pool the combined effect, which indicated no significant difference between misoprostol and dinoprostone [RR = 1.14; 95% CI (0.73, 1.79) $p = 0.56$]. No significant heterogeneity was observed among the studies ($p = 0.37$, $I^2 = 8\%$).

Leave-one-out analysis

No outcomes exhibited significant heterogeneity except for vaginal delivery. The leave-one-out sensitivity analysis revealed that the rate of vaginal delivery was influenced by a single study, namely Ayaz et al. (58). Excluding this study led to a notable reduction in I^2 values ($p = 0.16$; $I^2 = 34\%$) and altered the overall effect [RR = 1.01, 95% CI (0.93, 1.10), $p = 0.74$] (Supplementary Figure S1).

Discussion

This meta-analysis of eight RCTs comparing intravaginal misoprostol and dinoprostone for labor induction in women with unfavorable cervices at term found no significant differences between the two groups in key maternal and neonatal outcomes, such as vaginal delivery within 24 h, cesarean delivery, and overall vaginal delivery rates. While oxytocin augmentation was needed less frequently in the misoprostol group, other outcomes—including the incidence of uterine tachysystole, hyperstimulation, NICU admissions, low APGAR scores, and abnormal cardiotocograph readings—showed no notable differences between groups (Figure 13).

Wang et al.'s (19) study showed non- significant result in terms of oxytocin augmentation for dinoprostone group with a p value of ($p = 0.11$), while our meta-analysis clearly showed the significance need of oxytocin augmentation in dinoprostone group with a p value of (0.02). This could be attributed to the inclusion of two studies in the meta-analysis by Wang et al. (19) not aligning with inclusion criteria. This finding is supported by a study conducted by Meyer et al. (27) which states that misoprostol decreased the dose of oxytocin. Another meta-analysis by Liu et al. (60) comparing intravaginal misoprostol to intracervical dinoprostone concluded that the misoprostol group required less oxytocin augmentation than the dinoprostone group.

According to our findings, there were no appreciable changes in the two groups' rate of Cesarean sections, which is consistent with meta-analysis by Wang et al. (19) and study by Wing et al. (61) that have reported inconsistent results regarding the impact of misoprostol on Cesarean section rates. Similarly, a study by Moodley et al. (62) also supports our findings by suggesting that neither intervention affects the rate of C-sections. Regarding vaginal delivery within 24 h, our results showed no significant difference, which is consistent with an observational study conducted by Moodley et al. (62). This lack of difference may be attributed to both interventions being equally efficient in promoting vaginal delivery. In addition to this, our study found out that there was no significant difference in instrumental delivery between the two groups. A recent comparative study by Sire et al. (63) aligns with the results of our analysis. However, a study

conducted by Akhtar et al. (64) at a hospital in Pakistan shows that there is difference between two groups and use of dinoprostone shows greater incidence of instrumental delivery which could possibly be due to small sample size of the study.

Furthermore, this meta-analysis did not find a significant difference in hyperstimulation between the misoprostol and dinoprostone groups. This aligns with a randomized controlled trial conducted by Madaan et al. (65) which also found no significant difference between the two groups. In terms of neonatal outcomes, our study did not find any significant differences in NICU admissions, abnormal cardiotocographs, or APGAR scores below 7. These findings align with a previous meta-analysis conducted by Wang et al. (19). Another randomized controlled trial by Wing et al. (53) comparing dinoprostone vaginal insert with vaginal misoprostol insert also found no association between neonatal outcomes in treatment groups.

When compared to women who received dinoprostone treatment, women treated with misoprostol had a significantly lower rate of oxytocin augmentation (17, 18, 41, 54–59). This shows that misoprostol might be more efficient at accelerating the course of labor, hence minimizing the requirement for additional interventions. On the other hand, although not statistically significant, the occurrence of tachysystole was higher in women administered misoprostol (18, 54, 56–58). This may suggest that misoprostol may raise the incidence of tachysystole and could perhaps suggest that lower doses must be administered which calls for additional research. Furthermore, a review by Boulvain et al. (66), comparing misoprostol to other controls, also supports this association, suggesting that misoprostol is linked to uterine tachysystole. Additionally, Farah et al. (67) found that a higher dose of 50 μg misoprostol showed a greater incidence of uterine tachysystole. This could be explained by the slow decline in plasma concentration of misoprostol after reaching maximum levels, resulting in abnormal uterine contractions (68). The American College of Obstetricians and Gynecologists recommends a lower dose of 25 μg misoprostol due to these potential uterine contractile abnormalities (69–71).

Our study had several limitations. Firstly, our meta-analysis included only eight studies with a limited sample size. Despite an extensive search strategy, few studies met the inclusion criteria for the meta-analysis. Additionally, this meta-analysis considered only publications in English, which could introduce bias and exclude pertinent studies published in other languages. Secondly, the dosages of misoprostol and dinoprostone varied across the studies, potentially affecting the interpretation of the results. Finally, the meta-analysis focused solely on the short-term effects of labor induction. Long-term outcomes, such as neonatal morbidity and maternal complications beyond the first few weeks postpartum, were not assessed.

These limitations should be considered when interpreting the findings of this meta-analysis and applying them to clinical practice. Future trials with larger sample sizes, standardized dosing protocols, and comprehensive outcome reporting are necessary to gain a clearer understanding of the efficacy and safety of misoprostol compared to dinoprostone for labor induction at term.

Conclusion

In summary, our findings suggest that misoprostol and dinoprostone are comparably effective and safe for labor induction and misoprostol requires less oxytocin augmentation. The majority of analyzed outcomes exhibited low heterogeneity, indicating overall consistency among the included studies.

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

NL: Conceptualization, Methodology, Supervision, Writing – original draft. MH: Conceptualization, Formal analysis, Methodology, Software, Writing – original draft, Writing – review & editing. TA: Conceptualization, Data curation, Formal analysis, Writing – original draft. SKh: Data curation, Formal analysis, Methodology, Writing – original draft. AK: Data curation, Formal analysis, Methodology, Writing – original draft. MJ: Data curation, Software, Writing – original draft. MaK: Data curation, Formal analysis, Writing – original draft. AQ: Data curation, Project administration, Writing – original draft. SKu: Data curation, Writing – original draft. MuK: Data curation, Writing – original draft. FD: Data curation, Writing – original draft. KR: Data curation, Writing – original draft. AA: Data curation, Writing – original draft.

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Supplementary material

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Removal of an incarcerated intrauterine device reaching the serosal surface of the uterus by hysteroscopy alone: a case report

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Background: An intrauterine device (IUD) is a widely used long-term contraceptive device for family planning. However, the IUD can lead to various complications. Severe complications and remedial measures caused by IUDs have been reported in the literature; however, detailed surgical approaches for safely removing the IUD within the minimum surgical range have rarely been described especially in postmenopausal women. Therefore, this article aims to share our surgical experience in removing an IUD that had reached the serosal surface of the uterus using hysteroscopy alone after menopause to provide new clinical ideas.

Case introduction: We report the case of a 63-year-old Chinese patient with a 12-year history of menopause. She had an IUD placed after an abortion more than 30 years ago. She came to the hospital because of occasional a small amount of unprovoked vaginal bleeding, the preoperative examination suggested an embedded IUD that appeared to have reached the serosal surface of the uterus. The IUD was not visible during hysteroscopic surgery because of uterine adhesions. Microscissors were employed to cut along the white adhesion band, revealing a faintly visible metal wire. We successfully removed the IUD using hysteroscopy only. The patient has recovered well after surgery and has been in good health for more than 5 months, with no complaints of abdominal pain or vaginal bleeding.

Conclusion: This case suggests that hysteroscopic exploration can be performed in patients whose preoperative examination indicates that the IUD has reached or protrudes from the serosal surface of the uterus. If necessary, laparoscopic or open surgery can be performed. For patients whose IUD is not visible in the uterine cavity, preoperative imaging can help assess the thickness of the uterine myometrium and the distance to the serosal surface. Intraoperatively, scissors can cut through tissue or adhesions, and instruments can measure the separation distance or visualize the device within the adhesions. In addition, it is crucial to know the patient's expectations, assess the pros and cons, and discontinue the procedure if necessary.

KEYWORDS

complications, intrauterine devices, incarceration, hysteroscopy, postmenopausal women

Introduction

An intrauterine device (IUD) is a contraceptive device placed in the uterine cavity. It is widely used worldwide as a long-acting contraceptive due to its safety, cost-effectiveness, high efficiency, and reversibility. According to the Fourth International Conference on IUDs, more than 100 million people use IUDs globally, with more than 80 million in China, accounting for approximately 40% of contraceptive use among women of reproductive age (1).

However, in addition to contraceptive failure, IUDs can lead to complications, including ectopic pregnancy, detachment, and uterine incarceration (2, 3). Incarceration is the most common complication, with perforation due to incarceration and the consequences of damage to adjacent organs being potentially more severe; its incidence has been reported to be between 0.2 and 3.6 per 1,000 (3–5). Therefore, for women who choose IUD contraception, how to avoid the occurrence of complications, especially for postmenopausal women, and how to safely remove the IUD while preventing complications such as IUD incarceration due to organ atrophy have become challenging problems in clinical practice. Serious complications related to IUDs and their remedial measures have been reported in the literature (6), but for IUD incarceration, especially in postmenopausal women, employing the least damaging surgical technique to remove the IUD completely and safely is rarely described in detail. Therefore, in this study, we share our surgical experience in removing an incarcerated IUD that reached the serosal surface of the uterus by using hysteroscopy alone to provide new clinical diagnosis and treatment ideas.

Case presentation

A 63-year-old Chinese woman presented with a 12-year history of menopause, 1-0-1-1, spontaneous delivery. She had an IUD placed after an abortion more than 30 years ago. The patient reported having regular menses lasting 3/30 days and no physical examination after menopause. The past surgical history included vaginal delivery and IUD placement after abortion, with no other past medical history. In 2022 and March 2023, she experienced a small amount of unprovoked vaginal bleeding for several days, neither of which was seen by a physician. Over the last 6 months, she had occasional small amounts of reddish vaginal discharge. In January 2024, an ultrasound performed at an outside hospital revealed an incarcerated V-type copper IUD and possible uterine fluid. In March 2024, she came to our hospital. She underwent an ultrasound, which showed a posterior uterus measuring 32 mm in length, 40 mm in width, 28 mm in thickness, with a single layer of endometrium measuring 2.2 mm in thickness, a 6.5 mm in uterine cavity separation, and 22 mm in long diameter of the cervix. The IUD was located in the myometrium of the right anterior wall and appeared to reach the extraserosa on the right side (Figure 1A). No free pelvic effusion was noted. A pelvic computed tomography (CT) scan revealed an incarcerated IUD with margins protruding from the serosal surface (Figure 1B). Gynecological examination revealed the following: cervix atrophy, light, pinpoint appearance of the external orifice; corpus uteri: posterior position, atrophy; and adnexa: negative.

Hysteroscopic exploration was performed first after adequate communication and discussion with the patient, while laparoscopic preparation was also made. Hysteroscopic surgery was conducted under general anesthesia on 1 April 2024. Cervical atrophy and pinpointing of the external orifice were observed during the procedure. A probe was used to explore the uterine cavity under ultrasound monitoring, encountering resistance. After breaking through the resistance, a No. 2 dilator rod was used to explore the middle and posterior positions of the uterus, reaching a depth of 6.5 cm. After dilating to No. 7.5, a small amount of pale brown effusion was released. Hysteroscopy was then performed revealing no obvious IUD shadow in the cervical canal or uterine cavity with maintained pressure at 100 mmHg by inflation instrument (Figure 2A). The endometrium was thin, and local white scar-like adhesions were observed in the right anterior wall of the fundus (Figure 2B). The opening of the right fallopian tube was visible, while the opening of the left fallopian tube was not discernible. Under direct vision, microscissors were employed to cut along the white adhesion band, revealing a faintly visible metal wire (Figure 2C). As the scar-like adhesion band around the IUD was gradually broken from the outside, approximately 1 cm of iron wire and silicone sleeve was exposed. Under direct vision, microforceps and microscissors were

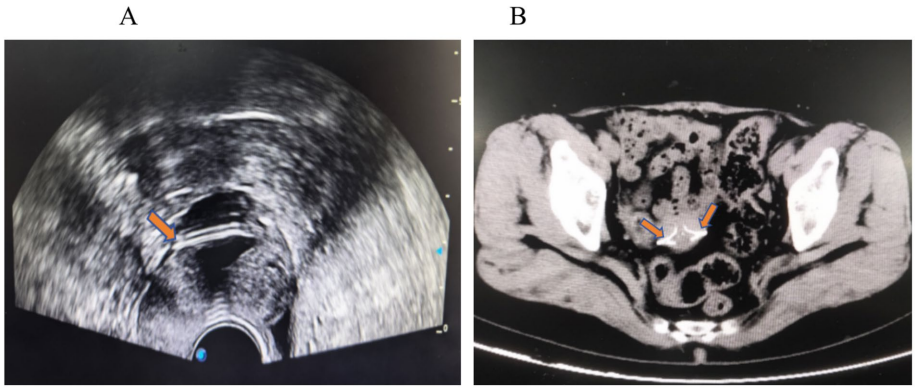

FIGURE 1
(A) Gynecological ultrasound: the right side of the IUD appears to reach the extraserosal aspect of the uterus. **(B)** Pelvic CT: the IUD is incarcerated, with edges protruding from the serosal surface of the uterus.

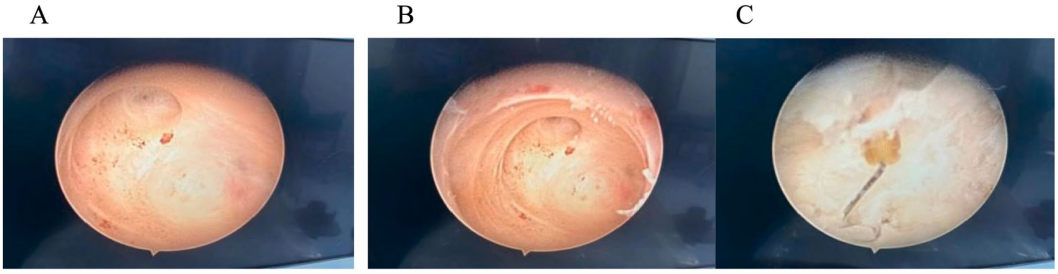

FIGURE 2
(A) Hysteroscopy: no obvious IUD shadow was observed in the cervical canal or uterine cavity. **(B)** In the endometrium, local white scar-like adhesions were observed in the right anterior wall of the fundus. **(C)** Faintly visible metal wire.

used to gradually release the adhesion surrounding the IUD. Microforceps were then used to clamp the IUD. The V-type IUD was slowly pulled and removed (Figure 3). Hysteroscopy again revealed no obvious abnormalities in utero (Figure 4).

Intraoperatively and hysteroscopically, no intrauterine residue was observed. Although the removed IUD was intact, it had a patina on the surface. Postoperatively, we reviewed the plain abdominal film to check for any residue. The plain abdominal film revealed a punctate, slightly high-density shadow approximately 2 mm in length located 5.4 cm above the pubic symphysis in the pelvic cavity (Figure 5). After discussion with the patient, the possibility of residual copper rust was considered, noting that there was no obvious abnormality in utero on hysteroscopy at the end of the surgery. Reoperation might not detect high-density shadows, so the patient was scheduled for outpatient follow-up. The patient consented to publication and agreed to follow-up. Currently, more than 5 months after surgery, the patient has reported no abdominal pain, vaginal bleeding, or other discomfort during follow-up.

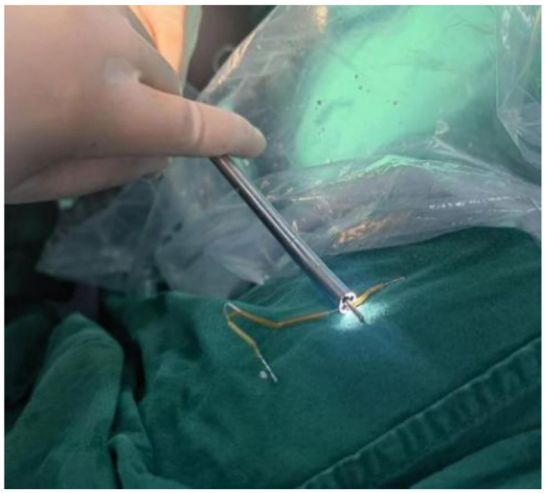

FIGURE 3
"V" IUD removed during surgery.

Discussion

Technology developments have led to continuous updates in IUD design, an increasing number of users, and an expanding scope of use (7). However, in postmenopausal women who no longer require contraception, the IUD should be removed to reduce complications from organ atrophy. Compared to premenopausal women, removing IUDs in postmenopausal women is more challenging and significantly increased risks. Therefore, this study shares the surgical experience after IUD incarceration to provide new insights for reducing complications, limiting surgical risk, and minimizing the scope of surgery in clinical practice.

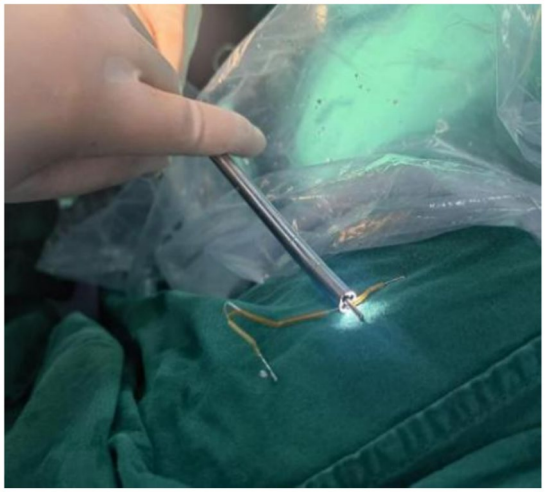

FIGURE 4
After IUD removal, hysteroscopy was performed again, and no significant abnormalities were observed in utero.

Avoid from patients with IUD who have high risk factors

The incarceration of an IUD is influenced by many factors, which are most closely related to the individual, type of IUD, timing of placement, placement process, and duration of placement.

A history of multiple abortions, abnormal uterine location (e.g., severe uterine flexion and congenital malformations), and fibroids can increase the risk of incarceration (3, 8, 9). In addition, IUD

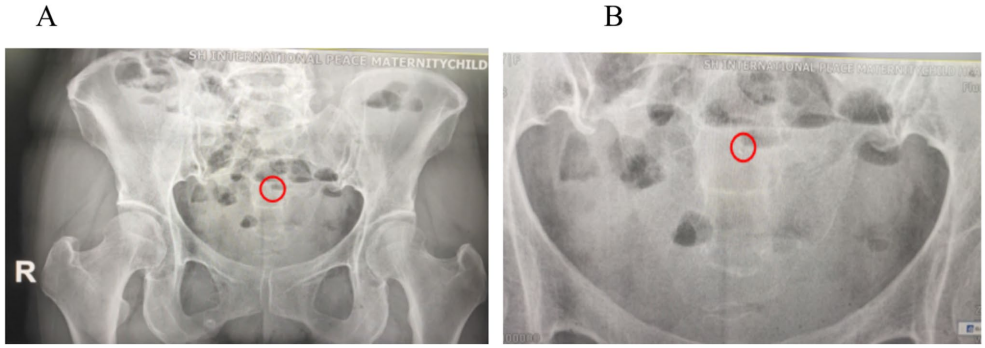

FIGURE 5
(A) Postoperative abdominal plain film: A punctate, slightly high-density shadow approximately 2 mm in length was observed 5.4 cm above the pubic symphysis in the pelvic cavity (red circle). **(B)** An enlarged high-density shadow of 2 mm (red circle).

incarceration, especially those in the deep myometrium and extrauterine incarceration, is most commonly associated with "V" shaped IUDs (10). In postmenopausal women, IUD incarceration primarily involves "O" shaped IUDs (11). Finally, the timing of placement also matters; insertion during lactation or following induced abortion heightens the risk (12–14). In addition to the above factors, the longer the placement time, the greater the risk of incarceration (10, 11, 15).

Discussion on experience in removing incarcerated IUDs

Comprehensive inspection assessment

A thorough preoperative workup is essential. This includes evaluating the patient's medical history, IUD type, duration of use, and a careful gynecological examination to assess uterine position and cervical conditions (16). Imaging studies, particularly ultrasound, provide critical insights into the IUD's intrauterine position and integrity. Pelvic X-rays can clarify the shape and composition of metal-containing IUDs, while CT scans help delineate the IUD's relationship to the uterine wall and adjacent organs (17, 18). In this case, imaging suggested that part of the IUD reached the uterine serosal surface. A hysteroscopic evaluation was chosen as the initial surgical approach, with laparoscopic surgery as a backup if required (19).

Adequate preoperative conversation to understand expectations

Comprehensive preoperative counseling is essential to ensure that patients are thoroughly informed about potential risks, including device breakage, residual fragments, and incomplete removal. Transparent and effective communication not only manages patient expectations but also mitigates postoperative psychological distress.

Adequate preoperative preparation

Adequate cervical preparation, such as with estrogen or prostaglandins, facilitates safer IUD removal, particularly in postmenopausal patients with cervical atrophy or those who have undergone cervical surgeries. In addition, intraoperative ultrasound guidance and the involvement of experienced senior surgeons enhance the likelihood of successful IUD extraction.

Flexible and gentle surgical procedure

Identify the position of the uterus

A comprehensive preoperative ultrasound and gynecological examination are essential to determine the uterine location and exclude the presence of the IUD in the vagina or posterior fornix. Under ultrasound guidance, a probe is used along the uterine axis to measure the depth of the uterine cavity. In patients with a history of cesarean section, abnormal cervical canal, or prior cervical surgery, the length of the cervical canal should be carefully evaluated to avoid excessive force. If perforation occurs during the procedure, the surgery should be immediately halted to assess the perforation's location, depth, and any potential damage to surrounding organs, with laparoscopic or exploratory laparotomy performed if necessary. In addition, the uterine position may shift after clamping the anterior or posterior cervical lips with forceps. For a uterus with extreme anteversion and flexion, the posterior lip should be clamped, whereas for extreme retroversion and retroflexion, the anterior lip can be clamped. Uterine flexion can be reduced by appropriate traction of the cervical forceps, but the process should be performed gently.

Reasonable and skillful use of device

To understand the position of the uterus, after successful cavity exploration, a probe or removal hook and curette can be used after the cervix is dilated to determine the position of the IUD. If the IUD is not detected, hysteroscopy can be used to evaluate the number and position of the IUD (20), the presence or absence of incarceration, and the depth of incarceration. For IUDs primarily located within the uterine cavity, hooks and forceps facilitate gentle extraction. In cases of extensive incarceration or limited mobility, scissors are used to

bluntly and sharply dissect surrounding tissues. Considering postmenopausal uterine atrophy, myometrial thickness and distance from the IUD to the uterine serosal surface can be understood using ultrasound and CT before surgery. During surgery, the depth of separation can be measured in relation to the tip length of scissors, forceps, and other instruments used to manipulate the uterine cavity to avoid perforation due to excessive separation distance.

Flexible surgical procedures

For patients who have no palpable IUD, no IUD is visible hysteroscopically, and a preoperative examination still suggests that the IUD is in the uterine cavity, and the uterine cavity tissue can be separated appropriately first. In this case, the patient had intrauterine adhesions, and no obvious IUD was found in the uterine cavity or cervix. After decomposing the adhesions, metal wires were faintly visible during surgery. In addition, after the IUD is visualized under hysteroscopy, the decomposition of adhesions should be gradually separated from the outside to the inside, following the direction of the IUD to control the depth and direction of separation. Once the IUD position is loosened, it can be removed by hooking part of the IUD in the uterine cavity and gently pulled out of the cervix with vascular forceps. When one end is tight, it should be cut near the external cervical os, the other end is clamped with straight vascular forceps, and the IUD wire can be pulled slowly. After removal, it is necessary to check for completeness, and when both ends are tight, avoid strong pulling. The patient should be transferred for laparoscopy if no IUD was found under hysteroscopy.

Various surgical methods

When IUD incarceration is deep, perforation occurs during removal, and organ injury cannot be excluded or ectopic to a location other than the uterus, and laparoscopic or open surgery should be performed promptly and decisively. There have been case reports of IUDs ectopically located in the rectum (21), so if laparoscopic exploration does not reveal the IUD, anal examination or even enteroscopy should not be overlooked.

Evaluate pros and cons and stop in a timely manner

For IUD incarceration, most of the IUD wires pulled out can be cut off, and the two broken ends are left approximately 1 cm at the external cervical os. Surgery can be performed within 7 days of clean menstruation the next month (22). For small amounts of residual material incarcerated in the muscular layer that cannot be removed, postoperative follow-up can be performed. The advantages and disadvantages should be thoroughly assessed during surgery and stopped if necessary (23, 24). The risk of complications such as perforation should not be increased solely to pursue surgical outcomes, and a combined hysteroscopic and laparoscopic approach can be used if necessary (25). A 2018–2022 retrospective cohort study on HELIYON was performed in 2022 (26). The study included 135 patients with ring breaks, 41 with persistent ring breaks, and 82 with spontaneous expulsion, with a mean time to expulsion of 45 days. Therefore, in patients with partial residual ring breaks, the decision to re-operate should be made after a full assessment of the pros and cons.

Conclusion

In postmenopausal patients, the removal of intrauterine devices is more challenging due to uterine atrophy and the presence of adhesions. Comprehensive preoperative evaluation, patient counseling, and imaging guidance are essential to minimize surgical risks. For incarcerated IUDs, initiating less invasive hysteroscopic techniques while maintaining surgical flexibility is recommended. If necessary, promptly transitioning to laparoscopic or open surgery ensures patient safety. The primary objective is successful removal with minimal trauma, underscored by meticulous planning, precise technique, and adaptability.

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

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

MY: Writing – original draft, Writing – review & editing, Formal analysis, Supervision. Q-FC: Conceptualization, Data curation, Supervision, Writing – review & editing. H-QL: Project administration, Resources, Supervision, Validation, Writing – review & editing.

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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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1486745/full#supplementary-material

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Female genital tuberculosis presenting as a protruding anterior vaginal wall mass: a case report

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Although pulmonary tuberculosis is a common infectious disease, especially in low-and middle-income countries, female genital tract tuberculosis (TB) is rarely reported. Female genital TB might be asymptomatic or manifest clinically in an unusual way, making an early diagnosis challenging. The most often affected regions of the genital system are the fallopian tubes and endometrium. Menstrual abnormalities, infertility, and chronic pelvic pain are frequent presenting symptoms. Rare reports of vulvar and vaginal TB exist. This case report features a 35-year-old woman who had a bulging tumor in her vagina for a year before being identified with anterior vaginal wall TB, treated with anti-tuberculosis medication, and made improvements.

KEYWORDS

female genital tract tuberculosis, vagina, tuberculosis, vaginal wall mass, case report

Introduction

Tuberculosis (TB) is a communicable disease that is a major cause of morbidity and mortality. Its etiologic agent is a bacterium called *Mycobacterium tuberculosis* (1). The disease typically affects the lungs (pulmonary TB) but can affect other sites as well (2). A survey done in the national adult population in Ethiopia estimated that the prevalence of smear-positive TB was 108/100000 and that of bacteriologically confirmed TB was 277/100000 (3). Morgagni documented the first instance of female genital tuberculosis in 1744, following a post-mortem examination of a 20-year-old lady who died of tuberculosis and whose uterus and tubes were found to be packed with caseous contents (4, 5).

Female genital tuberculosis (FGTB) is a kind of extrapulmonary tuberculosis (EPTB) that affects the female reproductive organs, most commonly the fallopian tubes (90%), ovaries (10–30%), and endometrium (50%). The highest incidence of genital tuberculosis occurs in child-bearing age women. Because it is detected in approximately 10% of individuals with pulmonary tuberculosis, one may expect a high incidence of pelvic tuberculosis in areas where the incidence of pulmonary tuberculosis is high (6).

FGTB can present with chronic pelvic inflammatory disease, menstrual abnormalities, and infertility (7). The actual number of FGTB incidences cannot be estimated accurately, as it is often asymptomatic, and only 50% of cases are diagnosed without surgery (8). Vaginal tuberculosis is extremely rare (9) and may present as a differential of vaginal cancer (10). Vaginal tuberculosis was also found as a multifocal mass in the area of the vaginal introitus, with the main lesion reaching a diameter of 3 cm (11). This case report described an

uncommon symptom of genital TB in the vagina, which has been rarely recorded in the literature.

Case presentation

A 35-year-old Para Five woman presented with a 1-year history of a progressively increasing bulging mass per vagina which was initially small but increased in size progressively. She also reported loss of appetite and a 30% weight loss. She had severe dyspareunia and discomfort during vaginal intercourse. She had five children, the youngest of whom was 4 years old. She delivered all of her children vaginally. After the last child, she was using Depo-Provera injection as a contraceptive method. She had no history of past TB treatment and no contact with a known TB patient. For these complaints, she visited a health center and was referred for further evaluation after she was told that her diagnosis was uterovaginal prolapse. She came to our hospital with these complaints, her history was taken, and she was examined. Her vital signs were all in the normal range, but she appeared emaciated; her weight was 35 kg, and her BMI was 13 kg/m^2. On examination of the external genitalia, there was a 5 by 4 cm pink smooth protruded mass outside the introitus (Figure 1) which had a cystic consistency, was non-tender, and emerged from the mid-anterior vaginal wall. The urethral opening, the distal and proximal anterior vaginal walls, the lateral and posterior vaginal walls, the vaginal fornixes, and the cervix are all normal. Pelvic ultrasound revealed a normal size and outline of the urinary bladder, uterus, and adnexa (Figure 2). On laboratory evaluation, the erythrocyte sedimentation rate (ESR) was 100 mm/h, and a complete blood count showed lymphocytosis. The chest x-ray showed normal findings. Fine needle aspiration was done on the cystic mass (Figure 3) and using Ziehl Neelson Staining, microscopy showed Acid-Fast Bacilli (Figure 4). The sample was sent for culture, and tuberculosis was confirmed. The patient was given standard daily anti-tuberculosis therapy (isoniazid, rifampicin, ethambutol, and pyrazinamide) for the first 2 months and continued daily therapy with isoniazid and rifampicin for the next 4 months, and the anti-TB was given for a total of 6 months. She was counseled on drug adherence, put on a high-protein diet, and had an optimal follow-up in the hospital. After she completed the treatment, she was examined and the bulging mass per vagina disappeared (Figure 5), her BMI was corrected, and her overall wellbeing improved a lot.

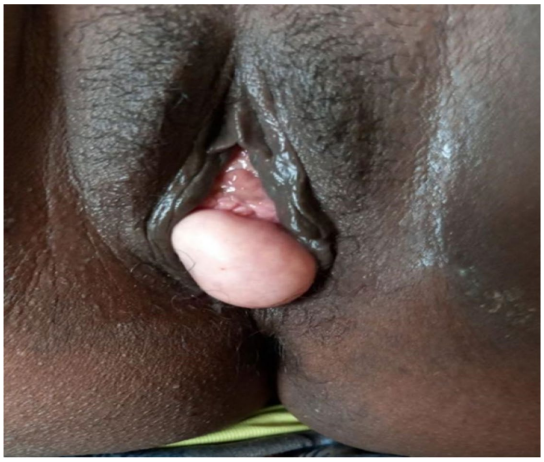

FIGURE 1
Protruding cystic mass through the vagina arising from the mid-anterior vaginal wall.

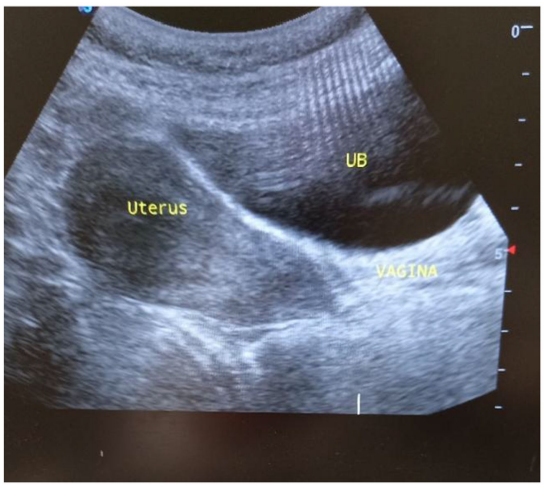

FIGURE 2
Pelvic ultrasound showing a sagittal view of a normal uterine and cervical outline, UB, Urinary bladder.

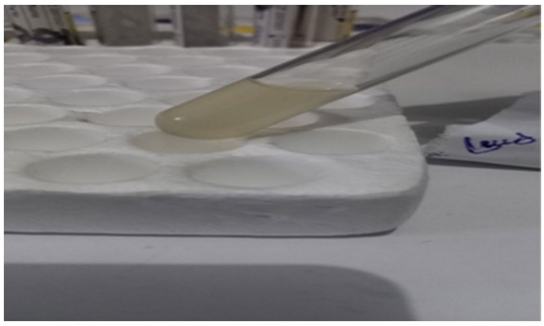

FIGURE 3
Aspirated fluid from the anterior vaginal wall mass.

Discussion and conclusion

Genitourinary TB was reported to be responsible for 27.1 percent of cases of EPTB with genital TB being seen in 9 percent of cases (12). However, the exact incidence of FGTB is not known due to underreporting, asymptomatic cases, vague symptoms, and the lack of reliable and highly sensitive diagnostics (13, 14). The

Abbreviations: AFB, Acid fast bacilli; BMI, Body mass index; EPTB, Extrapulmonary tuberculosis; FGTB, Female genital tuberculosis; Fig, Figure; Kg, Kilograms; Mm/h, Millimeter per hour; TB, Tuberculosis.

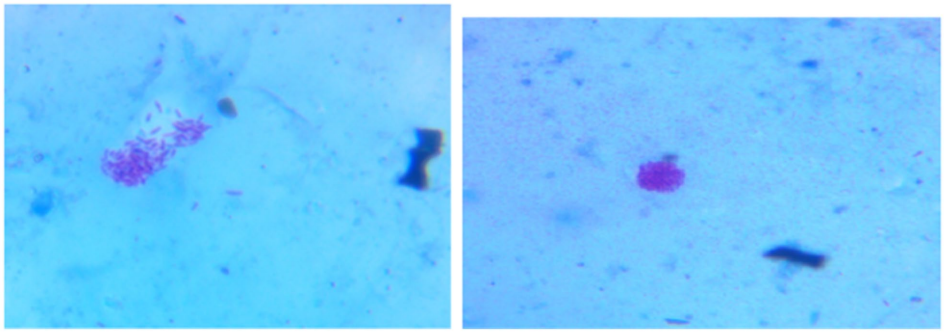

FIGURE 4
Acid-fast bacilli seen under the microscope from the aspirate fluid.

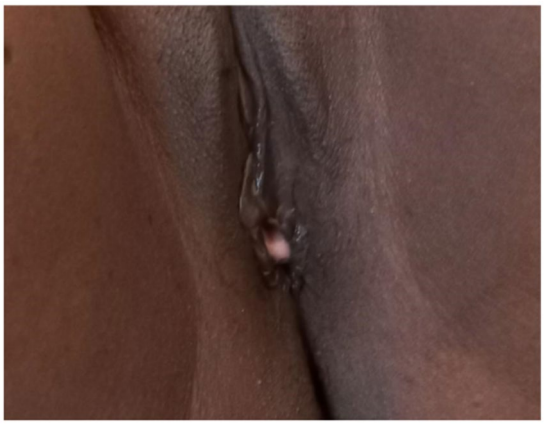

FIGURE 5
Protruded cystic mass disappeared after anti-TB treatment (6th month).

diagnosis of FGTB is made by detecting acid-fast bacilli under microscopy or culture on endometrial biopsy, or by detecting epithelioid granuloma during biopsy. The polymerase chain reaction is insufficient to make a diagnosis because of the higher rate of false positives. Laparoscopy and hysteroscopy can detect genital TB based on numerous findings (13). In our case, acid-fast bacilli were seen on a sample taken from the vaginal mass under microscopy, and tuberculosis was confirmed with culture.

Genital tract TB has been associated with up to 21% of infertility cases in low-and middle-income countries, due to tubal obstruction or adhesions in the uterine cavity (15, 16) and is even higher in patients with tubal factor infertility (17). Although the symptoms of genital TB are often absent, patients can present with infertility, pelvic/abdominal pain, or menstrual disturbances (18). Tuberculosis in the genital tract is usually secondary to tuberculosis elsewhere, most commonly in the lungs, but also in the kidneys, gastrointestinal tract, bones, or joints. (19). In our case, the chest x-ray was normal, and the patient did not have clinical evidence of tuberculosis in the internal female genital tract. Primary vaginal wall tuberculosis is highly likely.

Tuberculosis affecting the vagina and vulva is uncommon (20, 21) and is usually an extension from the endometrium or cervix, or very rarely primary due to transmission from an infected partner's semen (22). Our case did not have menstrual abnormalities, infertility, or cervicitis. Her partner was not having tuberculosis. A hypertrophic ulcer or growth on the vulva or vagina may necessitate a biopsy and histological demonstration of granuloma, as well as the exclusion of cancer and other diseases such as syphilis and lymphogranuloma venereum (13, 14, 23). In our case, there was neither an ulcer nor hypertrophic mass, but it was just a cystic and soft anterior vaginal wall swelling protruding through the introitus. A giant vulval tumor has also been reported in FGTB (24). Even vesicovaginal and rectovaginal fistulas have also been reported (25). In this case, the vesicovaginal septum was normal before, during, and after treatment, and the mass disappeared with no sequelae.

Genital TB should be treated with anti-tuberculous therapy consisting of rifampin, isoniazid, pyrazinamide, ethambutol (RIPE) for 2 months followed by rifampin and isoniazid for 4 months (26). In this case, the standard anti-TB treatment was administered with proper follow-up for 6 months, and the patient improved.

In conclusion, it is always better to have a high index of suspicion in any mass arising from the female genital tract, particularly in areas where tuberculosis is rampant. Vaginal tuberculosis could be one of the differential diagnoses in women presenting with vaginal mass.

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

Our institution does not require ethical approval to report individual cases. Written informed consent was obtained from the patient for her anonymized information to be published in this article.

Written informed consent was obtained from the patient for the publication of this case report.

Author contributions

MB: Conceptualization, Writing – original draft, Writing – review & editing. TK: Writing – review & editing. AA: Writing – review & editing. EM: Writing – review & editing.

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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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The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

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Prevalence and contributing factors of depression among women with infertility in low-resource settings: a systematic review and meta-analysis

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Background: Depressive symptoms are the most common manifestations of psychiatric disorders among women with infertility. In low-resource settings, the overall prevalence and contributing factors of depressive symptoms among women with infertility remain unknown.

Objectives: To estimate the prevalence and contributing factors of depression among women with infertility in low-resource settings.

Methods: A review was conducted using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The PubMed, MEDLINE, Google Scholar, and Cochrane databases were used to identify eligible studies published up to 30 November 2024. Three authors independently extracted the data. Studies that reported depression among women with infertility were included in this review. The data were analyzed with STATA version 14, and a meta-analysis was conducted using a random-effects model. Publication bias and heterogeneity were assessed via Eager's tests and I^2. Subgroup and sensitivity analyses were performed to identify the potential source/s of heterogeneity. A *p*-value of 0.05 was declared as statistically significant. The findings were synthesized and presented using texts, tables, and forest plots with measures of effect and 95% confidence interval (CI).

Results: Seventeen published cross-sectional studies that met the inclusion criteria with a total of 3,528 women with infertility were selected for this study. The pooled prevalence of depression among women with infertility was 48.77% (95% CI (35.86, 61.67). Good functioning family {OR 0.71 [95% CI (0.51, 0.97), I^2: 0.00%]}, good husband support {OR 0.52 [95% CI (0.34, 0.79), I^2: 0.00%]}, primary infertility {OR 2.55 [95% CI (1.36, 4.79), I^2: 68.53%]}, history of divorce {OR 4.41 [95% CI (2.11, 9.24), I^2: 0.00%]}, and duration of infertility lasting more than 10 years {OR 6.27 [95% CI (2.74, 14.34), I^2: 15.26%]} were statistically significant.

Conclusion: Depression was high among women with infertility in low-resource settings such as Africa compared to those in high-income countries, men, and pregnant mothers. Good functioning family, good husband support, primary infertility, history of divorce, and duration of infertility lasting more than 10 years were statistically associated. Therefore, African countries and the stakeholders

in collaboration with mental health experts and gynecological care providers should address these problems in order to reduce or prevent depression among women with infertility.

Systematic Review Registration: PROSPERO (ID: CRD42024516458).

KEYWORDS

depression, depressive symptoms, infertility, women with infertility, systematic review and meta-analysis, Africa

Introduction

Infertility is defined as not being able to get pregnant (conceive) after 1 year (or longer) of unprotected sex for women of age less than 35 years or after 6 months for women of age 35 years old or older (1, 2). It is a significant global public health problem, affecting approximately 186 million (3), with an estimated prevalence of 8–12% among couples (4–7). However, the prevalence of infertility is higher in low-resource settings, such as in low- and middle-income countries, where it is estimated to be 31.1% (8). According to a World Health Organization (WHO) report, infertility is associated with various forms of disability, including physical, emotional, functional, or social, which may arise from its causes, treatments, or societal consequences (5, 9). These impacts may include chronic pelvic pain, reproductive organ loss, sexual dysfunction, psychiatric disorders, stigma or marginalization, and dependency (5, 9, 10). Infertility can be caused by multiple factors including male and female reproductive issues, lifestyle factors, socioeconomic status, and infections (7).

In low-resource settings, such as Africa, infertility in women commonly occurs due to pelvic inflammatory disease (39.38%), tubal factors (39.17%), and abortion (36.41%) (11). The burden of infertility is the highest (17.7%) in women in the age group of 35–44 years compared to those below this age group (12). Infertility affects women in low-resource settings in many ways, creating challenges not only for the couple but also for the entire family, leading to social and psychological issues (13). Infertility can be classified into two types: primary infertility with an estimate of 0.6–3.4% and secondary infertility with an estimate of 8.7–32.6% (14). Mental health disorders such as depressive symptoms are the most common psychiatric disorders among women with infertility problems (5, 6, 15–18).

Depression is a common and serious mental health condition characterized by persistent feelings of sadness, hopelessness, and a loss of interest or pleasure in activities once enjoyed. It can significantly interfere with a person's daily life, relationships, and ability to function (19). In order to prevent or reduce the prevalence of depressive symptoms in women with infertility problems, interventions such as counseling, support, and treatment are essential within fertility centers (15, 20). Moreover, raising awareness of the burden and risk factors associated with infertility is essential to facilitate the provision of psychological interventions (6). However, the extent of depression and its risk factors among women with infertility may vary across different populations due to differences in culture, beliefs, healthcare settings, and socioeconomic status of the population (21).

The line of evidence shows that various contributing factors including duration of infertility, education status, employment status, income level, and social and family support, as well as spiritual wellbeing, have a remarkable association with this problem (17). Women with infertility and those without children often face societal discrimination and stigmatization, which can lead to psychological disorders such as anxiety and depression (22–25).

Depressive symptoms have major consequences on the mental wellbeing of women with infertility (26). This is because, in many low-resource settings, a woman's identity and value are closely tied to her ability to bear children, especially sons. As a result, infertility often leads to social stigma, discrimination, and marginalization (9, 26). Women may experience rejection from their families and communities, marital strain, or even abandonment and divorce (7, 9, 26), which can ultimately affect their overall health and quality of life (21).

Although primary study findings from different parts of Africa exhibited different results that range between 21.8 and 92.7% (27, 28), there is a lack of comprehensive report findings on this issue. This highlights the need for a comprehensive assessment of the prevalence and contributing factors of depressive symptoms in women with infertility. To address this gap, the current study aimed to conduct a systematic review and meta-analysis to provide an estimated prevalence of depressive symptoms and its contributing factors in women with infertility in Africa. This study highlights the burden of infertility in Africa, raises awareness of the associated problems, and can help formulate strategies to prevent infertility in women and improve their quality of life.

Methods

Search strategy

Various search engines, such as PubMed, MEDLINE, Google, Google Scholar, EMBASSE, and Hinari, were used in this study to acquire relevant data from studies published until 10 November 2024. The following Medical Subject Headings (MeSH) terms were used to search published studies: (((((((depression) OR (depressive symptom)) AND (infertility)) OR (infertile)) AND (prevalence)) OR (magnitude)) AND (risk factor)) OR (determinant). Additionally, the references of the identified articles were also assessed.

Inclusion and exclusion criteria

All observational studies reporting the prevalence of depressive symptoms and/or associated factors among women with infertility problems in Africa and those reported in English were included in this study, whereas case reports, review articles, studies of mental illnesses,

Abbreviations: CI, Confidence Interval; OR, Odds ratio; PICOS, Population, intervention, comparison, outcomes, and study design; PRISMA, Preferred reporting items for systematic reviews and meta-analyses.

non-English articles, and studies whose full text were not found were excluded from this study.

Population, Intervention, Comparison, Outcomes, and Study design (PICOS) criteria were applied to determine the eligibility criteria of the studies included in this review.

Participants/population

All women of reproductive age with infertility problems were included.

Intervention(s) and exposure(s)

Sociodemographic characteristics, personal habits and life experience, and medical and psychological health-related characteristics were the exposures of interest.

Comparator(s)/control

Women with better sociodemographic status, good personal habits and life experiences, and no medical and/or psychological health problems were treated as a comparator/control group.

Outcomes

The main outcomes of this study were the prevalence and associated factors of depression in women with infertility (both primary and secondary infertility), which were assessed using standard tools. These standard tools were Zung's questionnaire sample, the Patient health questionnaire (PHQ-9), the Copenhagen Multi-Centre Psychosocial Infertility-Fertility Problem Stress Scales, the Beck Depression Inventory questionnaire, the Hospital Anxiety and Depression Scale, the 20-item Center for Epidemiologic Studies for Depression Scale, and the 30-item General Health Questionnaire.

Data extraction

The data were extracted into Excel independently by three trained researchers. Then, the required data such as author names, year of publication, study settings, sample size, types of depression measurement tools, and prevalence and factors associated with depression were extracted (Supplementary Table 1). For studies with missing summary statistics, we reached out to the authors, when possible, to obtain the necessary data. If additional data could not be obtained, we applied statistical methods to estimate missing values. The PRISMA flow diagram was used to identify included studies (Figure 1).

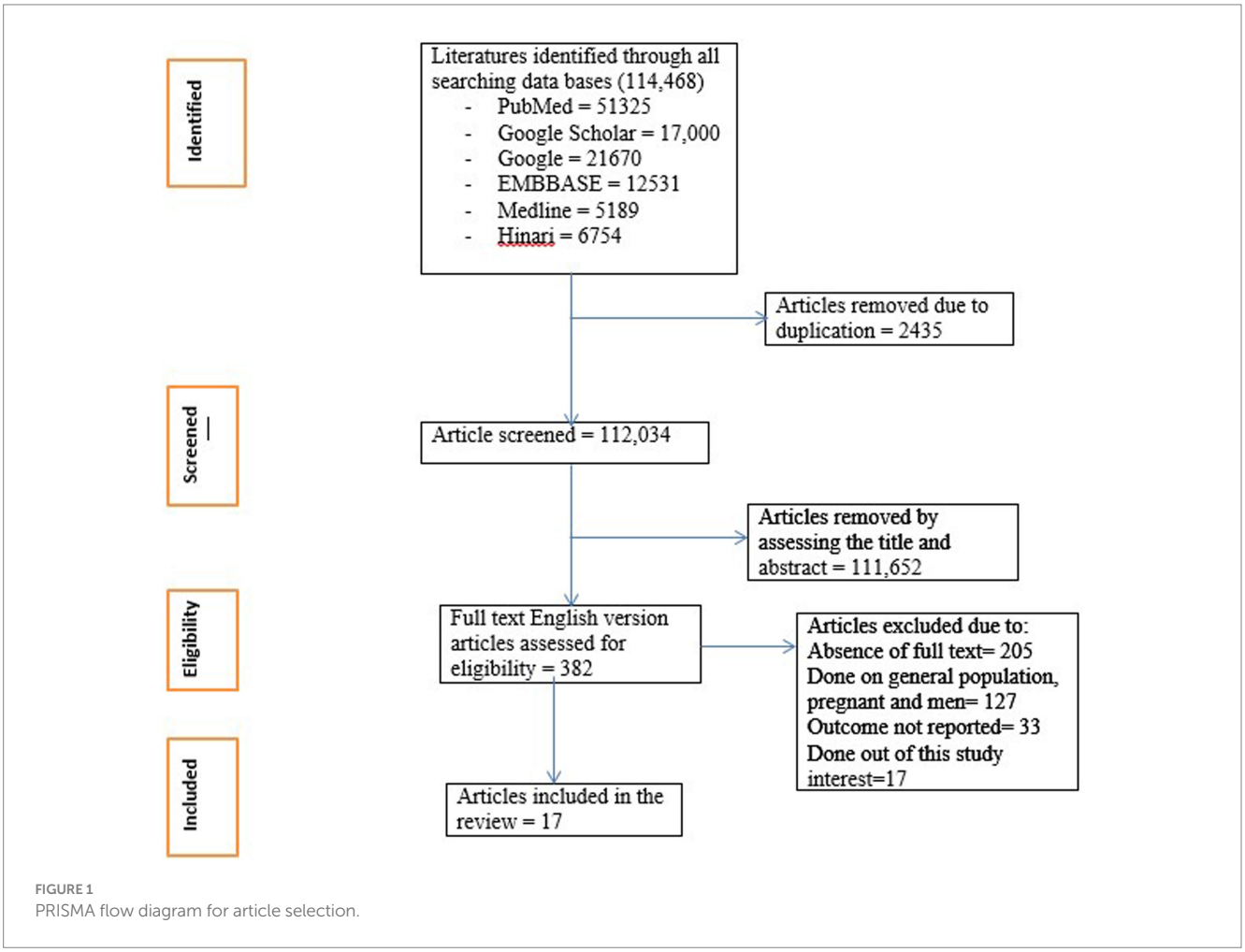

FIGURE 1
PRISMA flow diagram for article selection.

Data analysis

The quality of studies included in this review was assessed using the Joanna Briggs Institute (JBI) quality assessment tool (29, 30), and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was strictly followed throughout the study (31). The data were analyzed with STATA version 17. Publication bias was assessed via Egger's test and with a funnel plot. Heterogeneity among included studies was assessed by computing the I^2 tests. Subgroup and sensitivity analyses were performed to identify the potential source/s of heterogeneity. A random-effects model was used for variables with moderate to high heterogeneity, and a fixed-effects model was used for those with low heterogeneity. A *p*-value of 0.05 was declared to be statistically significant.

Protocol

The protocol for this systematic review and meta-analysis was registered on PROSPERO (ID: CRD42024516458).

Results

Characteristics of included studies

A systematic review and meta-analysis was conducted on 17 published studies, with a total of 3,528 women with infertility, from four African countries (Figure 1). All the included studies were cross-sectional. Twelve studies were from Nigeria (32–43), two studies were from Ethiopia (28, 44), two studies were from Ghana (45, 46), and one study was from Uganda (47). Three studies were from East Africa (28, 44, 47), and fourteen studies were from West Africa (32–43, 45, 46).

Prevalence of depression among women with infertility in Africa

In this systematic review, publication bias and heterogeneity among studies were assessed. The graphical presentation via a funnel plot and Egger's test ($p = 1.00$) did not identify the presence of possible publication bias (Supplementary Figure 1). However, there

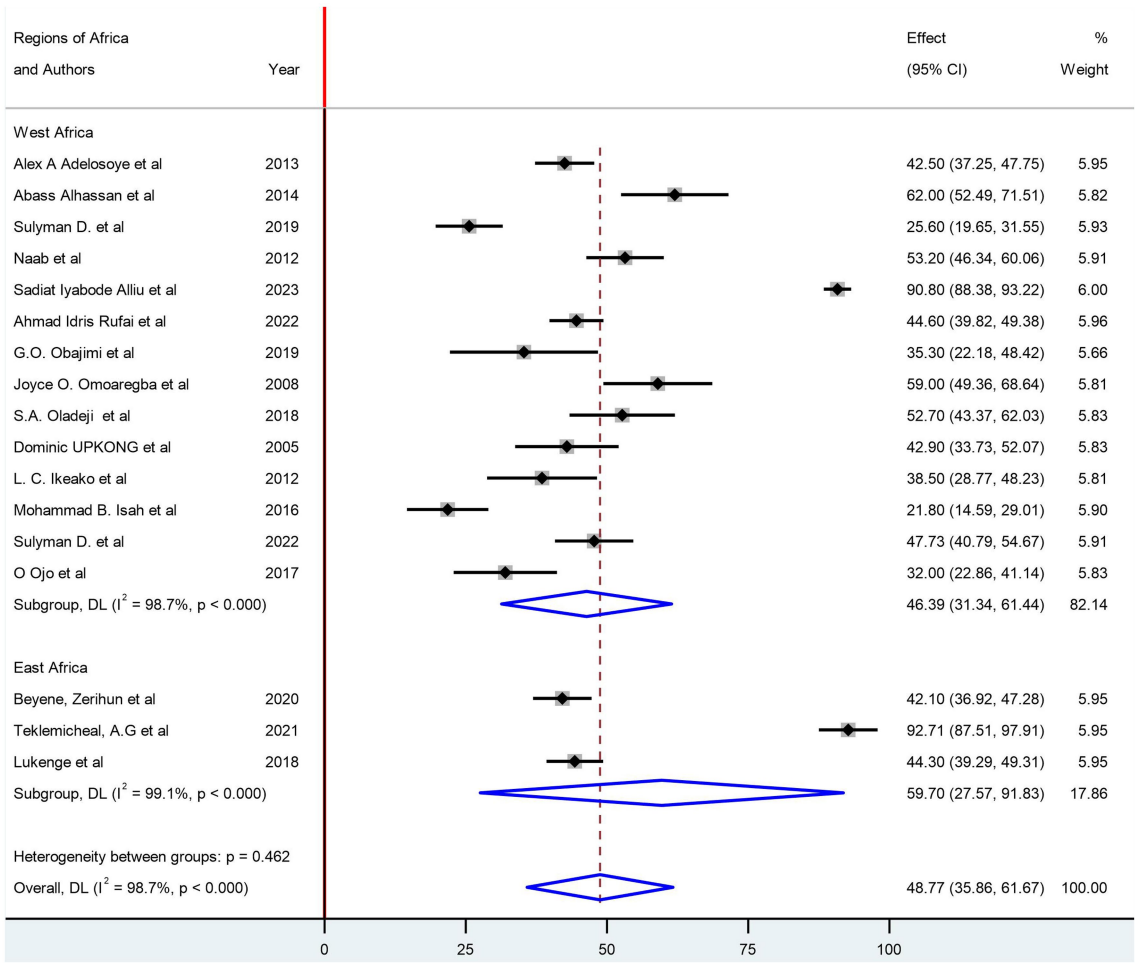

FIGURE 2
Subgroup analysis of the prevalence of depression based on the region of the country.

was a significant heterogeneity (I^2: 98.7%) among the included studies (Figure 2).

The pooled prevalence of depression among women with infertility was identified as 48.77% (95% CI: 35.86, 61.67; I^2 = 98.7%). In the subgroup analysis, based on the region of countries, the pooled prevalence of depression among women with infertility was 46.39% (95% CI: 31.34, 61.44; I^2 = 98.7%) in West African countries and 59.70 (95% CI: 27.57, 91.83; I^2 = 99.1%) in East African countries (Figure 3). Based on their sample size, studies with a sample size greater than the median value have a pooled prevalence of 48.90% (95% CI: 29.50, 68.29; I^2 = 99.2%) and 48.64% (95% CI: 30.18, 67.11; I^2 = 97.6%) (Figure 3). Additionally, a subgroup analysis based on the assessment tools was conducted (Figure 4).

Factors associated with depression among women with infertility in Africa

Sociodemographic characteristics

Age (32, 34, 36, 37, 44), type of marriage (32, 34, 36, 39, 43, 45), history of divorce (43, 44), monthly family income (34, 44), educational level (34, 43), and religion (34) were identified from previous studies (Figure 5).

Sociocultural characteristics

Verbal assault by spouse and others (47), physical assault by spouse (47), sexual assault (47), stigmatizing behaviors (43), poor support from in-laws, difficulty in social function (37), willingness to adopt children (39, 40, 42), dysfunctional family support (32, 34), and dysfunctional husband support (32, 40, 43) were the sociocultural characteristics identified in the included studies (Figures 5, 6).

Infertility-related characteristics

Duration of infertility lasting more than 10 years (39, 44), primary infertility (36, 37, 39, 40, 42, 44, 45), surgical method of treatment (43), tubal factor as the cause of infertility (43), and a miscarriage history (47) were identified during data extraction. From the listed gynecological characteristics, the meta-analysis was performed only for the duration and type of infertility, as there was only a single study report for the other variables (Figures 5, 6).

After including the above-listed variables, this meta-analysis identified that depression among women with infertility was significantly associated with good functioning family (AOR: 0.71; 95%

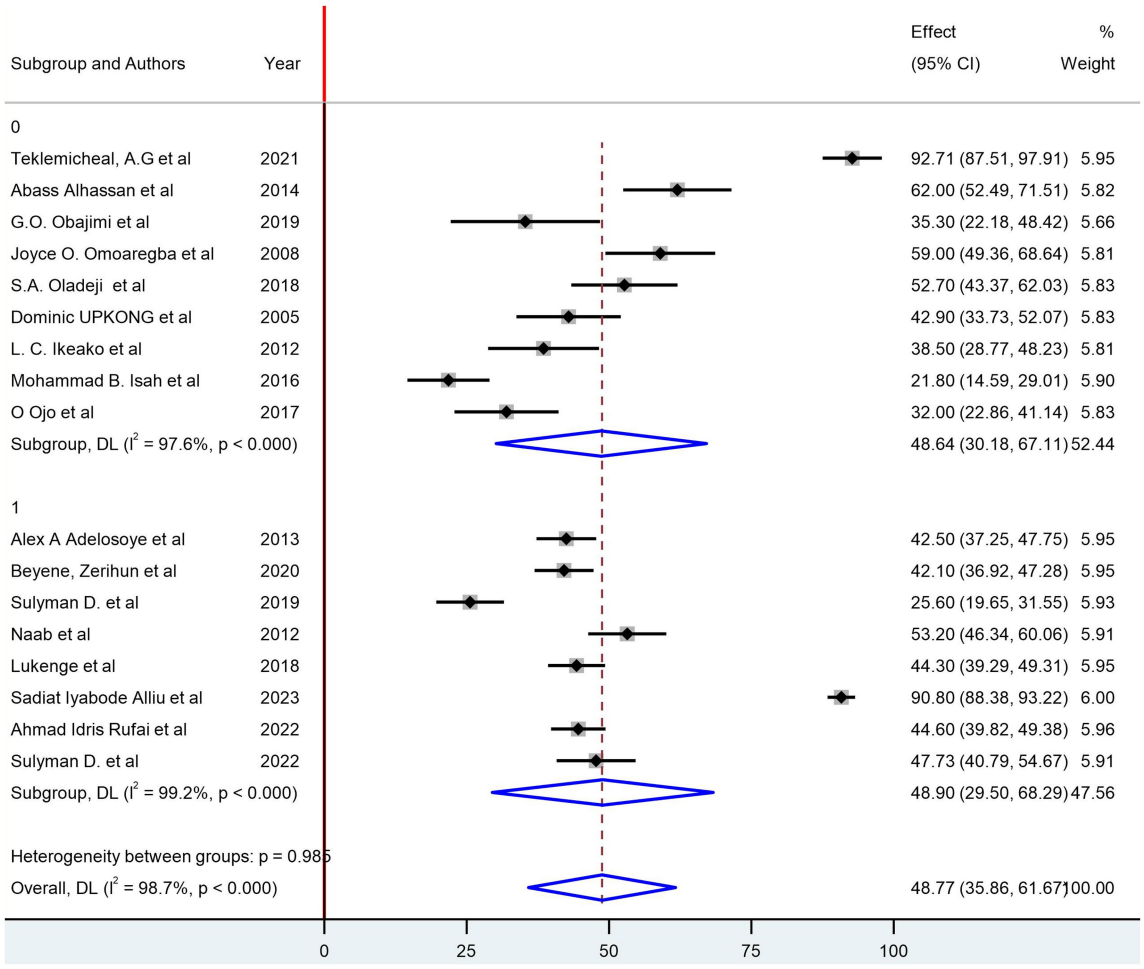

FIGURE 3
Subgroup analysis of the prevalence of depression based on the median sample size of included studies.

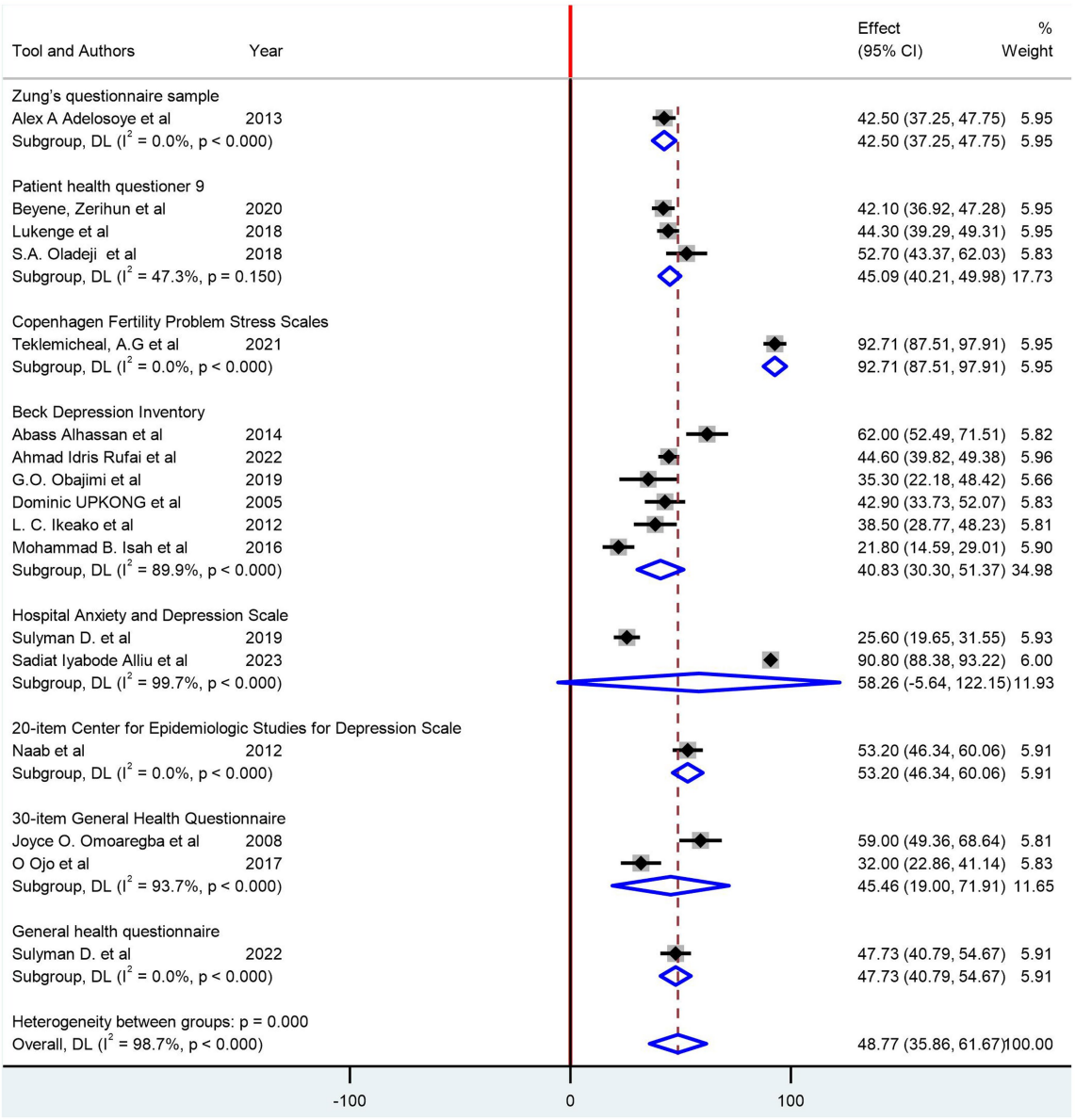

FIGURE 4
Subgroup analysis of the prevalence of depression among women with infertility based on the depression assessment tool.

CI: 0.51, 0.97; I^2: 0.00%), poor husband support (AOR: 2.01; 95% CI: 1.32, 3.07; I^2: 0.00%), primary infertility 2.55 (95% CI: 1.36, 4.79; I^2: 68.53%), history of divorce 4.41 (95% CI: 2.11, 9.24; I^2: 0.00%), and duration of infertility lasting more than 10 years 6.27 (95% CI: 2.74, 14.34; I^2: 15.26%). However, age greater than 35 years (AOR: 0.96; 95% CI: 0.73, 1.27; I^2:0.00%), polygamous marriage (AOR: 1.02 95% CI: 0.77, 1.36; I^2:58.55%), and women's intention to adopt children (AOR: 0.70 95% CI: 0.11, 4.64; I^2: 78.26%) were not significantly associated with depression among women with infertility. The funnel plot and Egger's tests showed that there was no significant publication bias among the included studies (Supplementary Figures 2, 3).

The heterogeneity test (I^2) among the variables significantly associated with depression revealed that, except for primary infertility (I^2 = 68.53%), there was no significant heterogeneity for good functioning family, good husband support, history of divorce, or age greater than 35.

Discussion

This study conducted a systematic review and meta-analysis to investigate the prevalence of depressive symptoms and the underlying factors associated with them in women struggling with infertility across Africa. The study found an overall pooled prevalence of depressive symptoms among women with infertility problems to be 48.77% (95% CI: 35.86, 61.67). The prevalence of depressive symptoms found in this study was higher than those among men with infertility problems (18.30%) (48) and pregnant mothers (20.7%) (49).

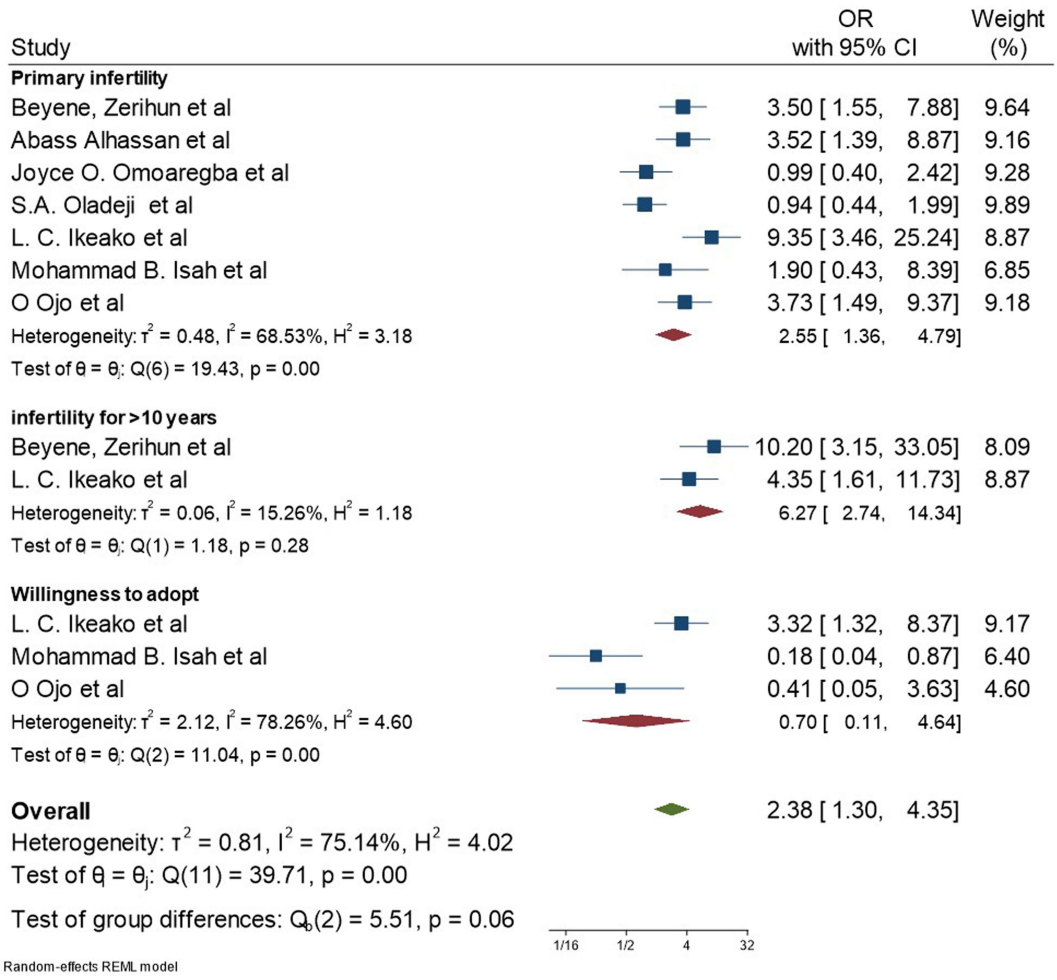

FIGURE 5
Forest plot for socio-cultural factors associated with depression among women with infertility.

The possible explanation is due to the fact that depressive symptoms are the most common disorder manifestations in women with infertility problems (16, 48), and this highlights the significant association between depressive symptoms and infertility problems (50). The prevalence of depressive symptoms found in the present study was also higher than that among high-income countries (28.03%) (21). A plausible explanation is due to the difference in sociodemographic characteristics, limited access to fertility and mental health treatment, cultural expectation and stigma, delay in seeking medical attention for their infertility due to lack of awareness, and under-resourced healthcare facilities to treat both infertility and depressive symptoms (21).

The present study identified the factors associated with depressive symptoms among women with infertility problems. These factors demonstrated that women who had a good functioning family were 29% less likely to have depressive symptoms than women who had a poor functioning family. This result was in line with a study conducted in Iran (51). A possible explanation for this is that women with a good functioning family will have proper behavioral control, roles, emotional responsiveness, and emotional involvement. These result in improving depressive symptoms among women with infertility problems (52).

In this study, women who had good husband support were 48% less likely to have depressive symptoms compared to their counterparts. This finding was supported by a study conducted in Japan that revealed that the lack of husband support was associated with depressive symptoms among women with infertility problems (53). A possible explanation is that women with infertility who get good husband support may have better decision-making practices about their health compared to their counterparts (53).

It was also revealed that women with primary infertility were 2.55 times more likely to have depressive symptoms than women with secondary infertility. This finding is supported by different studies conducted in Pakistan (54), Turkey (55), and Iraq (56). A possible reason may be that religious denial coping strategy was expected to be high in women with primary infertility, which resulted in the highest rate of depressive symptoms (57).

In this study, women who had a history of divorce were 4.41 times more likely to have depressive symptoms than women who had no history of divorce. This finding was supported by a study conducted in Iran. A possible reason could be because marital status is directly associated with happiness, and happiness is directly associated with mental health (58).

In this study, women with a duration of infertility lasting more than 10 years were 6.27 times more likely to have depressive symptoms than their counterparts. This finding is supported by different studies conducted in Iran (59), Iraq (56), and Turkey (60). This could be due to the fact that infertility for a prolonged period could reduce the possibility of treatment, resulting in higher depressive symptoms (60). This highlights the importance of early diagnosis and treatment of infertility to prevent or reduce depressive symptoms.

As a limitation, this review included only quantitative studies and studies that were published in the English language. Additionally, the cross-sectional nature of the studies does not indicate the true cause of the problem.

Conclusion and recommendations

The results of this study indicated a higher prevalence of depressive symptoms in women with infertility problems in Africa than in high-income countries, men, and pregnant mothers. To prevent or reduce the problem, responsible organizations in Africa, in collaboration with mental health experts and gynecological care

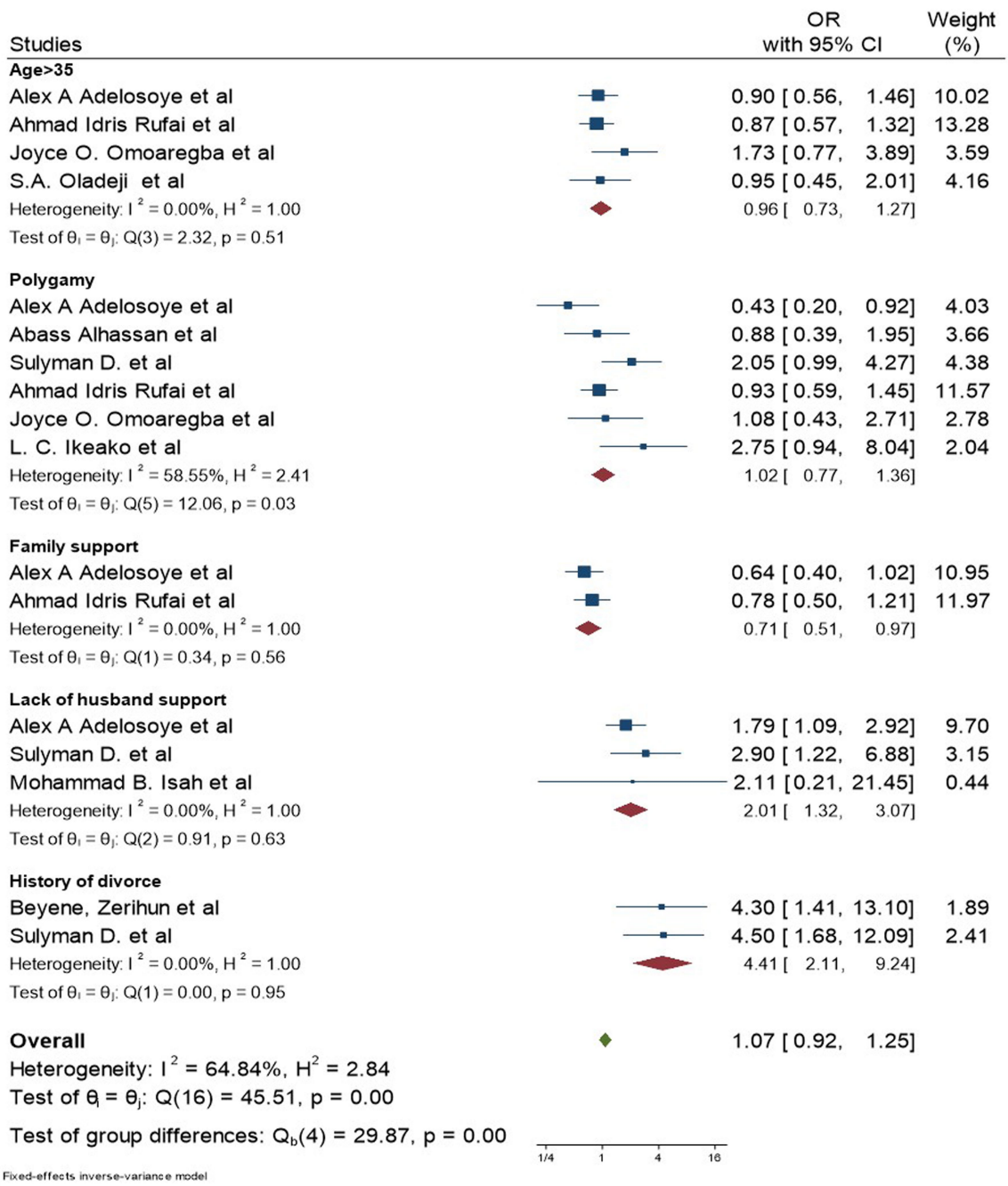

FIGURE 6
Forest plot for socio-demographic factors associated with depression among women with infertility.

providers, should focus on improving proper family functioning and husband support, while giving special attention to women with primary infertility, a history of divorce, and infertility lasting more than 10 years. Therefore, African countries and the stakeholders can use this information to develop evidence-based strategies, policies, and health service delivery systems, as well as propose solutions to reduce or prevent depressive symptoms among women with infertility. It is also important for healthcare providers to consider depression when providing care for women with infertility and for future researchers to design interventional studies to address this problem.

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

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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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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2025.1477483/full#supplementary-material

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Effects of calcium supplementation on the prevention of preeclampsia: an umbrella review of systematic reviews and meta-analyses

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Background: Preeclampsia is the leading cause of maternal and fetal morbidity and mortality. Calcium supplementation has been considered a potential intervention to reduce the risk of preeclampsia. This umbrella review aims to summarize the effects of calcium supplementation in the prevention of preeclampsia based on existing systematic reviews and meta-analyses studies.

Methods: A systematic search of electronic databases, such as MEDLINE, Web of Science, SCOPUS, and the Cochrane Library, was conducted from inception to 30 December 2023. The methodological quality of the included studies was assessed using the revised version of the Assessing the Methodological Quality of Systematic Reviews (AMSTAR 2) tool. A random-effects model was used to estimate the effect of calcium supplementation on preeclampsia. Heterogeneity among included studies and publication bias were assessed using the I^2 statistic and the Egger's test, respectively.

Results: Calcium supplementation reduced the risk of preeclampsia by 47% (RR: 0.53, 95% CI: 0.42, 0.68) with a considerable level of heterogeneity (I^2 = 84.39%). Our subgroup analyses revealed that the risk of preeclampsia was significantly lower in high-risk pregnancies that received calcium supplementation (RR: 0.35, 95% CI: 0.26, 0.47), indicating a 65% risk reduction. In comparison, low-risk pregnant women who received calcium supplementation experienced a 33% risk reduction (RR: 0.67, 95% CI: 0.59, 0.77). Furthermore, the effects of calcium supplementation were more pronounced in women from developing countries compared to those from developed countries.

Conclusion: This umbrella review provides a summary of the evidence supporting the use of calcium supplementation to reduce preeclampsia. Incorporating calcium supplementation into antenatal care interventions may help to reduce the burden of preeclampsia and improve maternal and fetal outcomes. Further studies are needed to explore the impact of baseline calcium levels, optimal dosage, timing, and routes of supplementation to effectively decrease the incidence of preeclampsia.

KEYWORDS

preeclampsia, calcium supplementation, umbrella review, systematic review, meta-analysis

Background

Preeclampsia is a pregnancy-specific multisystem complication characterized by high blood pressure, proteinuria, and organ damage that poses a significant risk to both the mother and the fetus. Its incidence varies across regions, affecting 2–5% of pregnancies worldwide (1). Evidence suggests that the burden of preeclampsia is greater in developing countries, with a reported rate of 2.8% of live births, which is seven times higher than the rate in developed countries (0.4%) (2). Preeclampsia is one of the leading causes of maternal and perinatal morbidity and mortality worldwide, accounting for up to 29,000 maternal deaths annually (3). Calcium supplementation has emerged as a topic of interest and investigation for the prevention of preeclampsia (4, 5).

Calcium plays a crucial role in muscle contraction, maintaining water balance, and regulating blood pressure. Insufficient calcium levels trigger the release of parathyroid hormone, resulting in elevated intracellular calcium concentrations in vascular smooth muscle cells. This leads to vasoconstriction and high blood pressure (6). Consequently, maintaining adequate calcium levels ensures vascular stability, thereby reducing the risk of hypertension (6). Moreover, dietary calcium supplementation has been observed to decrease renin levels in the blood, although it does not completely eliminate them. In addition, the renin-angiotensin-aldosterone system, which plays a pivotal role in regulating blood pressure, is influenced by the acute activation of calcium-sensing receptors in juxtaglomerular cells due to high extracellular calcium concentrations. Taken together, these factors contribute to the preventive effect of calcium against hypertension (7, 8).

During pregnancy, adequate blood calcium levels are associated with positive maternal–fetal health outcomes and a reduced risk of maternal and fetal cardiovascular disease (9). However, the demand increases due to a combination of physiological, metabolic, and hormonal factors in a period of pregnancy (10, 11). Calcitonin hormone, which is responsible for calcium deposition in the bones, is also elevated during pregnancy (12). Furthermore, vitamin D, which plays a crucial role in calcium metabolism and bone health, can also be affected during pregnancy (13). These conditions indicate the need for a relatively high calcium intake during pregnancy. However, insufficient dietary calcium intake can impair the body's ability to maintain calcium balance, potentially causing maternal calcium deficiency and complications, such as disrupted vascular tone regulation, preterm birth, and fetal growth restriction (13, 14). This is particularly concerning in mothers who have a low dietary calcium intake (5). In 2015, the World Health Organization (WHO) recommended calcium supplementation for pregnant women (15) and has subsequently updated its guidelines to emphasize the potential benefits of calcium in the prevention of preeclampsia (15–17). However, a review of low- and middle-income countries revealed that the average calcium intake was less than 900 mg/day (18). Subsequent reviews in 2004 and 2018 indicated that dietary calcium intake remained at approximately 600 mg/day in these regions, with no significant improvement, compared to over 1,000 mg/day in high-income countries, resulting in a difference of approximately 300 mg/day mean calcium intake (19, 20).

There is limited and inconsistent evidence regarding the effectiveness of calcium supplementation in preventing preeclampsia. A systematic review and meta-analysis of four randomized trials that included 7,272 women reported that calcium supplementation led to an 11% reduction in the incidence of preeclampsia (10). Another review conducted by Christina Oh et al. (21) indicated a 70% reduction in the risk of preeclampsia (21).

Therefore, this umbrella review aims to summarize and address the inconsistencies found in systematic reviews and meta-analyses on the effectiveness of calcium supplementation in preventing preeclampsia. Furthermore, this review aims to consolidate current knowledge, identify potential sources of heterogeneity, and provide valuable insights into the effectiveness of calcium supplementation in reducing the burden of preeclampsia, ultimately guiding clinical practice and informing future research endeavors.

Methods

Design

This umbrella review was conducted to evaluate the effects of calcium supplementation on the prevention of preeclampsia using existing systematic reviews and meta-analyses studies. The review process adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (22). The target population (P) comprised pregnant women at risk of developing preeclampsia, the intervention (I) was calcium supplementation, the comparator (C) was pregnant women who did not receive calcium supplementation, and the outcome (O) was preeclampsia, defined as a pregnancy-specific illness characterized by the onset of hypertension after 20 weeks of gestation, with or without proteinuria (23). This review was registered with PROSPERO (CRD42024547701).

Search strategy

Using a combination of Medical Subject Headings (MeSH) and keywords, we systematically searched MEDLINE via PubMed, Embase, Web of Science, Scopus, the Cochrane Database of Systematic Reviews, the PROSPERO register, and the Google Scholar web search engine. MeSH terms and keywords included 'preeclampsia,' 'hypertensive disorders during pregnancy,' 'pregnancy-induced hypertension,' 'calcium,' 'Ca++,' 'supplementation,' 'systematic review,' and 'meta-analysis.' The search period was from inception to 30 December 2023. Additionally, citations of the eligible studies were manually searched. The detailed search strategy is included in the Supplementary Table S1.

Study inclusion criteria

Types of studies

This umbrella review included all systematic reviews and meta-analyses studies that assessed the effects of calcium supplementation in the prevention of preeclampsia.

Types of participants

The participants included in this review were women who received calcium supplementation during their pregnancy, regardless of whether the pregnancy was a singleton or multiple gestation. A

pregnant woman considered to have an unknown status was defined as one who received calcium supplementation despite her risk for preeclampsia, her country of residence and her baseline status. In contrast, pregnant women participating in the study were categorized into two subgroups based on their risk profile. The high-risk group consisted of pregnant women who exhibited calcium deficiency, a history of gestational hypertension or preeclampsia, a positive roll-over test, a positive angiotensin-sensitivity test, or other high-risk factors as defined in the original study. The low-risk group included healthy pregnant women with a lower risk of developing these conditions (5). Additionally, baseline calcium intake levels were categorized as low if they were below 900 mg/day and adequate if they were 900 mg/day or above (5). Moreover, for the analysis, a high dose was defined as ≥1 g of elemental calcium per day, a medium dose was defined as 0.6–1.5 g, and a low dose was defined as <1 g of elemental calcium per day.

Types of interventions

Studies were eligible if they compared calcium supplementation during pregnancy with a placebo group, no treatment. The included studies considered different risk factors for preeclampsia, dietary intake, dosage variations, and the economic status of the countries involved.

Outcomes of interest

The primary outcome of interest was the incidence of preeclampsia.

Setting

This umbrella review included studies conducted globally without any geographical limitations.

Publication condition

This review included only published articles in English that had full texts and reported the effect of the outcome of interest.

Selection and data extraction

The retrieved systematic review and meta-analysis studies were exported into EndNote software to eliminate any duplicate studies. Two independent reviewers (HK and NBY) retrieved records from the databases and then screened the articles based on their titles and abstracts. The records retained during this screening phase underwent full-text assessment by the two reviewers. Disagreements between the two reviewers were resolved through consensus and the involvement of a third reviewer. A data extraction form was used to extract information from the included studies. The form includes author, year of publication, sample size (number of primary studies), intervention and control group sample sizes, effect estimates with confidence intervals, dose levels, the economic status of the countries, calcium dietary status, and risk status of women. Furthermore, the data extraction process in Microsoft Excel involved transforming each factor's relative risk (RR) to its logarithmic form.

Additionally, the upper and lower confidence intervals were also log-transformed. The standard error (SE) of these confidence intervals was then calculated using the formula SE = (logUCL—logLCL) / 3.92, where logUCL and logLCL represent the logarithmic upper and lower confidence limits. The log-transformed RR and the SE of their corresponding confidence intervals were utilized in the pooled RR estimation to estimate effect sizes.

Quality assessment

The methodological quality of the included studies was assessed using the revised version of the Assessing the Methodological Quality of Systematic Reviews (AMSTAR 2) tool (24). AMSTAR 2 has 16 method-related questions that serve as a critical appraisal tool for systematic reviews and meta-analyses that include randomized or non-randomized studies. Two independent reviewers, EM and MW, critically appraised the included studies using the checklists. As suggested in AMSTAR 2, we rated the confidence in the results of the included reviews as follows: high (no or one non-critical weakness), moderate (more than one critical weakness but no critical flaws), low (one critical flaw with or without non-critical weaknesses), and critically low (more than one critical flaw with or without non-critical weaknesses). The Supplementary Material includes the quality assessment of the studies included in this umbrella review (Supplementary Table S2). The quality of the primary studies included in each of the research syntheses was rigorously evaluated to ensure their robustness and reliability. The list of primary studies in the meta-analyses is in the Supplementary Table S3.

Data synthesis and statistical analysis

After extracting the data using Microsoft Excel, we imported them into STATA version 17.0 for further analysis. This allowed us to perform statistical tests and sensitivity analyses and to apply meta-analytic techniques to ensure robust and reliable results. The findings of the included studies were presented quantitatively and qualitatively to provide comprehensive evidence about the current use of calcium supplementation and its potential effects on the reduction of preeclampsia. A random-effects model meta-analysis was conducted to summarize the effects of calcium supplementation on the reduction of preeclampsia. The estimates were reported as relative risks with corresponding 95% confidence intervals.

Heterogeneity between studies was assessed using the I^2 statistic. The I^2 statistic describes the percentage of variation across different studies due to heterogeneity (25). We used the Q test to estimate I^2, and heterogeneity was classified by I^2. The findings of the I^2 test were classified as low (25% and below), moderate (26–50%), high (51–75%), and very high (above 75%) (25). If there was evidence of heterogeneity, we used a subgroup analysis using different characteristics of the included studies, such as preeclampsia risk status, baseline dietary status, and dosage of calcium supplement. Publication bias was assessed using a funnel plot and an Egger's regression test. An asymmetric funnel plot and an Egger's test with results lower than 0.05 were considered indicative of publication bias. Sensitivity analyses were performed to evaluate the influence of individual studies on the overall pooled effect estimate. This involved systematically removing one study at a time from the meta-analysis and recalculating the overall effect size to observe any significant changes.

Results

This umbrella review of systematic reviews and meta-analyses includes published studies on calcium supplementation for the prevention of preeclampsia. The included studies were systematic reviews and meta-analyses published from 1996 to 2022. A total of 1,157 records were retrieved through electronic searches, and 12 studies were included to estimate the effects of calcium supplementation in the prevention of preeclampsia (Figure 1).

Characteristics of included studies

In the systematic reviews and meta-analyses, the number of primary studies included ranged from a minimum of 3 to a maximum of 29. The minimum and maximum sample sizes in these included studies were 1,324 participants (660 in the experimental group and 664 in the control group) and 27,765 participants (13,896 in the experimental group and 13,869 in the control group), respectively. With the exception of the review by Christina Oh et al. (21) which included quasi-experimental studies, the remaining reviews included only randomized controlled trials in their meta-analyses. Eight systematic reviews and meta-analyses reported the effects of calcium supplementation on the reduction of preeclampsia, regardless of dose, duration, baseline dietary intake, and risk status for preeclampsia. Additionally, systematic reviews and meta-analyses classified calcium-supplemented women based on their risk status for preeclampsia, baseline calcium diet status, dosage, and the economic status of the countries in which the studies were conducted (Table 1).

Effects of calcium supplementation on preeclampsia

Using eight systematic review and meta-analysis studies, the effects of calcium supplementation on the reduction of preeclampsia incidence were reported, regardless of the risk for preeclampsia, baseline calcium diet status, and dose. The results revealed a significant reduction in the risk of preeclampsia in women receiving calcium supplementation [0.53 (95% CI: 0.42, 0.68)] (Figure 2). The level of heterogeneity was high, as evidenced by an I^2 value of = 83.74%. Due to publication bias (p value less than 0.0001), a trim-and-fill analysis was conducted. However, differences in the results were not seen. The Galbraith and funnel plots are also available in Supplementary Figures S1, S2.

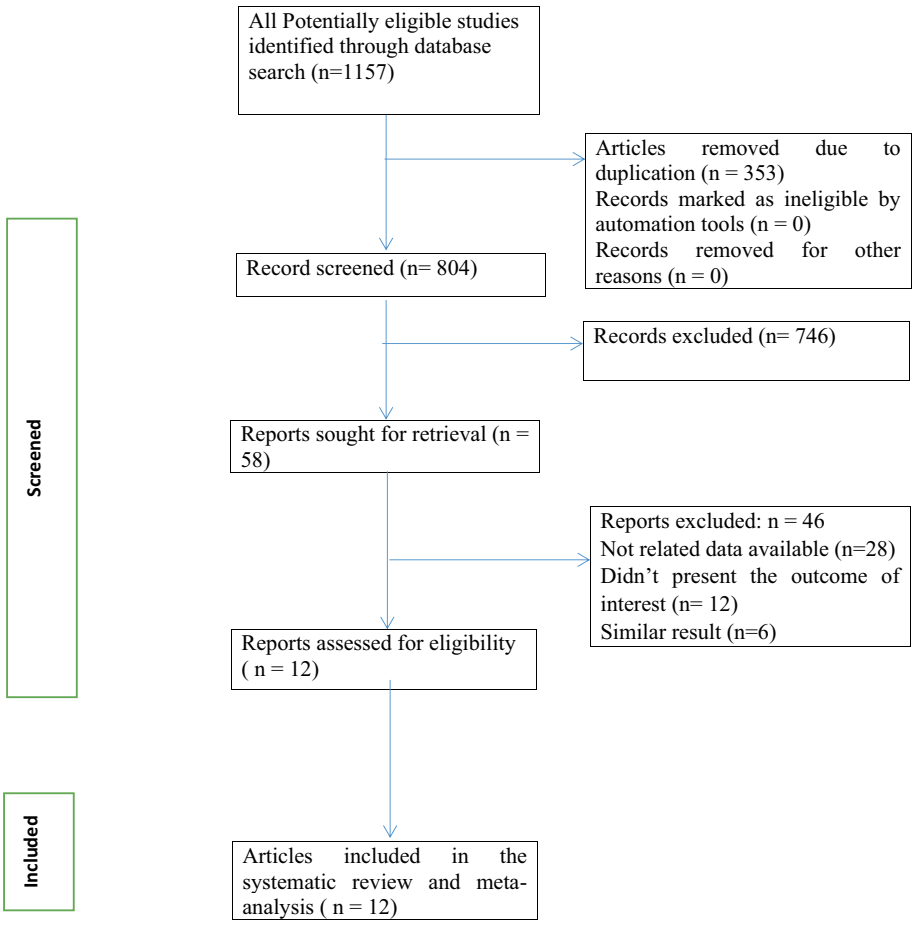

FIGURE 1
Flow chart of study selection for an umbrella review of systematic reviews and meta-analyses of the effect of calcium supplementation on prevention of preeclampsia in calcium supplemented group compared to placebo.

TABLE 1 Characteristics of the included systematic reviews and meta-analyses, 2023.

Author	Year of publication	No primary article	Experimental	Control	Sample size	Status of women
Calcium supplementation despite the risk status of the pregnant women						
Imdad and Bhutta (40)	2012	15	8,231	8,259	16,490	Unknown status
Tang et al. (28)	2014	10	12,399	12,388	24,787	Unknown status
Li-bin An et al. (10)	2015	4	7,252	7,272	14,524	Unknown status
Win Khaing et al. (30)	2017	16	12,876	13,060	25,936	Unknown status
G. J. Hofmeyr et al. (5)	2018	13	7,851	7,879	15,730	Unknown status
Xiaotong Sun et al. (27)	2019	25	13,896	13,869	27,765	Unknown status
Christina Oh et al. (21)	2020	3	660	664	1,324	Unknown status
Mai-Lei Woo et al. (29)	2022	31	NR	NR	17,915	Unknown status
Risk status for preeclampsia						
Tito Silvio P. et al. (26)	2012	3	162	184	346	High risk
Tang et al. (28)	2014	4	4,320	4,345	8,665	High risk
G. J. Hofmeyr et al. (5)	2018	5	281	306	587	High risk
Win Khaing et al. (30)	2017	8	1,140	1,160	2,300	High risk
Xiaotong Sun et al. (27)	2019	12	797	820	1,617	High risk
Tippawan L. et al. (31)	2022	13	NR	NR	26,021	High risk
Dexin Chen et al. (32)	2022	3	99	100	199	High risk
Mai-Lei Woo et al. (29)	2022	17	1,540	2,121	3,661	High risk
José Villar et al. (9)	2000	6	3,146	3,161	6,307	Low risk
Tito Silvio P. et al. (26)	2012	7	5,535	5,524	11,059	Low risk
Tang et al. (28)	2014	6	8,049	8,043	16,092	Low risk
Win Khaing et al. (30)	2017	8	12,876	13,060	25,936	Low risk
G. J. Hofmeyr et al. (5)	2018	8	7,570	7,573	15,143	Low risk
Xiaotong Sun et al. (27)	2019	13	13,119	1,305	14,424	Low risk
Mai-Lei Woo et al. (29)	2022	13	8,423	8,361	16,784	Low risk
Baseline calcium dietary level status						
José Villar et al. (9)	2000	6	907	935	1842	Low baseline
Tito Silvio P. et al. (26)	2012	6	5,958	5,096	11,054	Low baseline
Imdad and Bhutta (40)	2012	10	5,711	5,727	11,438	Low baseline
Tang et al. (28)	2014	6	5,272	5,262	10,534	Low baseline
G. J. Hofmeyr et al. (5)	2018	8	5,331	5,347	10,678	Low baseline
Mai-Lei Woo et al. (29)	2022	24	7,266	7,784	15,050	Low baseline
Tito Silvio P. et al. (26)	2012	6	4,815	4,826	9,641	Adequate baseline
G. J. Hofmeyr et al. (5)	2018	4	2,505	2,517	5,022	Adequate baseline
Mai-Lei Woo et al. (29)	2022	6	2,697	2,698	5,395	Adequate baseline
Tang et al. (28)	2014	2	4,605	4,602	9,207	Unknown
G. J. Hofmeyr et al. (5)	2018	1	15	15	30	Unknown
Level of calcium supplementation dose						
Xiaotong Sun et al. (27)	2019	16	404	445	849	High
Mai-Lei Woo et al. (29)	2022	19	8,249	8,447	16,696	High
Dexin Chen et al. (31)	2022	13	12,942	12,839	25,781	High
Xiaotong Sun et al. (27)	2019	5	137	137	274	Moderate
Dexin Chen et al. (31)	2022	3	678	695	1,373	Moderate
Xiaotong Sun et al. (27)	2019	4	236	235	471	Low

(Continued)

TABLE 1 (Continued)

Author	Year of publication	No primary article	Experimental	Control	Sample size	Status of women
Mai-Lei Woo et al. (29)	2022	12	2035	1714	3,749	Low
Dexin Chen et al. (31)	2022	13	1,498	1,498	1,498	Low
Economic status of the countries						
Win Khaing et al. (30)	2017	12	10,253	10,415	20,668	Developed
Xiaotong Sun et al. (27)	2019	4	4,508	4,526	10,034	Developed
Aamer Imdad et al. (33)	2011	10	5,697	5,708	11,405	Developing
Win Khaing et al. (30)	2017	4	2,641	2,645	5,286	Developing
Xiaotong Sun et al. (27)	2019	21	11,278	11,252	22,530	Developing

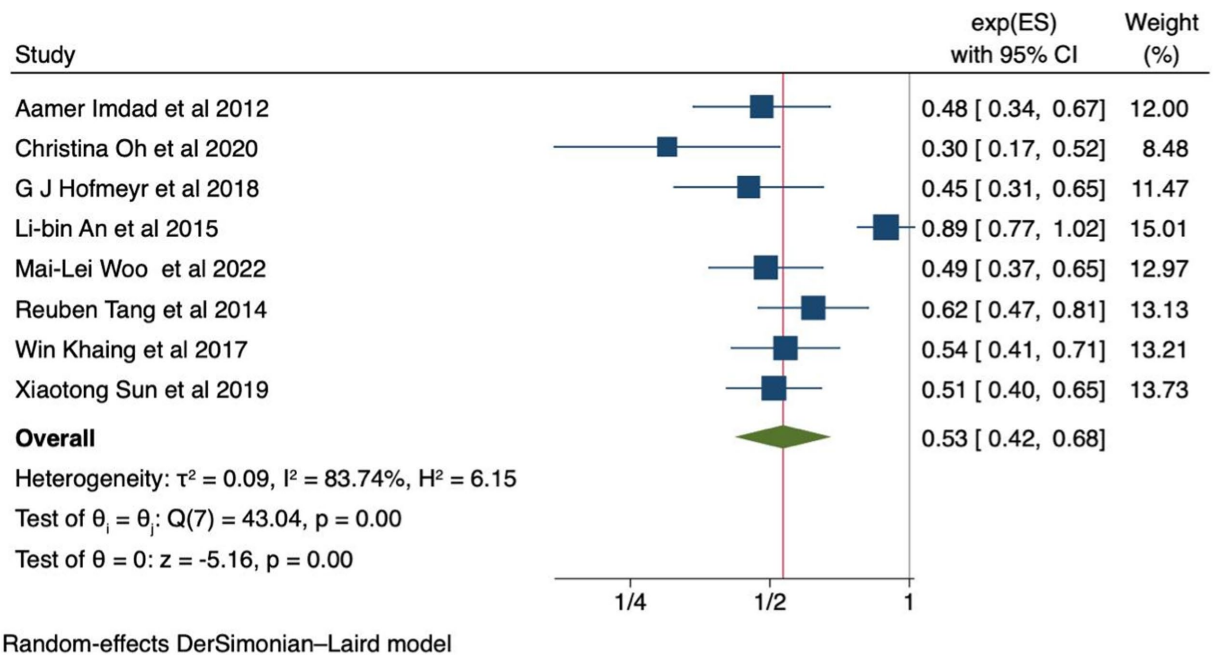

FIGURE 2
Forest plot of calcium supplementation and preeclampsia.

Effects of calcium supplementation based on risk status for preeclampsia

Calcium supplementation in high-risk pregnancies was evaluated in eight studies (5, 26–32). The pooled relative risk showed a 65% reduction in the incidence of preeclampsia [RR 0.35 (95% CI: 0.26, 0.47)] (Figure 3). On the other hand, in seven studies, calcium supplementation in low-risk pregnancies showed 33% of reduction of preeclampsia [RR 0.67 (95% CI: 0.59, 0.77)] (Figure 3). We conducted an Egger's test to evaluate the presence of publication bias, and the obtained *p*-value of 1 indicates that there is no evidence of publication bias. The Galbraith and funnel plots are available in Supplementary Figures S3, S4.

Effects of calcium supplementation based on baseline dietary status

A pooled analysis of six studies found that women with a low baseline diet experienced a 59% reduction in the risk of developing preeclampsia with calcium supplementation [RR 0.41 (95% CI: 0.35–0.48)] compared to those who received a placebo, without heterogeneity between the studies ($I^2 = 0.0\%$). Similarly, calcium supplementation in women with an adequate baseline calcium level, as reported by three studies, was found to be associated with a 33% reduction in the risk of preeclampsia [RR 0.67 (95% CI: 0.56, 0.80)] without moderate heterogeneity ($I^2 = 0.0\%$), compared to placebo (Figure 4). Additionally, the Egger's test yielded a p-value of 1, indicating no publication bias. The Galbraith and funnel plots are available in Supplementary Figures S5, S6, respectively.

Effects of calcium supplementation based on dose

Sun et al. (27) and Chen et al. (32) classified calcium supplementation into three categories: high, moderate, and low doses, while Mai-Lei et al. (29) classified it into high and low. The

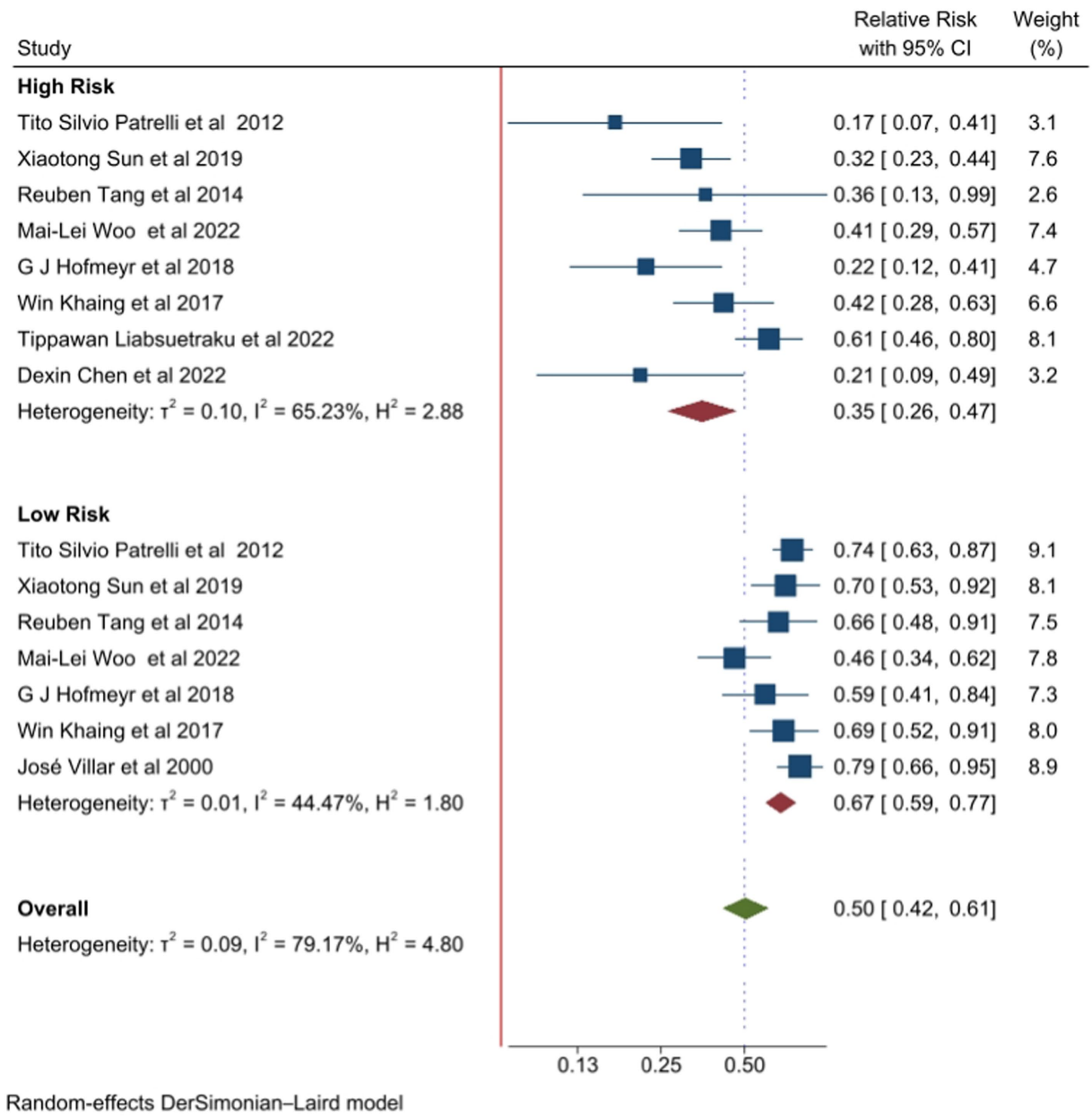

FIGURE 3
Forest plot of calcium supplementation and preeclampsia based on risk status.

pooled analysis of high-dose supplementation showed a steadily decreasing incidence of preeclampsia [RR 0.59 (95% CI: 0.51–0.69)]. The level of heterogeneity was low (I^2 value of 19.05%). The forest plot is available in Figure 5. Furthermore, the Egger's test yielded a *p*-value of 1. The Galbraith and funnel plots are available in Supplementary Figures S7, S8, respectively.

Effects of calcium supplementation based on the economic status of the countries

We conducted a subgroup analysis based on the economic status of the countries using five studies (27, 30, 33). In developed countries, calcium supplementation reduced the risk of preeclampsia by 38% [RR 0.62 (95% CI: 0.41, 0.95)]. In developing countries, a 56% reduction was noted [RR 0.44 (95% CI: 0.36, 0.56)] without heterogeneity (I^2 = 00%) (Figure 6). Additionally, the Egger's test yielded a *p*-value of 1, and funnel plots are also available in the Supplementary Figure S9.

Sensitivity analysis

A leave-one-out sensitivity analysis was performed to identify the impact of each individual study on the overall pooled effect. The results of this sensitivity analysis showed that the pooled finding was not dependent on a single study (Supplementary Tables S4–S6).

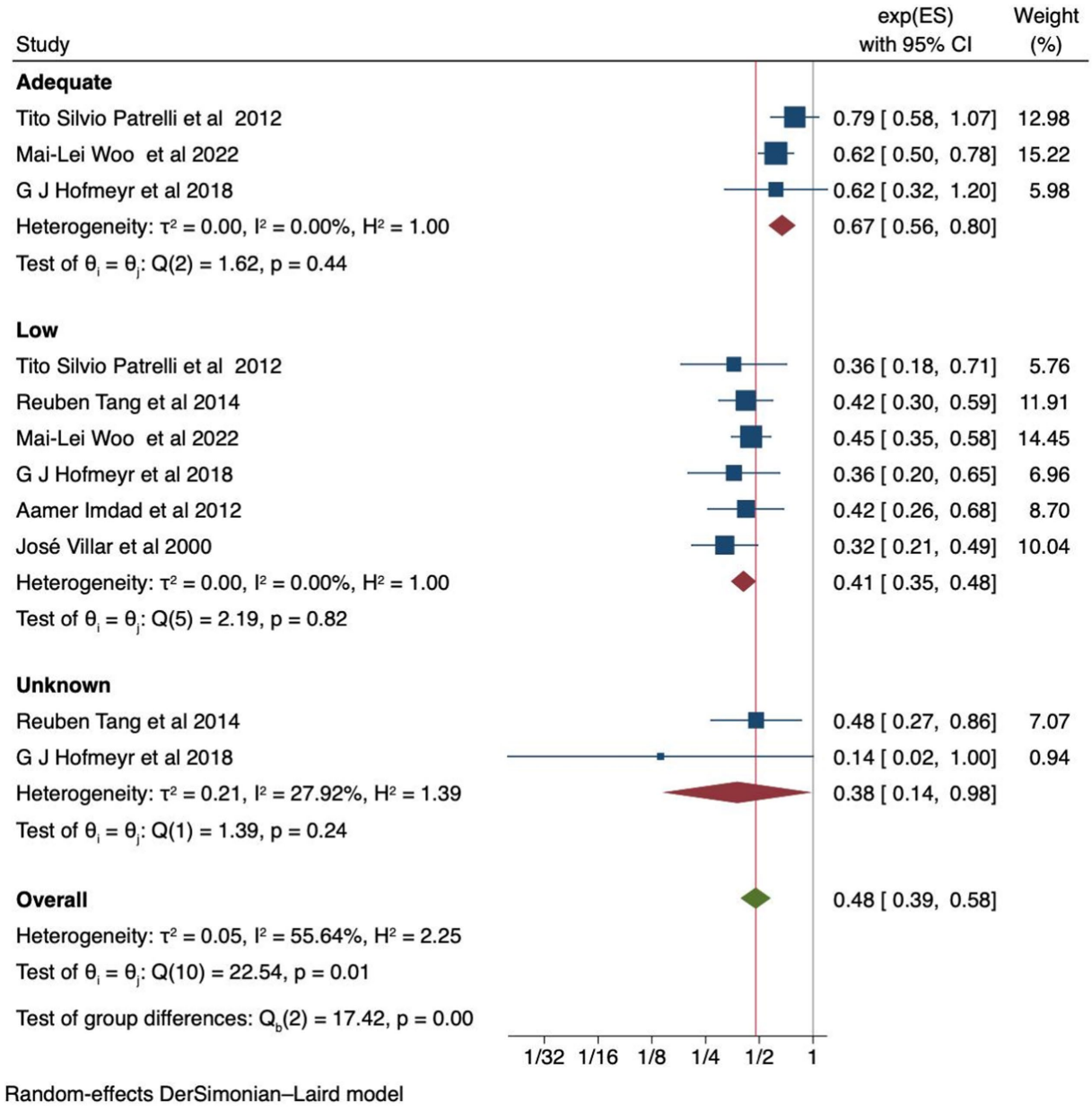

FIGURE 4
Forest plot of calcium supplementation and preeclampsia based on baseline calcium dietary status.

Discussion

Calcium supplementation to prevent preeclampsia is recommended by different guidelines (16, 34). However, there has been no prior umbrella review on using calcium supplementation to prevent preeclampsia. An umbrella review of eight systematic reviews and meta-analyses showed a significant reduction (47%) in the incidence of preeclampsia with the use of calcium supplements compared to control groups. Furthermore, it was observed that calcium supplementation significantly reduced the risk of preeclampsia in both high-risk women (65%) and low-risk women (33%) compared to placebo group.

In this umbrella review, calcium supplementation was associated with a 47% reduction in the incidence of preeclampsia among pregnant women. With the exception of one meta-analysis of multicenter randomized controlled trials, which reported an 11% reduction (10), the remaining seven meta-analyses included in this review consistently demonstrated a significant reduction in preeclampsia incidence in the calcium supplementation group compared to the control or placebo groups (5, 35). The discrepancy in findings may be due to the majority of the included primary studies being from developed or middle-upper income countries (10). Additionally, out of the four studies used for the meta-analysis, only one indicated that pregnant women had a low-calcium diet (10). However, the baseline calcium level is a crucial factor in reducing the incidence of preeclampsia with calcium supplementation.

In the current review, the pooled relative risk of preeclampsia in high-risk women with calcium supplementation compared to

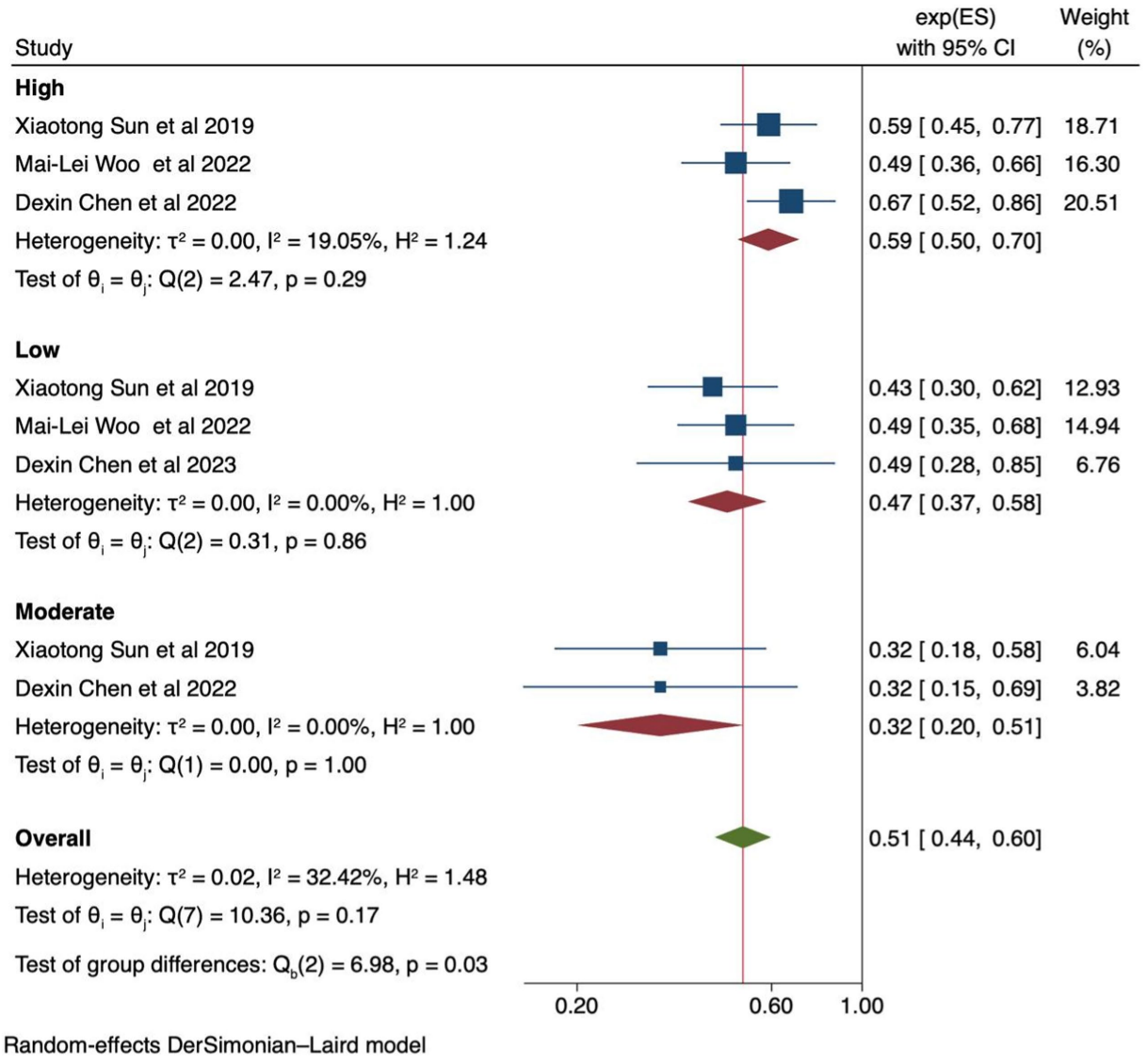

FIGURE 5
Forest plot of calcium supplementation and preeclampsia based on supplemented calcium dose level.

placebo reduced the risk of preeclampsia by 65% [0.35 (95% CI: 0.26, 0.47)] and $I^2 = 65.23$. Although the effect was less pronounced in low-risk women, calcium supplementation still demonstrated a significant reduction in the incidence of preeclampsia (RR 0.67 95% CI: 0.59, 0.77). All the meta-analyses used in this umbrella review, both for high- and low-risk subgroup analyses, agreed on the reduction of preeclampsia incidence with calcium supplementation compared to placebo. However, the high level of heterogeneity observed among high-risk women for preeclampsia might be due to differences in risk definitions, variations in calcium dosage, and discrepancies in the timing of supplementation initiation among the primary studies included in the meta-analysis. Incorporating calcium supplementation into the guidelines for antenatal care, with special attention to high-risk pregnancies, may help to reduce maternal morbidity and mortality.

Recommended calcium intake for pregnant women varies between 900 and 1,200 mg/day, depending on the country (36, 37). However, actual intake among pregnant women often falls short of these recommendations, particularly in developing countries and even in developed countries where calcium-rich foods are readily available and affordable (19, 38). Furthermore, inconsistent results have been observed in systematic reviews and meta-analyses, with no effects in the prevention of preeclampsia on women with adequate calcium serum levels. However, a study conducted by Mai-Lei et al. showed a reduced incidence of preeclampsia. This umbrella review supports their finding that calcium supplementation in women with adequate baseline calcium levels has an effect on the prevention of preeclampsia. This finding suggests a potential need for increased calcium intake during pregnancy or that preeclampsia may involve multiple systems despite normal serum calcium levels. This can be explained by the significant physiological, metabolic, and hormonal changes that occur during pregnancy, which increase calcium demand (10, 11). One key factor is the heightened calcium demand of the developing fetus and growing placenta. This leads to increased

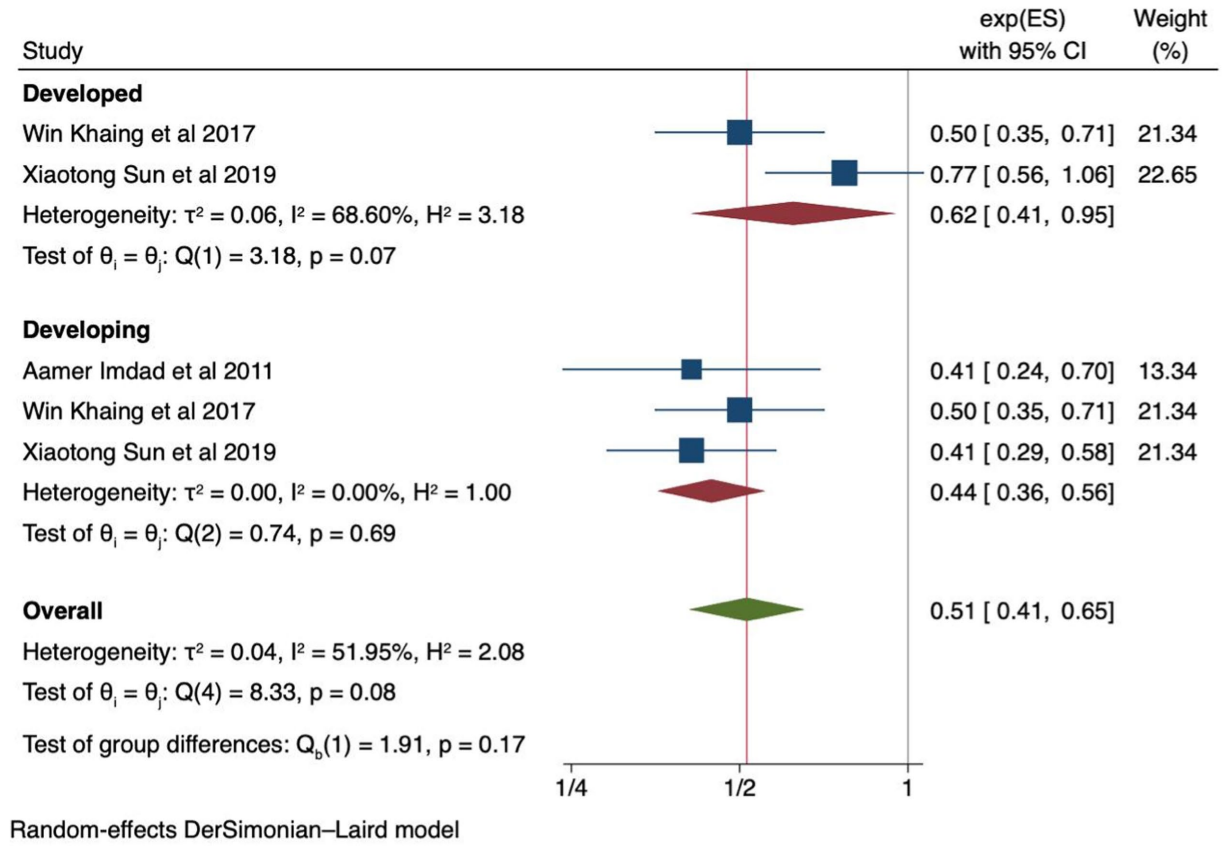

FIGURE 6
Forest plot of calcium supplementation and preeclampsia based on economic status economic status of the countries.

calcium transfer from the mother to the fetus, depleting maternal calcium levels and heightening the risk of preeclampsia (11).

We found that calcium supplementation in women with low baseline calcium levels significantly reduced the risk of preeclampsia compared to placebo. Inadequate calcium intake, defined as consuming less than 600 mg daily, is associated with an increased incidence of hypertensive disorders during pregnancy (39). Moreover, the incidence of preeclampsia decreased significantly in the supplemented group in developing countries (56%) compared to developed countries (38%). This may explain the association between low calcium levels and hypertension (7, 8). Therefore, in regions where the diet is traditionally low in calcium and in developing countries, the recommendation of calcium supplementation during pregnancy is a safe approach. The authors also support the WHO recommendation of calcium supplementation as part of antenatal care in populations with low calcium intake (15).

We also found that high-dose and low-dose calcium supplementation have different effects on decreasing the incidence of preeclampsia. However, no strong signals indicated which group of women was more likely to benefit or be harmed, or which type of administration maximized the effect. Our findings do not suggest any superiority of high-dose over low-dose calcium supplementation. It should be noted that the study conducted by Chen et al. (22) used high-dose calcium supplementation only in high-risk pregnant women and low-dose in low-risk women, which may have influenced the results. High-dose calcium poses challenges in terms of cost, transportation, and storage. Low-dose calcium is equally effective as high-dose supplementation when initiated before 20 weeks of gestation (21). Lower dosages are recommended by the WHO (1.5–2.0 g/day) (16), and the fortification of staple foods with calcium could be considered for populations with low-calcium diets (21).

We categorized the outcomes based on various factors to provide a comprehensive perspective on calcium supplementation. This thorough inclusion of studies enhances the breadth of our review and offers a more detailed understanding of the efficacy of calcium supplementation in preventing preeclampsia.

Our findings should be considered in light of the limitations present in the included studies. The optimal timing of calcium supplementation for the prevention of preeclampsia may not be fully elucidated in the included studies. Variations in the timing and dosage of calcium supplementation across studies could introduce additional heterogeneity and affect the effect estimates. Furthermore, variations in the definition of preeclampsia across studies can lead to inconsistencies in pooled analyses, especially when combining data from trials with different control groups, such as placebo, no treatment controls, and alternative agents used. Additionally, the definition of risk varied between the individual studies and the pooled analysis, leading to potential inconsistencies in the findings. A few primary studies in the meta-analysis included co-supplementation of Vitamin D, which could be a potential source of heterogeneity.

Conclusion

In conclusion, our findings indicate that daily calcium supplementation during pregnancy may be an effective strategy to prevent preeclampsia. The beneficial effect is more pronounced in women with low baseline calcium intake, those at high risk for preeclampsia, and those in developing nations. Considering the guidelines provided by the WHO, calcium supplementation can help reduce the incidence of preeclampsia and its associated complications. Furthermore, fortifying staple foods with calcium will be vital for populations with low-calcium diets.

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

HK: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. EM: Conceptualization, Data curation, Project administration, Resources, Writing – review & editing. MA: Data curation, Investigation, Resources, Validation, Writing – review & editing. BA: Data curation, Investigation, Methodology, Visualization, Writing – review & editing. MB: Formal analysis, Investigation, Methodology, Writing – review & editing. MR: Formal analysis, Writing – original draft, Writing – review & editing. NY: Conceptualization, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing.

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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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2025.1434416/full#supplementary-material

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Case Report: Heterotopic pregnancy after adenomyosis surgery: a rare case highlighting diagnostic pitfalls and clinical insights

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We present an extremely rare heterotopic pregnancy (HP) in a 33-year-old patient with multiple adenomyosis surgeries and bilateral salpingectomy, who conceived via assisted reproductive technology (ART). According to a review of the literature spanning two decades, concurrent intrauterine and extrauterine pregnancies are uncommon, especially in the case of intramural ectopic gestations. On day 31 post-embryo transfer, only an intrauterine pregnancy (IUP) was observed by ultrasound. However, early vaginal bleeding and high-risk factors prompted further ultrasound, revealing an intramural ectopic pregnancy. Though MRI initially misdiagnosed the lesion, reevaluation led to the correct diagnosis. Surgical removal of the ectopic pregnancy was performed while preserving the IUP, which progressed uneventfully. In the late second trimester, follow-up MRI confirmed an intact posterior uterine myometrium, ruling out uterine rupture and resolving lingering concerns. This case illustrates a progression from incomplete ultrasound assessment to an initial misinterpretation of MRI. Ultimately, complementary imaging was vital for accurately diagnosing and managing the intramural ectopic pregnancy, while safeguarding the intrauterine pregnancy by confirming uterine wall integrity later on. Highlighting the complexity of HP in a patient with adenomyosis conceived via ART, it underscores the importance of multiple imaging techniques for early diagnosis and ongoing monitoring in high-risk scenarios. These findings guide clinical strategies and emphasize the critical role of accurate imaging in protecting both maternal and fetal wellbeing.

KEYWORDS

heterotopic pregnancy, intramural pregnancy, adenomyosis, ultrasound, magnetic resonance imaging

1 Introduction

Heterotopic pregnancy (HP) refers to the coexistence of intrauterine and ectopic pregnancies. Rare in natural conception, it becomes more likely with assisted reproductive technologies (ARTs) (1). Ectopic pregnancy rates rise from approximately 1 in 30,000 in natural conception (2) to 1 in 900 after ovulation induction, and 1 in 100 with ART (3). Maternal mortality for HP is approximately 5 per 1,000,000 (4).

Most ectopic pregnancies occur in the fallopian tube (1), but non-tubal varieties (cornual, ovarian, cesarean scar, cervical, intramural, and abdominal) also occur. Intramural pregnancy, involving implantation entirely within the myometrium without connection to the endometrial

cavity or fallopian tube, is extremely rare, particularly when coexisting with an intrauterine gestation. Risk factors include prior uterine interventions (e.g., myomectomy, tubal surgery, or curettage), ART, and adenomyosis. Early diagnosis can be challenging due to variable presentations, and surgical intervention is usually required.

In this report, we describe a patient with adenomyosis, three prior surgeries, and bilateral salpingectomy, who underwent two ART cycles. The first cycle ended in an anembryonic miscarriage; after the second transfer of two embryos, she was diagnosed with a heterotopic pregnancy consisting of concurrent intrauterine and intramural ectopic gestations, the latter eventually arresting. Initially, MRI misinterpreted the intramural lesion as cystic adenomyosis, but subsequent reevaluation established the correct diagnosis. MRI then proved vital for continued monitoring. This case highlights the complementary roles of MRI and ultrasound in managing high-risk pregnancies and offers insights for more effective future monitoring.

2 Case report

We present a 33-year-old woman with a history of three adenomyosis surgeries and bilateral salpingectomy, who underwent two frozen embryo transfers: the first failed, and the second resulted in a heterotopic pregnancy (comprising intrauterine and intramural components). Confirming the intramural component and monitoring the uterine wall throughout pregnancy proved diagnostically challenging (Figure 1).

The patient had a 10-year history of dysmenorrhea, which was managed with diclofenac. In July 2019, she underwent laparoscopic adenomyomectomy, left ovarian cystectomy, right mesosalpinx cystectomy, and bowel adhesiolysis. By 2022, her symptoms had worsened, leading to goserelin treatment on 28th September and open myomectomy on 7th October. The excised mass measured 60 × 60 × 45 mm, extending beyond half the myometrium; both adnexa were densely adherent to the posterior uterus. The rAFS score was 88.

After a failed embryo transfer in May 2023 and subsequent dilation and curettage (D&C) in June, she underwent combined laparoscopy and hysteroscopy in September, including bilateral salpingectomy, adhesiolysis, hysteroscopic lesion resection and biopsy, and laparoscopic coagulation of endometriosis. Dense adhesions formed a sealed pelvic cavity, and both tubes were rigid and narrowed, with a 30 × 20 mm hydrosalpinx on the left. Methylene blue showed no patency; the left tubal score was 21/24, and the rAFS score was 22.

On 14 March 2024, the patient underwent another embryo transfer. At 13th April (31 days post-transfer), ultrasound confirmed an intrauterine pregnancy (gestational sac 24.4 × 22.2 × 12.9 mm, embryo 7.2 mm) with slight bleeding. At 10 weeks (day 69 post-transfer), a 1.5 T MRI (United Imaging uMR560) confirmed an intrauterine pregnancy (gestational sac 62 × 41 × 70 mm, CRL 34 mm) but initially misidentified a 23 × 22.7 × 21 mm intramural pregnancy as cystic adenomyosis. Routine T2-FSE sequences obscured the intramural embryo, but a smaller-field T2-FSE revealed an 8.9 mm embryo in the intramural sac. A 3D T1 axial sequence partially depicted the embryo despite moderate signal limitations (Figure 2).

On the same day, transvaginal ultrasound showed an enlarged intrauterine sac (38.9 × 57.6 × 65 mm) with an embryo (CRL 38.9 mm) and cardiac activity. A smaller posterior myometrial lesion (23.7 × 18.9 mm) contained a 10.7 mm embryo-like structure without a yolk sac or cardiac activity, which was attached to the serosal layer with minimal myometrium and abundant blood flow. A 43.6 × 34.4 × 54.3 mm fluid-filled cystic area was noted near the right

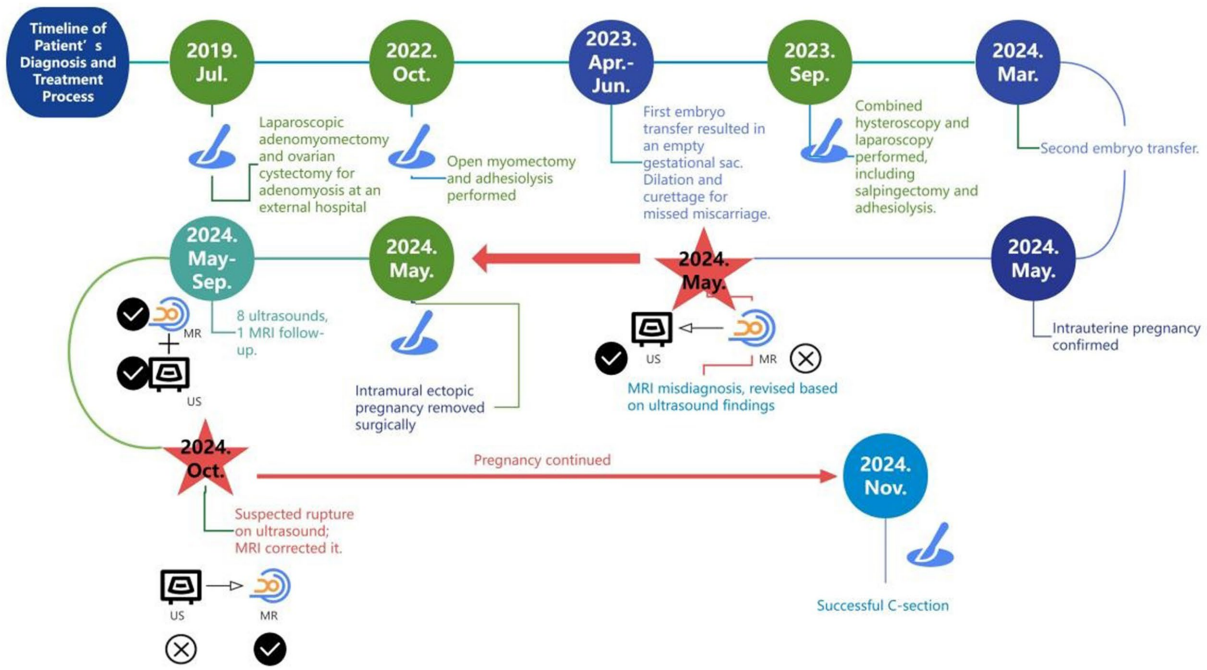

FIGURE 1
Timeline of the patient's diagnosis and treatment process.

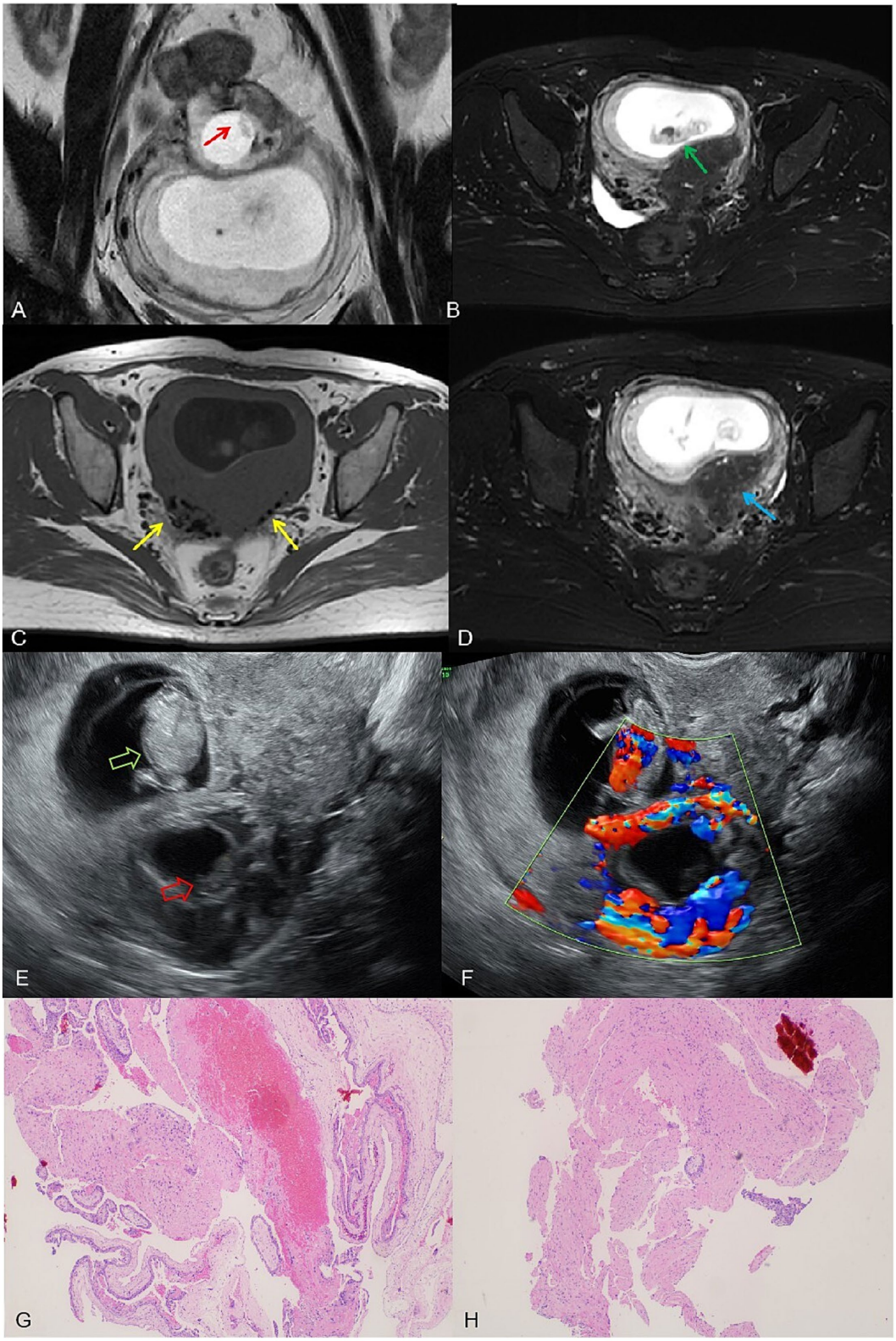

FIGURE 2
(A) A complete embryonic bud, measuring 8.9 mm, visible within the intramural gestational sac on the small T2 FSE sequence (red arrow). **(B)** A normal intrauterine pregnancy with a fetus measuring a crown-rump length of 34 mm on the T2-fs-FSE sequence (yellow arrow). **(C)** T1WI shows black speckled hypointense signals, considering postoperative changes (red arrow). **(D)** T2-FSE-SPAIR reveals residual adenomyosis with visible small cysts (yellow arrow). **(E)** Ultrasound image shows the intrauterine pregnancy fetus (green hollow arrow) and the intramural pregnancy fetus (red hollow arrow). **(F)** Color Doppler ultrasound image: cardiac activity detected in the intrauterine fetus, but absent in the intramural fetus; ring-shaped blood flow signals can be observed around the intramural gestational sac. **(G,H)** Postoperative pathological slides showing chorionic tissue (hematoxylin and eosin stain, magnification ×40).

ovary. These findings led to a multidisciplinary MRI review, which confirmed intramural ectopic pregnancy. MRI also revealed adenomyosis, minor cystic changes in the lower uterine segment, and postoperative scarring (low-signal areas). The cervix measured 37 mm, showing stromal thickening likely due to pregnancy hormones. The patient underwent exploratory laparotomy under combined spinal-epidural anesthesia. A 5 × 4 cm intramural mass was found on the posterior uterine wall, densely adhered to the surrounding tissues. After careful adhesiolysis, the ectopic gestational tissue was excised from the myometrium, and the uterus was repaired in two layers with absorbable sutures. Both fallopian tubes were absent due to prior bilateral salpingectomy. Intraoperative blood loss was approximately 200 mL. The patient had an uneventful recovery and was discharged in stable condition.

From 27 May to 30 September 2024, the patient had nine ultrasounds as part of prenatal care, including cervical length assessment and uterine scar surveillance. By 30th September, the posterior uterine wall's thinnest area had measured 3 mm. On 11th October (32 weeks), MRI showed that the myometrium was thinned to 2 mm but remained intact, and a 50 × 16.3 × 67 mm low-signal region in the left posterior wall. The cervix was 27.4 mm, the anterior placenta was normal, and fetal measurements included a BPD of 81 mm and an HC of 293.9 mm (Figures 3A,B).

On 28th October (36 weeks), ultrasound revealed a hypoechoic zone between the posterior uterine serosa and myometrium, which suggested an intramyometrial blood sinus or partial rupture. The same-day MRI (United Imaging 1.5 T uMR680) confirmed a dilated blood sinus with no rupture. A 70 × 22 × 90.9 mm low-signal area in

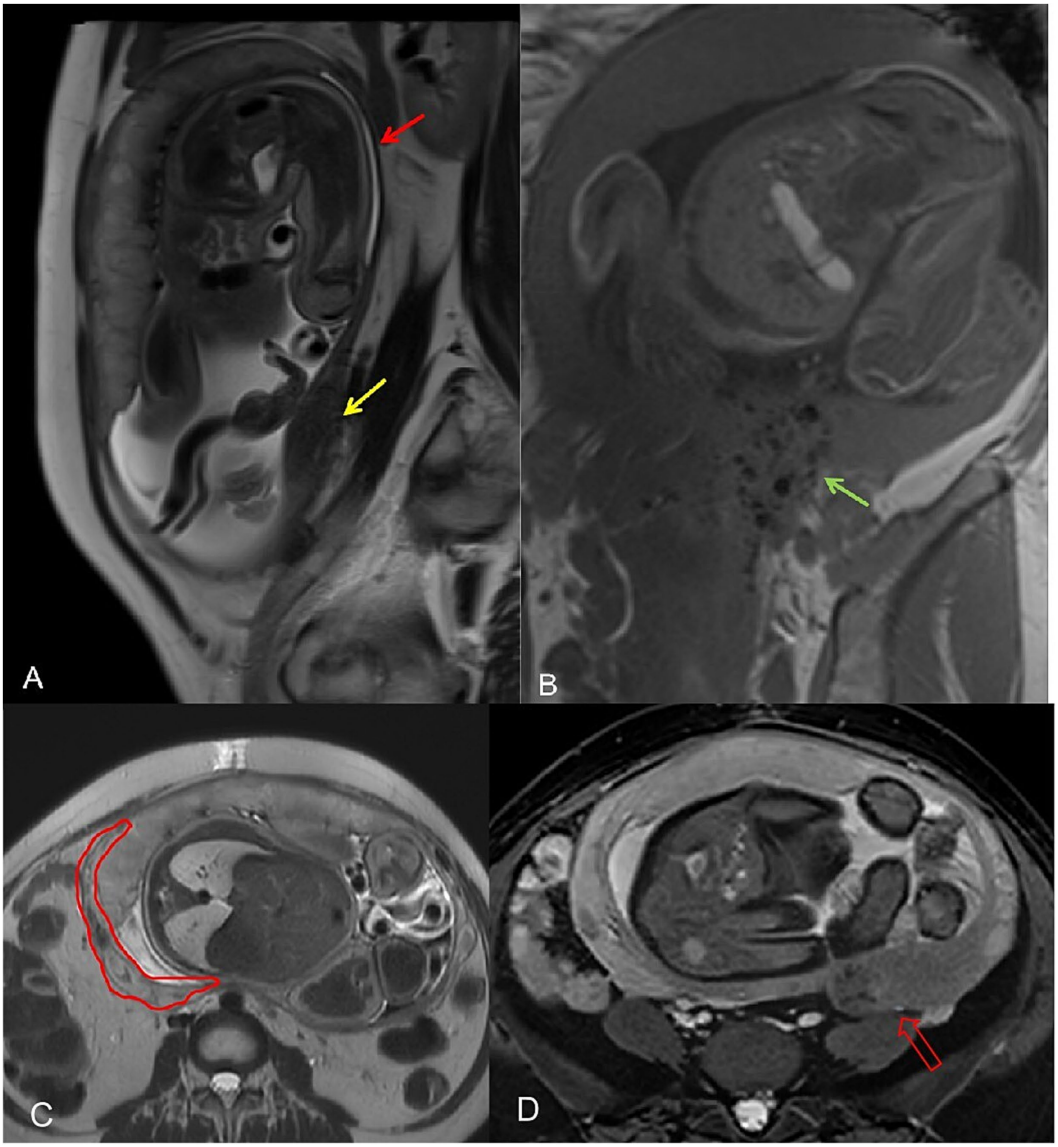

FIGURE 3
(A) The thinnest area of the myometrium in the posterior uterine walled arrow. A hypointense area is observed in the myometrium of the left posterior wall, considered to be an adenomyosis lesion (yellow arrow). **(B)** Postoperative speckled hypointense changes (green arrow). **(C)** The red outline indicates thickened intramural vessels, which were mistakenly interpreted as myometrial rupture on ultrasound. **(D)** The red hollow arrow points to the adenomyosis lesion area and the surrounding black speckled postoperative changes.

the left posterior uterine wall contained several cystic foci, likely adenomyosis with postoperative changes (Figures 3C,D).

On 1st November (35 weeks), the patient underwent a cesarean section, delivering a healthy female infant (Apgar scores 10 and 10 at 1 and 5 min, respectively). The placenta was delivered intact, and localized thinning was noted in the posterior midline uterine wall (Figure 4). Estimated blood loss was 400 mL.

3 Discussion

Ectopic pregnancy (EP) remains a significant cause of morbidity and mortality in early pregnancy. Its signs and symptoms can be subtle; up to 50% of patients may initially be asymptomatic (5–7). The two primary symptoms—abdominal pain and vaginal bleeding—can also occur in intrauterine pregnancies (IUPs) or threatened miscarriages, often complicating diagnostic accuracy. Even when both symptoms are present, an EP diagnosis may still be overlooked (8). Although the primary function of β-hCG is to confirm pregnancy and evaluate early gestational development, it does not indicate the implantation site if there is a concurrent viable IUP (1). Ultrasound serves as the most important diagnostic tool. However, identifying an intrauterine embryo on ultrasound may give a false sense of security regarding a normal pregnancy, thereby overshadowing the potential for an ectopic pregnancy (9). In a study by Jeon et al. (7), only 16% of asymptomatic heterotopic pregnancies were diagnosed early via transvaginal ultrasound in IVF patients. This increases the risk of rupture, life-threatening hemorrhage, and possible hypovolemic shock. Therefore, early and accurate identification of ectopic pregnancy is crucial for improving both maternal outcomes and preserving fertility (10). Alongside imaging, monitoring pregnancy risks, increasing the frequency of early pregnancy ultrasound and closely observing clinical symptoms are all essential.

The patient in this case had multiple risk factors for EP: adenomyosis, a history of multiple surgeries (including bilateral salpingectomy), and two cycles of assisted reproductive technology (ART) (11–13). Adenomyosis not only indicates structural changes in the uterus and compromised endometrial integrity but is also associated with implantation failure and an increased risk of ectopic pregnancy (14). Although surgical interventions may alleviate symptoms and improve fertility, they can also weaken the uterine wall, potentially creating myometrial defects that predispose patients to intramural or other forms of ectopic pregnancy. ART further elevates the risk of multiple gestations and ectopic implantation; women undergoing ART have an approximately 8-fold higher risk of EP (15). Additionally, mechanical manipulations during embryo transfer and uterine contractions induced by luteal support may encourage ectopic embryo implantation. Recognizing these risk factors is crucial, as they align with known risk factors for both heterotopic pregnancy (HP) and EP, including pelvic inflammatory disease, a history of ectopic pregnancy, prior tubal surgeries, endometriosis, the use of intrauterine devices (IUDs), advanced maternal age, smoking, and infertility treated with ART (6, 16, 17).

In this case, frequent imaging during the early pregnancy phase enabled the timely detection of the intramural pregnancy without severe complications. Careful and thorough imaging is vital for identifying EP at an early stage. Locating an intrauterine pregnancy does not exclude the possibility of an ectopic pregnancy, and vice versa (18). The patient's IUP was initially diagnosed on ultrasound at 31 days post-embryo transfer. Early vaginal bleeding and multiple risk factors prompted closer ultrasound surveillance, leading to the diagnosis of HP at day 54 post-transfer. Thus, detailed clinical history and imaging evaluation play equally important roles (17–20). Although ultrasound remains the frontline imaging modality for pregnancy, magnetic resonance imaging (MRI) can further delineate complex anatomy and guide treatment planning (17). MRI is increasingly utilized in complicated pregnancies, as it offers high-resolution anatomical detail. Intramural pregnancy typically appears on MRI as a cystic lesion within the myometrium, often surrounded by a rim of hypointense myometrium; an embryo or a gestational sac-like structure may be identifiable within the lesion.

In this case, the initial MRI failed to detect the intramural pregnancy, largely due to the lack of baseline imaging prior to conception and partial volume effects that obscured the embryo (Supplementary Data S2: The Mechanism of Misdiagnosis of MRI).

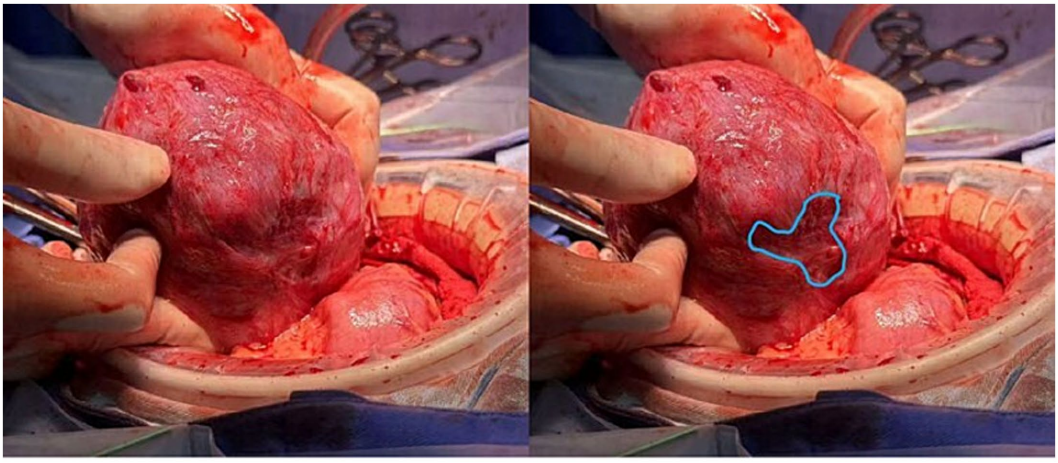

FIGURE 4
Intraoperative view of the uterus after delivery of the fetus and placenta. The posterior myometrium was routinely examined. A well-defined area of myometrial thinning was delineated (outlined in blue), with no signs of uterine wall rupture observed.

This underscores the importance of high-resolution, multi-sequence imaging. In later pregnancy, MRI can also compensate for ultrasound's limitations, particularly in assessing uterine wall integrity, placental location, and lesion progression. Here, MRI was instrumental in ruling out uterine rupture and informing subsequent pregnancy management. Ultrasound excels at early pregnancy detection and real-time observation of the embryo; however, MRI provides crucial supplemental information in complex scenarios (20). Indeed, ultrasound correctly identified HP in this case, while MRI initially misdiagnosed the lesion as cystic. Contributing factors to the misdiagnosis included an incomplete clinical history, inadequate review of ultrasound findings, the small size of the failed embryo (approximately 10 mm in length and 3 mm in thickness), and the relative rarity of early pregnancy MRI, which may limit radiologists' experience with diagnosing blastocyst morphology. Nevertheless, MRI proved invaluable later on by compensating for ultrasound "blind spots." At 33 weeks, MRI confirmed intact myometrial continuity, enabling her pregnancy to continue and alleviating the patient's anxiety. At 35 weeks, when ultrasound suggested possible partial myometrial rupture but was hindered by fetal positioning, MRI showed that the uterine wall vascularity was increased but intact, thereby ruling out rupture. Three days later, the patient underwent an elective cesarean delivery.

Throughout this case, imaging was pivotal in diagnosis, guiding treatment decisions, and follow-up. Heterotopic pregnancy (HP) significantly differs from standard EP in that preserving the IUP is paramount. Methotrexate is contraindicated, making treatment more complex (21, 22). Once an EP is diagnosed, prompt intervention is ideal to prevent rupture and emerging complications. For unruptured ectopic gestations, local injection therapies (e.g., KCl or hypertonic glucose, excluding methotrexate) or surgical intervention can be considered. Surgical removal of an ectopic pregnancy is generally safe and does not elevate the risk of fetal loss in the concurrent IUP (7). Moreover, surgical treatment allows direct removal of the ectopic mass while preserving the intrauterine pregnancy.

In summary, a comprehensive imaging strategy—combining ultrasound and MRI—is crucial for diagnosing, managing, and following up on heterotopic pregnancies. By integrating clinical risk factors with detailed imaging findings, clinicians can optimize patient outcomes and mitigate the potential complications associated with HP. To translate the insights from this case into practical guidance for clinical decision-making, especially in the context of assisted reproductive technology (ART) and complex uterine anatomy, we propose the following key takeaways for clinicians:

1 Ultrasound remains the first-line imaging modality for early pregnancy evaluation due to its accessibility, safety, and real-time capability in detecting intrauterine or ectopic gestations.

2 Upgrade to MRI when:

(1) Ultrasound findings are inconclusive or ambiguous, particularly in patients with uterine abnormalities such as adenomyosis or surgical scars.
(2) There is a discrepancy between clinical presentation and imaging findings, or suspicion of rare ectopic types (e.g., interstitial and intramural).
(3) Detailed anatomical evaluation of uterine wall integrity, lesion morphology, or placental location is needed in late gestation.

3 Continue with ultrasound when:

(1) Pregnancy findings are clear and consistent with the clinical scenario.
(2) Serial monitoring of IUP development or postoperative recovery is necessary.

4 In ART patients with complex uterine anatomy:

(1) Maintain a high index of suspicion for HP, even with confirmed IUP.
(2) Recognize adenomyosis, prior surgery, and ART as key risk factors for ectopic gestation.
(3) Combine clinical history, β-hCG trends, and serial imaging for accurate diagnosis.
(4) Acknowledge that early MRI may miss subtle gestational structures if protocols are not tailored for pregnancy.

5 Apply a phased imaging strategy:

(1) Early pregnancy: Use ultrasound for localization and viability.
(2) Mid-to-late pregnancy: Use MRI when ultrasound is compromised or high-risk features emerge.
(3) Postpartum/follow-up: Use ultrasound routinely; reserve MRI for deep or complex lesion evaluation.

6 In cases of diagnostic uncertainty:

(1) Repeat imaging with adjusted parameters.
(2) Document interpretive limitations.
(3) Consider surgical evaluation if imaging is non-diagnostic but clinical concern persists.

From the patient's perspective, initial diagnostic uncertainty and misdiagnosis were sources of anxiety and distress. However, once a definitive diagnosis was made and effective treatment was administered, the patient expressed a sense of relief and satisfaction. Her experience highlights the psychological impact of delayed diagnosis and underscores the importance of clear doctor–patient communication and the complementary use of various imaging modalities when dealing with rare or atypical diseases.

4 Conclusion

This case report presents a rare instance of concurrent intrauterine and ectopic pregnancy following IVF-ET in a patient with a history of adenomyosis and multiple pelvic surgeries. The diagnostic and management challenges underscore the critical importance of multimodal imaging in high-risk pregnancies. Future research should

aim to optimize imaging protocols and develop personalized management strategies for patients with adenomyosis and postoperative conditions, thereby improving pregnancy outcomes and enhancing maternal and neonatal safety.

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 humans were approved by Ethics Committee Approval letter of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The 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

QZ: Investigation, Writing – original draft, Supervision, Conceptualization, Formal analysis. SC: Validation, Investigation, Data curation, Software, Writing – original draft. QW: Project administration, Methodology, Supervision, Writing – original draft, Software. JX: Validation, Writing – original draft. HH: Project administration, Data curation, Supervision, Conceptualization, Writing – review & editing, Resources.

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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.2025.1606074/full#supplementary-material

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