CHANGING BACKGROUNDS AND GROUNDBREAKING CHANGES: GYNECOLOGICAL SURGERY IN THE THIRD DECADE OF THE 21ST CENTURY

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CHANGING BACKGROUNDS AND GROUNDBREAKING CHANGES: GYNECOLOGICAL SURGERY IN THE THIRD DECADE OF THE 21ST CENTURY

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Editorial: Changing backgrounds and groundbreaking changes: Gynecological surgery in the third decade of the 21st century

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KEYWORDS

gynecological surgery, surgical complication, pregnancy, laparoscopy, placenta increta, primum non nocere, lymphadenectomy, contained morcellation

Editorial on the Research Topic
Changing backgrounds and groundbreaking changes: Gynecological surgery in the third decade of the 21st century

By Watrowski R, Kostov S and Sparić R. (2022) Front. Surg. 9: 1060503. doi: 10.3389/fsurg.2022.1060503

In the third decade of the 21st century, gynecological surgeons are faced with new technical developments but also with new expectations. The surgical evolution is reflected by individualized approaches to patients and treatments (1), increasing role of "omics" and advanced imaging methods for surgical decisions (2, 3), the substantial shift from vaginal to laparoscopic concepts in urogynecology (4–6), increasing role of the robotic-assisted surgery or increased awareness about surgical complications and their prevention (7).

These favorable developments do not eliminate unresolved problems of the past (e.g., the role of the human factor in surgical complications) and add new pitfalls and uncertainties, e.g., the controversy about laparoscopic tissue morcellation (7), the doubts about the oncological risks and long-term results of minimally invasive procedures following the LACC trial (8–10), or issues regarding fertility preservation in oncological patients (11).

We welcome several high-quality articles within this Research Topic that perfectly illustrate these chances and challenges. The publication by *Alkatout* et al. introduces this topic by showing the milestones and pitfalls of gynecological laparoscopy from its beginnings to the present day. This contribution opens our Research Topic and can

serve as a compendium of historical knowledge, but also as a source of reflection that technical evolution alone does not absolve its pioneers from personal defeats and that each stage of development of gynecology brings with it challenges and risks that were unpredictable in the early days of laparoscopy. *Alkatout* et al. remember in the first sentence of their article that the maxim 'primum non nocere', originating from the Hippocratic tradition, remains relevant also with regard to current and future developments in surgery. Notably, we live in a time when many of the principles of the Hippocratic Oath—that formed a bedrock of medical ethics for centuries—are being increasingly ignored or overshadowed by non-scientific and non-medical concepts. Gratifyingly, and in keeping with the Research Topic, many authors have focused on the modern implementation of Hippocarates' principle: 'When dealing with illness, practice two things: either help or do not harm the patient' (12).

The papers published in this Research Topic address different laparoscopical approaches (classical, natural orifice, single-port), different areas of gynecologic surgery (urogynaecology, oncology) or deal with specific problems that are the price for the development of minimally invasive approaches, e.g., morcellation risks or safety concerns when performing laparoscopy in pregnancy. Importantly, all authors have proposed constructive solutions that go beyond simply reporting of difficulties. For instance, *Tinelli* et al. describe the management of an external iliac vein injury during laparoscopic pelvic lymphadenectomy, supplementing a didactic surgical video with case report and literature review; *Wang* et al. evaluated the utility of a novel multi-port system for contained laparoscopic morcellation; *Yang* et al. developed a nomogram predicting lymph node metastasis in early-stage cervical cancer.

One of the hallmarks of modern gynecological surgery is the changed paradigm of the surgical approach to pelvic organ prolapse (POP). While vaginal techniques, including transvaginal mesh applications, flourished in the late 20th century, laparoscopic concepts have rapidly evolved over the past two decades. Modern surgeons "discovered" fixation points for mesh or autografted tissue at different levels of the lateral pelvic wall, leading to the development of techniques like pectopexy or laparoscopic lateral suspension (LLS), both applicable *via* the classical and robotic laparoscopic approaches, and thus significantly expanding the therapeutic spectrum for POP beyond the laparoscopic sacrocolpopexy. *Dällenbach* compares the LLS vs. laparoscopic sacrocolpopexy for apical pelvic organ prolapse, and postulates the LLS as the new "gold standard". We are confident that this not entirely uncontroversial opinion can stimulate scientific debate and sharpen the senses of clinicians regarding the best current treatment for POP (4, 6).

A very special feature of this Research Topic is that every second article is dedicated to surgical interventions in women who are pregnant or want to preserve their fertility. The latter aspect in regard to young patients diagnosed with cervical cancer has been reviewed by *Theofanakis* et al. The challenge of any surgical procedure during pregnancy is that the preservation of the pregnancy should not significantly compromise the safety of the mother or the effectiveness of the treatment (13). In line with these considerations is the preliminary study of *Han* et al. reporting of positive experiences with laparoscopic removal of adnexal mass during pregnancy. The study by *Zhang* et al. applies a retrograde perspective to analyze peripartum outcomes in 12 patients with a prior transluminal endoscopic transvaginal natural opening (vNOTES), including 10 cases of vaginal delivery and 2 cases of cesarean section. A vaginal fornix incision during vNOTES does not appear to compromise the safety and feasibility of vaginal delivery in a subsequent full-term pregnancy. We believe this small study will enhance interest in vNOTES and stimulate larger, multi-center evaluations. Finally, two papers are dedicated to two serious complications of pregnancy and childbirth (which often occur concomitantly): the spectrum of placenta increta and placenta previa. *Fu* et al. describes a parallel loop binding compression suture as an an effective and safe method to reduce postpartum bleeding in women with placenta previa complicated with placenta increta. *Guan* et al. presents the results of a multi-center study evaluating the innovative treatment of placenta increta left *in situ* by high-intensity focused ultrasound ablation. Both articles show therapeutic options of potentially vital importance.

We thank all authors who contributed to this research topic—those whose contributions were accepted, but also those whose contributions were rejected—for their efforts and their openness to reviewer comments. We thank the reviewers for their insightful comments and constructive criticism. Finally, we thank the editorial team for their support in handling the manuscripts.

We sincerely hope that the works that constitutes this Research Topic will help clinicians make the right decisions, inspire researchers to further evaluate their surgical practice, and in view of the work of *Alkatout* et al. encourage someone to re-read the original Hippocratic Oath.

Author contributions

RW, RS, SK: conceptualization. RW, RS: writing–first draft. RW: writing final version, literature search. RW, RS, SK: reviewing of the final manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Parallel Loop Binding Compression Suture, a Modified Procedure for Pernicious Placenta Previa Complicated With Placenta Increta

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Objective: To evaluate the efficacy and safety of parallel loop binding compression suture of the lower uterus during cesarean section in pernicious placenta previa complicated with placenta increta.

Methods: This retrospective study was performed in patients with pernicious placenta previa complicated with placenta increta or percreta between November 2014 and December 2020 at the Qilu Hospital of Shandong University. Patients underwent parallel loop binding compression suture surgery were defined as study group, and patients underwent traditional surgery with figure-of-eight sutures as the main hemostatic method were defined as control group. Postpartum hemorrhage was evaluated as the primary outcome. The secondary outcomes included age, gestational weeks, operative time, fetal childbirth time, prevention of hysterectomy, blood transfusion, duration of postoperative catheterization, duration of antibiotic treatment, and postoperative hospitalization (days). Additionally, neonatal outcomes were evaluated.

Results: A total of 124 patients were enrolled in the study, including 38 patients receiving parallel loop binding compression suture surgery in the study group, and 86 patients in the control group. With parallel loop binding compression suture, the average operation time was significantly reduced (109.0 ± 33.5 vs. 134.4 ± 54.2 min, $p = 0.00$), and the volume of blood lost were also decreased (2152.6 ± 1169.4 vs. 2960.5 ± 1963.6 ml, $p = 0.02$), which correspondingly reduced RBC transfusion (7.2 ± 3.5 vs. 10.3 ± 8.7 units, $p = 0.03$) and FFP transfusion (552.6 ± 350.3 vs. 968.0 ± 799.8 ml, $p = 0.00$). The fetal childbirth time was extended (14.1 ± 5.6 vs. 11.0 ± 8.0 min, $p = 0.03$), however, there was no increase in NICU admission rates (36.9 vs. 34.9%, $p = 0.83$). Except for one premature infant (32 weeks) death in the control group, all infants at our hospital were safely discharged after treatment.

Conclusion: Parallel loop binding compression suture is an effective, swift, practical, and safe method to reduce postpartum bleeding in women with pernicious placenta

previa, complicated with placenta increta. Besides, it has no adverse effects on newborns.

Keywords: parallel loop binding compression suture, pernicious placenta previa, placenta increta, cesarean section, newborns

INTRODUCTION

Placenta previa is an obstetric complication in which the placenta is partially or wholly inserted in the lower uterine segment (1, 2). In the past decades, women have increasingly opted for cesarean section (CS), leading to an increasing incidence of placenta previa (3, 4). Globally, postpartum hemorrhage accounts for the death of 140,000 women annually (5). Placenta previa is an independent risk factor for maternal hemorrhagic morbidity (6) and can also lead to morbidity and mortality in pregnant women and neonates (7).

Pernicious placenta previa is a special type of placenta previa, in which the placenta attaches to previous cesarean delivery scars (8), remaining a challenge in obstetric practice. Placenta increta, whereby the villi invade the myometrium, is a type of accreta placentation (9). Pernicious placenta previa complicated with placenta accreta, particularly placenta increta or percreta, has a high risk of maternal hemorrhage prior to, during, and after CS (10).

In previous decades, various surgical methods have been proposed to control bleeding associated with placenta previa, including hysterectomy (11–13). Nevertheless, during the operative treatment of pernicious placenta previa, reducing blood loss remains a challenge. However, there is also the strong desire to preserve the uterus and fertility; therefore, an alternative to hysterectomy is required. This study aimed to evaluate the effectiveness of parallel loop binding compression suture of lower uterus regarding control of bleeding and prevention of hysterectomy during cesarean section in pregnant women with pernicious placenta previa, complicated with placenta increta.

PATIENTS AND METHODS

Patients

Between November 2014 and December 2020, patients at Qilu Hospital of Shandong University fulfilled with the following criteria were enrolled in this study: (1) diagnosis of pernicious placenta previa by ultrasound and/or magnetic resonance imaging (MRI), the specific image performance is shown in **Figure 1**; (2) placenta increta or placenta percreta complication. Emergency surgeries were excluded from the study. Patients underwent parallel loop binding compression suture surgery were defined as study group, and patients underwent traditional surgery with figure-of-eight sutures as the main hemostatic method were defined as control group. The application of this suturing technique was approved by the hospital's ethics committee, and all patients provided written informed consent before surgery.

Data Collection

The following clinical characteristics of patients and newborns were routinely collected, including age, history of gestation, number of cesarean sections, time since last CS (years), weeks of gestation, use of balloon occlusion of the abdominal aorta, operation time (min), adjunctive hemostatic procedures, blood transfusion (units), estimated blood loss (mL), duration of indwelling urethral catheter (days), postoperative hospital stay (days), duration of antibiotic use (days), neonatal birth weight, Apgar scores at 1- and 5 min, and duration of hospitalization (days) at the neonatal intensive care unit (NICU).

Normally distributed data are presented as means ± standard deviation and medians and interquartile ranges (IQRs), whereas categorical variables are expressed as numbers and/or percentages. Statistical analyses were performed using SPSS 26.0 (IBM SPSS Statistics, Armonk, NY, USA). Significance levels were $^{*}p < 0.05$; $^{**}p < 0.01$.

Parallel Loop Binding Compression Suture Procedure

An experienced multidisciplinary team involving anesthetists, interventional radiologists, hematologists, obstetricians, gynecologists, and neonatologists was consulted to prepare for the surgery. The decision whether to preset the abdominal aorta balloon was made by senior obstetrics professionals based on imaging and clinical characteristics of the patient. Balloon catheter occlusion of the abdominal aorta was performed by an interventional radiologist on the day of surgery. Elective cesarean section was preferentially routinely performed during weeks 35–38, but it also depended on the patient's clinical symptoms.

To expose the lower part of the uterus, the bladder is pushed down through top or side approach; the broken blood vessels on the bladder are ligated simultaneously, and the bladder is pushed down to the maximum extent. The exposure operation is aborted if the lower segment of the uterus ruptures or bleeding becomes difficult to control. The abdominal aorta balloon is inflated (if preset before surgery). When incising the uterus, the placenta should be avoided. If it is difficult to avoid the placenta, the placenta should be punched, and the fetus delivered quickly. The uterus is quickly moved out of the abdominal cavity and the lower segment of the uterus is bound with occluding cuff. The placenta is quickly removed, and the adhesion or implantation region cleaned. The bladder is pushed down until it is below the placenta attachment site. A Fr28 abdominal drainage silicone tube is placed from the uterine cavity to the vagina and a parallel loop binding suture ligation applied from the cervix to the lower part of the uterus. The first needle is inserted laterally near the front of the lower margin of the cervix, walked along the lateral wall, unto the lateral posterior

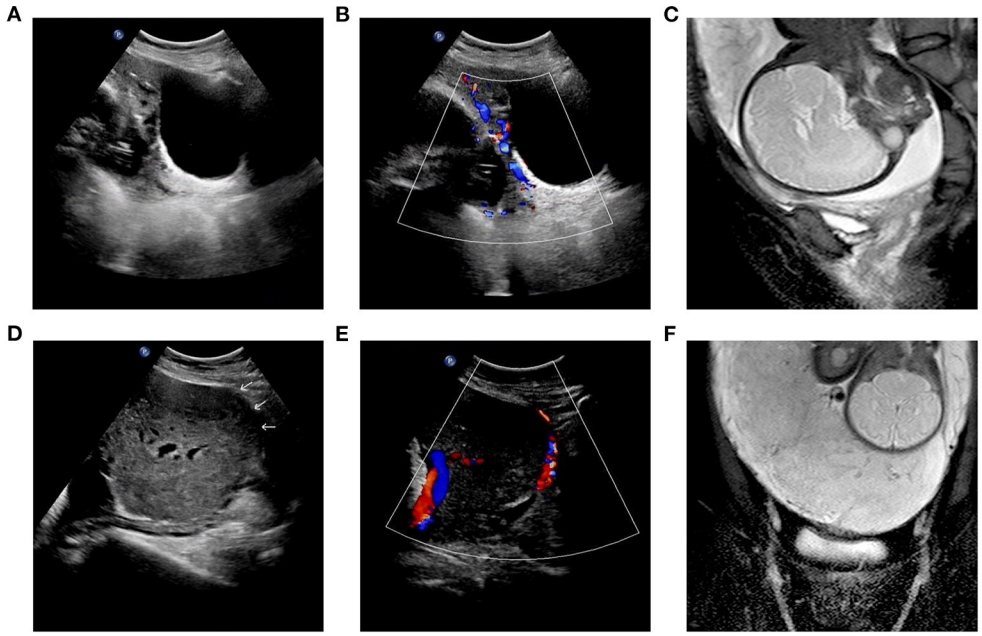

FIGURE 1 | (A–C) Patient No.16 of study group: marginal placenta previa. The placenta invaded the serous layer of the uterus and the posterior wall of the bladder, and the adjacent areas showed rich blood flow signals. **(D–F)** Patient No.23 of study group: complete placenta previa. The placenta invaded the serous layer of the uterus, and the adjacent areas showed rich blood flow signals.

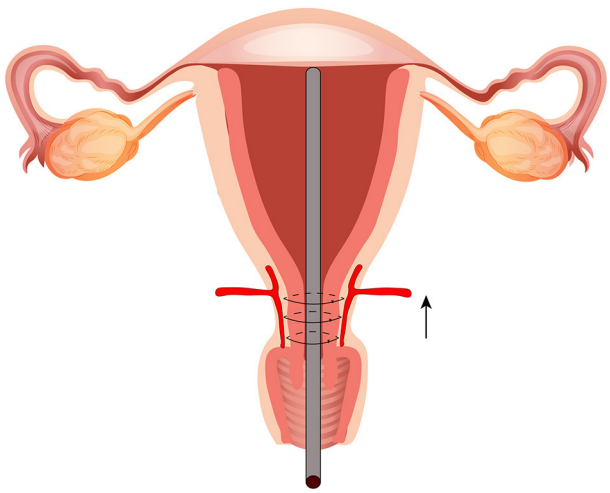

FIGURE 2 | Parallel loop binding compression suture procedure.

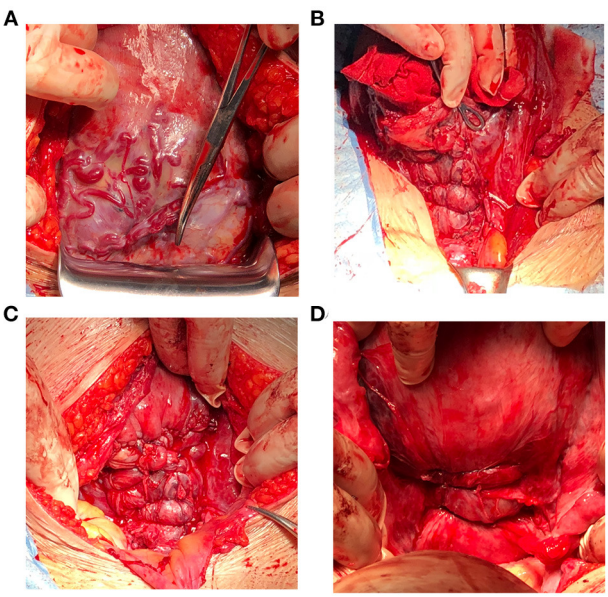

FIGURE 3 | Corresponding surgical pictures. **(A)** Pernicious placenta previa complicated with placenta increta. **(B,C)** The anterior wall of uterus after parallel loop binding compression suture was performed, and adequate hemostasis effect was achieved. **(D)** The posterior wall of uterus after parallel loop binding compression suture was performed.

of the cervix. The same procedure is performed ∼1 cm above the first suture site and is repeated 3–4 times to completely seal the bleeding on the placental dissection surface of the upper cervix and lower uterus, and then the weak myometrium is sutured and reinforced. Finally, the ascending branches of the bilateral uterine arteries are sutured (if necessary). B-Lynch uterine suture is performed (if necessary). Uterine cavity drains are kept for 4–6 h, and the Fr28 abdominal drainage silicone tube is subsequently removed (see **Figures 2**, **3** and **Supplementary Videos 1–3**).

TABLE 1 | Comparisons of surgical information between study and control groups.

Characteristic	Study group ($N = 38$)	Control group ($N = 86$)	*P*
Age (years)	34.6 ± 4.4	34.0 ± 4.6	0.53
GA (weeks)	36.3 ± 1.7	36.3 ± 1.4	0.81
No. of CS	1.3 ± 0.5	1.4 ± 0.6	0.66
Antibiotic (days)	4.7 ± 1.6	4.7 ± 1.4	0.95
Post-operation hospitalization (days)	6.6 ± 2.7	6.5 ± 2.7	0.74
Neonatal birth weight (g)	3,000.9 ± 530.2	2,948.3 ± 469.8	0.58
Fetal childbirth time (min)	14.1 ± 5.6	11.0 ± 8.0	0.03*
Total time of operation (min)	109.0 ± 33.5	134.4 ± 54.2	0.00**
Urethral catheter (days)	2.5 ± 1.2	4.1 ± 2.7	0.00**
Blood loss (ml)	2,152.6 ± 1,169.4	2,960.5 ± 1,963.6	0.02*
RBC Transfusion (unit)	7.2 ± 3.5	10.3 ± 8.7	0.03*
FFP Transfusion (ml)	552.6 ± 350.3	968.0 ± 799.8	0.00**

GA, Gestational age; CS, Cesarean section; RBC, Red blood cell; FFP, Fresh frozen plasma.
*$p < 0.05$; **$p < 0.01$.*

Follow-Ups

The first follow-up for all women was conducted at 6 weeks after the cesarean section and ultrasound was performed. Additional follow-up was conducted every 3 months for the first year and annually by telephone until May 2021.

RESULTS

Baseline Characteristics Between Two Study Groups

A total of 124 patients fulfilled with the criteria were included in the study, 38 of whom underwent parallel loop binding suture surgery, and another 86 patients underwent traditional surgery with figure-of-eight sutures as the main hemostatic method. The comparisons of surgical information between two study groups were listed in **Table 1**, and the detailed characteristics of the study group and control group were shown in **Table 2** and **Supplementary Material 1**, respectively.

The mean age of the study group and the control group were 34.6 (SD: ±4.4, range: 26–45) and 34.0 (SD: ±4.6, range: 22–46) years, respectively, with no statistical difference ($p = 0.35$), and the gestational weeks of termination were relatively consistent (36.3 ± 1.7 vs. 36.3 ± 1.4, $p = 0.81$). There were 13 cases (34.2%) in the study group and 26 cases (30.2%) in the control group of patients with more than one cesarean section, without statistical difference between the two groups ($p = 0.81$). Based on the imaging and clinical characteristics of the patients, an abdominal aortic balloon was placed preoperatively in 10 women (26.3%) of study group, and 15 women (17.4%) of control group ($p = 0.26$).

The Advantages of Parallel Loop Binding Compression Suture

The average operation time was 109.0 ± 33.5 min with parallel loop binding compression suture, which was significantly reduced compared with traditional operation method (134.4 ± 54.2 min, $p = 0.00$). The volume of blood lost were also decreased significantly (2,152.6 ± 1,169.4 vs. 2,960.5 ± 1,963.6 ml, $p = 0.02$), which correspondingly reduced RBC transfusion (7.2 ± 3.5 vs. 10.3 ± 8.7 units, $p = 0.03$) and FFP transfusion (552.6 ± 350.3 vs. 968.0 ± 799.8 ml, $p = 0.00$). Besides, parallel loop binding compression suture could shorten the duration of postoperative catheter indwelling (2.5 ± 1.2 vs. 4.1 ± 2.7 days, $p = 0.00$). Due to the hospital's routine surgical procedures, the durations of postoperative antibiotic use (4.7 ± 1.6 vs. 4.7 ± 1.4 days, $p = 0.95$) and postoperative hospitalization (6.6 ± 2.7 vs. 6.5 ± 2.7 days, $p = 0.74$) were consistent both in the study group and control group.

In the study group and the control group, 3 (7.9%) and 6 (7.0%) patients underwent hysterectomy due to massive blood loss, respectively, with similar proportions ($p = 0.86$), suggesting that parallel loop binding compression suture is also effective in avoiding hysterectomy compared with traditional surgery methods.

The most recent postoperative follow-up of study group was updated in May 2021, and the postoperative menstrual cycle and menstrual flow of patients both returned to normal levels.

Parallel Loop Binding Compression Suture had No Adverse Effect on Neonatal Prognosis

The corresponding dominant characteristics of the newborns were shown in **Table 3** and **Supplementary Material 2**. Because the bladder should be pushed down to the maximum extent to expose the lower part of the uterus in parallel loop binding compression suture procedure, the fetal childbirth time was extended (14.1 ± 5.6 vs. 11.0 ± 8.0 min, $p = 0.03$), however, there was no increase in NICU admission rates (36.9 vs. 34.9%, $p = 0.83$). Multiple neonatal complications were common in preterm infants, which delayed the discharge time. Except for one premature infant (32 weeks) death in the control group, all infants at our hospital were safely discharged after treatment.

DISCUSSION

Pernicious placenta previa remains a life-threatening obstetric problem, particularly in women with placenta increta. The increasing application of CS and medical abortion had a direct effect on the incidence of all grades of placenta accrete (14). Placental abnormality, including placenta accreta and placenta previa, is one of the most important causes of postpartum hemorrhage (15). Severe bleeding may lead to diffuse intravascular coagulation, multiple organ failure, and even death (16). Massive transfusion and aggressive surgical management, such as hysterectomy, have been the primary treatment to manage severe postpartum bleeding. Up to now, it is the first study to evaluate the safety and effectiveness of parallel loop

TABLE 2 | Clinical characteristics of study group.

No.	Age	GA (week)	G/P/A	No. of CS	Fetal childbirth time(min)	Total time (min)	Blood loss (ml)	Blood transfusion (unit PRBC/ml FFP)	Urethral catheter (days)	Antibiotic (days)	Post-operation (days)
1	28	36 + 2	2/1/0	1	12	83	1,000	2/0	2	4	4
2[a]	35	36 + 6	4/2/1	2	13	115	2,000	8/800	2	6	8
3	38	35 + 2	7/2/4	2	14	85	2,600	8/800	3	3	5
4	35	33 + 4	5/2/2	2	15	100	1,000	6/750	3	4	5
5	34	35 + 4	6/2/3	2	12	72	800	4/600	1	3	3
6	33	35 + 4	3/1/1	1	13	95	2,000	8/400	2	3	5
7	34	37 + 3	3/2/0	1	11	92	1,800	4/400	3	5	5
8[a]	35	32 + 6	5/3/1	2	15	105	2,000	8/800	4	8	8
9[a]	45	36 + 5	3/2/0	1	5	70	1,500	8/800	3	7	10
10	36	37 + 3	3/2/0	2	8	138	3,000	12/1,000	3	4	5
11	36	37 + 4	4/1/2	1	11	85	2,000	6/800	1	4	4
12	44	35 + 6	4/2/1	2	22	161	3,000	12/1,000	4	6	8
13	41	32 + 6	4/2/1	1	5	67	1,200	4/400	3	4	8
14	29	35 + 2	3/2/0	2	23	110	1,500	6/400	2	3	5
15	41	33 + 2	6/2/3	2	13	105	1,500	6/400	1	7	17
16	34	37 + 3	3/1/1	1	10	115	3,000	10/400	2	4	5
17[a]	35	37 + 4	5/2/2	2	10	105	2,000	6/400	7	8	8
18[a]	26	39 + 4	2/1/0	1	7	74	500	4/0	1	3	7
19[a]	28	39 + 6	4/1/2	1	12	107	2,000	8/800	4	4	4
20[a]	38	36 + 2	2/1/0	1	11	115	1,800	4/400	2	4	4
21[a]	32	36	3/2/0	2	10	113	1,800	8/800	3	5	5
22[a]	27	37 + 2	3/1/1	1	12	127	1,000	4/400	4	3	4
23[a]	29	36 + 5	2/1/0	1	12	102	700	4/0	2	7	12
24[b]	34	34 + 3	3/1/1	1	30	195	6,000	14/1,400	2	5	8
25	35	37 + 6	3/1/1	1	18	75	800	4/0	3	3	3
26	35	34 + 5	3/1/1	1	11	105	2,000	4/0	1	3	7
27	33	33	5/1/3	1	18	90	2,000	4/400	2	4	7
28	32	35 + 5	3/1/1	1	20	95	1,500	4/400	2	3	7
29	35	37 + 1	3/1/1	1	16	105	1,500	4/400	2	4	7
30	39	37 + 2	4/1/2	1	20	105	3,000	10/1,050	3	4	7
31[b]	37	35 + 6	3/1/1	1	15	150	5,000	16/1,200	2	5	7
32[b]	36	38 + 4	5/1/3	1	27	225	4,000	14/800	3	3	7
33[c]	37	35 + 4	6/2/3	2	13	144	3,000	12/800	1	5	7
34	29	37	3/1/1	1	13	70	1,800	4/400	2	5	7
35	33	37 + 4	5/1/3	1	8	85	2,000	6/200	3	4	5
36	31	38 + 1	2/1/0	1	10	118	2,500	6/400	2	5	5
37	35	37	4/2/1	2	22	97	3,000	8/400	2	6	9
38[d]	39	37 + 2	4/1/2	1	17	145	4,000	12/1,000	2	9	10

[a] *Abdominal aortic balloon was placed preoperatively.*
[b] *Hysterectomy was performed due to massive blood loss.*
[c] *20 units of cryoprecipitate were infused.*
[d] *20 units of cryoprecipitate and 1 unit of platelet were infused.*
G/P/A, Gravidity/Parity/Abortion; CS, Cesarean section.

binding compression suture in patients with pernicious placenta previa, complicated with placenta increta, which was proved to be effective, practical, and safe.

Various surgical sutures have been developed to reduce postpartum hemorrhage and preserve fertility in patients with placental abnormality during CS. Cho et al. (17) performed hemostatic multiple square suturing in women with postpartum hemorrhage who did not respond to conservative management during CS. However, the study was based on experiences from a limited number of women with placenta previa. Therefore, it could not be concluded that multiple square suturing can effectively treat postpartum hemorrhage in placenta previa. Hwu

TABLE 3 | Neonatal characteristics of study group.

No.	Neonatal birth weight(g)	Apgar scores (1 min/5min)	Neonatal complication	hospitalization days in NICU	Prognosis
1	2,900	10/10	None	0	Cure
2	2,270	6/8	1;2	21	Cure
3	2,690	5/8	3	12	Cure
4	2,100	8/10	4	12	Condition improved
5	4,000	9/10	3	0	Cure
6	2,900	10/10	2	7	Cure
7	3,400	10/10	None	0	Cure
8	2,150	7/9	5	17	Condition improved
9	3,400	10/10	None	0	Cure
10	3,000	10/10	None	0	Cure
11	3,400	10/10	None	0	Cure
12	2,700	6/8	1;2;4;5	36	Cure
13	1,900	8/8	None	Unknown	Unknown
14	3,000	10/10	6	8	Cure
15	2,625	10/10	3	13	Cure
16	3,900	8/9	None	0	Cure
17	3,100	10/10	None	0	Cure
18	3,200	10/10	None	0	Cure
19	3,500	10/10	None	0	Cure
20	3,200	10/10	None	0	Cure
21	2,550	9/10	None	0	Cure
22	2,500	10/10	None	8	Cure
23	3,400	10/10	None	0	Cure
24	2,500	4/5	3;7	8	Cure
25	3,300	9/10	None	0	Cure
26	2,650	7/9	3	10	Cure
27	2,200	7/8	3;8;9	14	Cure
28	2,800	10/10	None	0	Cure
29	2,900	10/10	None	0	Cure
30	3,050	10/10	None	0	Cure
31	3,000	10/10	None	0	Cure
32	3,900	10/10	None	0	Cure
33	2,800	10/10	2;3	10	Cure
34	3,900	10/10	None	0	Cure
35	3,200	10/10	None	0	Cure
36	3,050	10/10	None	0	Cure
37	3,800	10/10	None	0	Cure
38	3,200	10/10	None	0	Cure

Neonatal complication: 1, Neonatal hypoxic-ischemic encephalopathy; 2, Neonatal hyperbilirubinemia; 3, Neonatal pneumonia; 4, Neonatal anemia; 5, Neonatal feeding intolerance; 6, Neonatal diarrhea; 7, Neonatal toxic erythema; 8, Neonatal respiratory distress syndrome; 9, Neonatal apnea.

et al. (18) reported that parallel vertical compression sutures were used to control postpartum hemorrhage in women with placenta previa or accreta. They modified and simplified Cho's method, requiring only one stitch instead of four. Parallel vertical compression sutures avoided the construction of a square dead space, which would prevent complications such as pyometra (19). Dedes et al. (20) achieved satisfactory results in six cases with the use of circular isthmic-cervical sutures to control peripartum hemorrhage in placenta previa accreta. However, this method interrupted blood circulation of the uterine artery, which could affect the recovery of uterine blood circulation. In recent studies, Li et al. (12) reported the use of funnel compression sutures to control postpartum bleeding during CS in the presence of placenta previa with or without placenta accrete; Ratiu et al. (21) performed parallel vertical compression sutures, but the reduction in postpartum hemorrhage was not as advantageous as traditional surgical methods in cases of placenta increta and placenta percreta.

Our modified procedure, parallel loop binding compression suture, can be applied in all types of placental abnormalities to reduce lower uterine segment bleeding. Using our method in patients with placenta increta or percreta, the average blood loss was 2,152.6 ± 1,169.4 mL, which was lower than control group (2,960.5 ± 1,963.6), and the infusion of blood products was significantly reduced. Although we selected patients with pernicious placenta previa complicated with placenta increta, however, our method was still effective at controlling lower uterine segment bleeding without hysterectomy compared to a previously reported method by Li (12), [92.11% (35/38) vs. 86.7% (18/22, respectively)].

Our modified method is similar to BH Zhao's transverse parallel compression suture (22). The main differences between the two methods are as follows: First, as an authoritative hospital in China, we usually accept a large number of patients with critical conditions and poor health status. At the same time, the inclusion criteria for our study are more stringent and we enrolled patients who were diagnosed with pernicious placenta previa with placenta increta; therefore, our study provides guidance for complex and difficult situations. Second, BH Zhao's study routinely preset the balloon catheter occlusion of bilateral iliac artery in all patients on the day of surgery. However, the rate of preoperative abdominal aortic balloon placement in our study was 26.32% (10/38). A randomized controlled trial reported that hospitalization costs and the rate of postoperative fever with internal iliac artery balloon occlusion were higher than others; further, balloon catheter occlusion of bilateral iliac artery did not reduce the volume of blood transfusion in patients with placental abnormalities and might increase unexpected bleeding risk (23). Third, BH Zhao's study started suturing 1–2 cm below the cesarean incision. In our method, we start stitching from the upper edge of the cervix and have 3–4 stitches to completely seal the bleeding on the placental dissection surface of the upper cervix and lower uterus. Our bottom-up suture method is conducive to fully exposing the bleeding site and avoiding the construction of a dead space in order to achieve more effective hemostasis.

The mean fetal childbirth time of 14.1 ± 5.6 min was longer than that of the control group (11.0 ± 8 min), but it was better for bladder protection and did not increase the rate of hospitalization in the NICU. The duration of indwelling catheter was significantly shortened in the study group, which is of great significance to the postoperative recovery of patients.

All neonatal complications have been reasonably treated and eventually cured. Therefore, such surgical method and anesthesia time do not affect the outcomes of neonates. Parallel loop binding compression suture procedure is worthy of choice.

Unfortunately, some patients missed the optimal time to terminate the pregnancy due to lack of regular prenatal examination in our hospital. Three patients in study group underwent hysterectomy due to complete penetration of the placenta through the lower uterine segment. Based on ultrasound and MR evaluation, hysterectomy might be avoided if the pregnancy could be terminated earlier. Thus, planned termination of pregnancy needs to balance the risk of postpartum hemorrhage and the risk of prematurity. Placental abnormalities are associated with considerable maternal and fetal morbidity and even mortality. Maternal complications are mainly the result of massive hemorrhage (10). Therefore, it is essential to regular check-ups and timely termination of pregnancy.

The counseling regarding the subsequent pregnancy is also important. It should be emphasized that subsequent pregnancy is not recommended and effective contraception is necessary. As the number of cesarean sections increases, the probability of placental abnormalities is significantly higher, especially in patients with a history of placenta previa (24), which again puts the patient at risk of postpartum bleeding, hysterectomy and even death. Studies have shown that the hysterectomy rate was 6% in primary cesarean delivery for placenta previa, however, the rate was 25% for patients with placenta previa undergoing repeat cesarean delivery (25). For women with a strong desire for pregnancy, it is recommended to follow the WHO guidelines for contraception for at least 2 years (26), but it is necessary to perform a strict ultrasound examination to pay attention to whether there is a cesarean scar pregnancy and recurrent placental abnormality. In addition, assisted reproductive technology will also significantly increase the risk of placenta previa, which should be noted (27).

There are several highlights in our parallel loop binding compression suture. (1) We chose 35–38 weeks as a routine termination time of pregnancy. There were less risks than those chose delivery before 34 weeks (28). Among 38 patients with our method, 27 (71.05%) patients chose to terminate the pregnancy at 35–38 weeks. Others depended on the patient's clinical symptoms and evaluation based on ultrasound and MRI. (2) Our method is conducive to fully exposing the bleeding site and can extend the area of hemostasis to the whole lower uterus. (3) It is simple to operate, and conducive to rapid hemostasis. (4) Parallel loop binding compression suture is also effective in preventing hysterectomy. (5) Adjacent organs were not damaged.

CONCLUSION

Parallel loop binding compression suture is an effective, swift, practical, and safe method to reduce postpartum bleeding in women with pernicious placenta previa, complicated with placenta increta. Besides, it has no adverse effects on newborns.

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 authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Qilu Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MF: data curation and writing—original draft preparation. HB: methodology, visualization, and writing—original draft preparation. YF, ML, and YX: data curation and supervision. CJ: methodology and software. XS, CW, LZ, and YZ: data curation. YX and LC: conceptualization and writing—reviewing and editing. All authors helped to perform the research and agreed to be accountable for all aspects of the work.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.786497/full#supplementary-material

Supplementary Video Clips 1–3 | Parallel loop binding compression suture procedure.

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REVIEW
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The Development of Laparoscopy—A Historical Overview

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The advent of laparoscopy marked a fundamental change in the evolution of medicine. The procedure progressed consistently after the first time it was performed in a human being nearly a hundred years ago. The 1960's and 1980's witnessed groundbreaking changes. During this time, laparoscopy evolved from a purely diagnostic procedure into an independent surgical approach. Outstanding pioneers of the times were Palmer, Frangenheim and Semm. Laparoscopy advanced rapidly and influenced gynecology as well. The procedure was initially attacked most vociferously by the surgical fraternity. However, within a short period of time the pendulum shifted: laparoscopy became the preferred surgical approach for a variety of diseases—whether benign or malignant—in several medical disciplines. Laparoscopy has become a routine approach in the twenty-first century. Technical advancements have led to robot-assisted surgery. Future developments will include artificial intelligence and augmented reality. In the present article we address past milestones, current practices, and future challenges in laparoscopy.

Keywords: laparoscopy, history of medicine, Semm, kelling, minimally invasive surgery, Kiel

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INTRODUCTION

Primum non nocere. Possibly, the Hippocratic impulse underlying the demand for moral action on the part of doctors was one of the many factors responsible for the introduction of minimally invasive surgery as we know it today. Surgeons and physicians have been consistently focused on minimizing the risks and complications of surgery.

Endoscopic procedures have become an integral part of all surgical specialties and are now a standard approach in all fields of surgery. An increasing number of complex surgical procedures are performed by the laparoscopic approach. The generation of the 2000s takes laparoscopy for granted. Conventional laparoscopy has been extended to include robotic-assisted surgery. In fact, we are on the verge of implementing artificial intelligence and augmented reality in laparoscopy (1–3). The history of laparoscopy reveals that a large number of steps and individuals were involved in the establishment of complex surgical techniques as we know them today (4–6).

Georg Kelling was the first to describe the basic principles of endoscopy of the abdomen. Kelling performed the procedure in a dog (5–8). Almost exactly a hundred years ago, Jacobaeus performed the first endoscopy in humans. Major advancements in endoscopy were accomplished from the 1960s to the 1980s, accompanied by a transition from diagnostic to surgical laparoscopy. These developments are inseparably linked with the names of Raoul Palmer in Paris and Kurt Semm in Kiel (5).

The first laparoscopic appendectomy was performed by Semm on 13 September 1980 at the department of obstetrics and gynecology, University of Kiel (5, 9, 10). It was an absolute rarity and an international sensation at the time. As a gynecologist and trained toolmaker, Semm revolutionized the course of traditional surgery. However, he aroused the criticism of many of his colleagues in gynecology and surgery. In his words, the medical world at the time reacted with the most violent hostility and opposition he had experienced during his entire career (9): "Both surgeons and gynecologists were angry with me, they virtually stoned me. All my initial attempts to publish a report on laparoscopic appendectomy were rejected with the comment that such non-sense does not, and will never, belong in general surgery." Thus, his first report on laparoscopic appendectomy was published no earlier than 1983 (10). In an interview, his close colleague Liselotte Mettler (born in 1939) said that Semm was summoned from the operating room and had to undergo a computed tomography investigation of his skull in order to prove that he was in good health.

In a letter written in 1981, the President of the German Society of Surgery urged the German Society of Obstetrics and Gynecology to revoke Semm's medical license. The fact that a gynecologist wished to show surgeons how to perform an appendectomy was simply inconceivable. Semm had exceeded a limit that was considered impassable until the time. However, he was cognizant of the immense potential of laparoscopy not only in gynecology but also in surgery, and persisted in his unwavering efforts to minimize surgical trauma for patients (5, 9).

The rapidity of this development had a significant impact, especially on gynecology. Entirely new pathways could be broached after the introduction of laparoscopy in hysterectomy, uro-gynecological interventions, and oncological surgery, including lymphadenectomy in different compartments of the body. Laparoscopy became firmly established in other specialties as well, such as surgery and urology.

The increasing complexity of the interventions was accompanied by significant demands on surgeons and technological equipment. A surgeon comes close to his physical and mental limits when performing endoscopic operations for several hours (1).

The subsequent development of endoscopy was closely linked with technical advancements. The aim of laparoscopic interventions such as NOTES (natural orifice transluminal endoscopic surgery), or surgery performed through a single trocar (single-port technique) is to reduce access-related trauma by further minimization of the skin incision.

Robot-assisted surgery is the most dynamic form of minimally invasive surgery in our times. Better visualization of the field of surgery by means of 3D technology and extension of surgical instruments to 7 degrees of freedom permit the use of minimally invasive surgery even in complex situations. Robot-assisted guidance of the instruments enables the surgeon to work without tremor and with a low level of fatigue, which is very useful for surgeons as well as patients during complex interventions. Moreover, the surgeon is able to work simultaneously at two consoles. The learning curve is shortened, complication rates are reduced, and training in surgery is fostered (1).

The introduction of endoscopy in surgical practice is one of the greatest success stories in the history of medicine. As far as the development of minimally invasive options is concerned, there is still no end in sight.

This report provides a historical overview of laparoscopy from its early beginnings to current times.

HISTORY AND PIONEERS

Endoscopy is derived from Greek and means "viewing the inner spaces of the human body" ("endo" and "skopein"). In addition to the usual investigation methods of palpation, auscultation and percussion, the very first written records of medicine bear evidence of the fact that doctors were always interested in the possibility of "looking into" (endoscopy) the human body (4).

Hippocrates II (born in 460 B.C., died in 375 B.C.), the principal representative of the school of Kos, described the use of a speculum for investigation of the rectum (4). Similar instruments for examination of the vagina were found in the ruins of Pompeii (destroyed in 70 A.D.) and have been described in other cultures as well. However, the scope of investigation was limited by the need to illuminate the field of investigation. Illumination has been a persistent issue in the history of laparoscopy (4).

Albukasim (912-1013 A.D), an Arabian physician, was the first to use reflected light to view the inside of the body. He held a glass mirror in front of the vulva and thus reflected light into the vaginal vault (4). Cardan (1501–1576) was the first to use a mechanical lamp. Aranzi (1530–1589), a Venetian, bundled light with the aid of a camera obscura. In 1768, the French gynecologist and surgeon George Arnaud de Rosil (1698–1774) constructed the first endoscopic investigation lamp with a shielded lantern. He was able to illuminate the vagina, previously unfolded with specula (11).

Philipp Bozzini (1773–1809), a doctor in Frankfurt, played a significant role in the development of modern endoscopy because he marks the transition from ancient to modern medicine (12). In 1806 Bozzini (**Figure 1**) published his report about his light conductor, a device consisting of an optical part with lighting equipment and a mechanical part aligned to the anatomy of the body orifice (12). He thus created an instrument for the vagina, the rectum, and the oral cavity, which could be used for inspection and to a lesser extent for performing surgery. Although the light conductor was much too weak and the field of vision too small, all further attempts to perform cystoscopy during the next 70 years were based on Bozzini's principle of illumination, namely that of a reflected extracorporeal light source (5, 12).

Antonin Jean Desormeaux (1815–1894) advanced this historical development in 1843 with the creation of the first portable endoscope (13). Antonin Jean Desormeaux was the first to clinically use Bozzini's light conductor for which many regard him as the "father of endoscopy" (**Figure 1**). His endoscope was a system of mirrors and lenses with an open flame as the light source, and was primarily used for the clarification of urological questions. One of the disadvantages was the enormous

FIGURE 1 | Pioneers of laparoscopy. **(A)** Philipp Bozzini (1773–1809), **(B)** Antonin Jean Desormeaux (1815–1894), **(C)** Georg Kelling (1866–1945), **(D)** Maximilian Nitze (1848–1906), **(E)** Heinrich Kalk (1895–1973), **(F)** Raoul Palmer (1904–1985).

heat generated by the light source, which led to burns (13). Endoscopes illuminated by electricity were developed only after the invention of the light bulb by Thomas Alva Edison in 1879, and the miniature version of the bulb in the form of a mignon lamp (5). Subsequent developments in endoscopy were initially focused on cystoscopy. Maximilian Nitze (1848–1906) modified Edison's light bulb. In 1877 Nitze (**Figure 1**) created the first urethroscope and cystoscope with an integrated light source for the illumination of body cavities, and thus laid the foundations of clinical endoscopy (14). Johann Mikulicz-Radecki (1850–1905) and Joseph Leiter, an instrument maker from Vienna, adopted Nitze's principle of a rigid optical system in 1881 and developed the first gastroscope for clinical use (15, 16).

Era of Diagnostic Laparoscopy (1901–1933)

In 1901 Georg Kelling (1866–1945), a surgeon and gastroenterologist from Dresden, demonstrated the first laparoscopy at the end of his lecture entitled "About the inspection of the esophagus and the stomach with flexible instruments"; he referred to the technique as "coelioscopy" (6). In his doctoral thesis, Kelling had focused on the anatomy and physiology of the gastrointestinal tract. Based on this knowledge and his discoveries about the insufflation of air into the abdomen, he was the first to develop the method further. He investigated the abdominal cavity of a dog he had insufflated earlier with filtered air, using a Nitze cystoscope. This invervention may be regarded as the natal hour of laparoscopy (7, 8). At the time, Kelling (**Figure 1**) concluded his lecture with the following words (6): "Gentlemen, I conclude this lecture by expressing the hope that endoscopic methods will be used to a greater extent in the digestive tract than has been common practice so far. In fact, in many instances, endoscopic methods are destined to replace laparotomy." However, Kelling is not known to many as the primary creator of the technique. One of the reasons is definitely the course of Kelling's life. Along with his second wife, he died in a heavy air attack on Dresden in February 1945. His reports and personal documents were lost at the time (6–8, 17).

Nine years later, the Swedish internist Hans-Christian Jacobaeus (1879–1937) introduced the term "laparothoracoscopy" during the first endoscopic inspection of the human chest and abdominal cavity (18, 19). Jacobaeus published his experience of the first 17 laparoscopies in 1910 in the "Münchner Medizinischen Wochenschrift" (Munich Medical Weekly). The report was entitled "About the options of using cystoscopy for the investigation of serous cavities" (19). Jacobaeus recommended the technique for the endoscopic inspection of other body cavities as well. In contrast to Kelling, Jacobaeus introduced the trocars directly without creating a pneumoperitoneum. Jacobaeus started to release adhesions by viewing the body with the aid of thoracoscopy. He performed thoracoscopic investigations as early as 1913 and is therefore regarded as the founder of thoracoscopic operations (18, 19).

The first laparoscopy in the USA was performed by Bertram M. Bernheim (1880–1958) in 1911. He named his method organoscopy (20, 21). The instruments consisted of a proctoscope and simple lighting. Bernheim introduced his instrument through a mini-incision without creating a pneumoperitoneum (20). He was able to detect an enlarged gall bladder in his first patient. However, the actual diagnosis of a pancreatic carcinoma was established only after a subsequent laparotomy. After publication of his organoscopy, Bernheim lost interest in gastroenterology and devoted his attention to vascular surgery (21).

Insufflation of the abdominal cavity was improved. One day after the end of the First World War, a treatise on X-ray diagnosis of the abdominal cavity was published in the Munich Medical Weekly. Otto Goetze (1886–1957), an assistant surgeon and author, focused on radiological problems. He used oxygen to improve contrast on X-rays (22). In order to introduce oxygen safely into the abdomen, he developed a double-walled cannula in accordance with the "principle of solid displacement." The term "pneumoperitoneum" was also coined by him (22). In 1924 the Swiss gynecologist Richard Zollikofer replaced air with CO2 for the purpose of insufflation (19).

Laparoscopy became increasingly well-known and its application spread far and wide. The existing knowledge had to be summarized in a textbook. Roger Korbsch published the first textbook on the subject in 1927 (23).

Optics were also improved. Heinz Kalk (1895–1973), a gastroenterologist from Berlin, known as the founder of the German school of laparoscopy, developed a 135-degree lens system and a double trocar (24). Kalk (**Figure 1**) used laparoscopy as a diagnostic procedure for diseases of the gall bladder and the liver. In a publication of his experiences in 1939, he reported on more than 2,000 liver punctures under local anesthesia without encountering a single fatality. He also released adhesions by the laparoscopic procedure (5, 24).

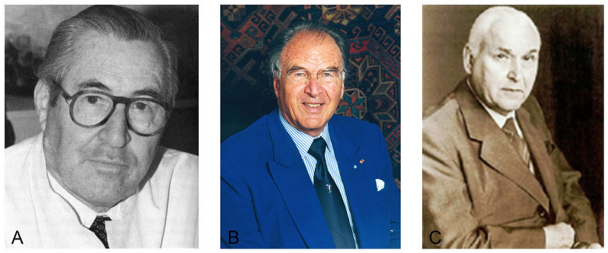

FIGURE 2 | Pioneers of operative laparoscopy. **(A)** Hans Frangenheim (1920–2001), **(B)** Kurt Semm (1927–2003), **(C)** Karl Storz (1911–1996).

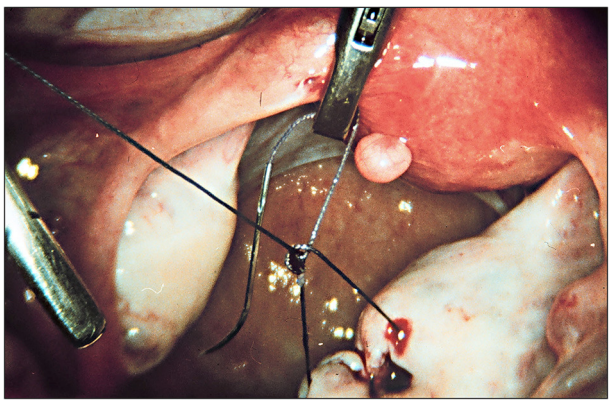

FIGURE 3 | Introduction of intracorporeal knots (1974). Source: Department of Obstetrics and Gynecology, University Clinic of Kiel.

Era of Operative Laparoscopy

Apart from significant progress in equipment and technology, the surgical spectrum was widened as experience with the technique increased. In 1933, Carl Fervers succeeded in performing the first laparoscopic adhesiolysis, which may be regarded as the first surgical laparoscopy in the current sense of the term (25).

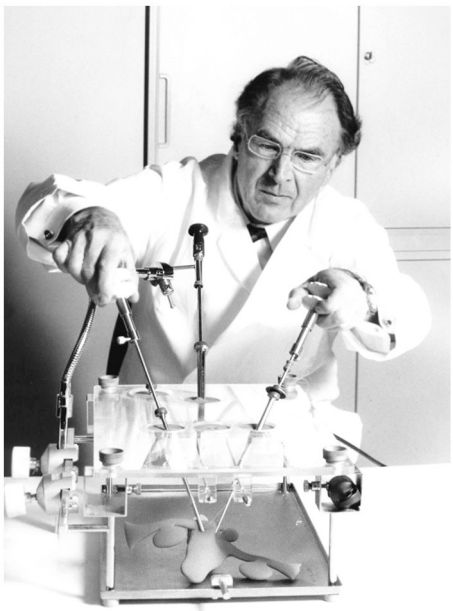

FIGURE 5 | Pelvi trainer (1985). Source: Department of Obstetrics and Gynecology, University Clinic of Kiel.

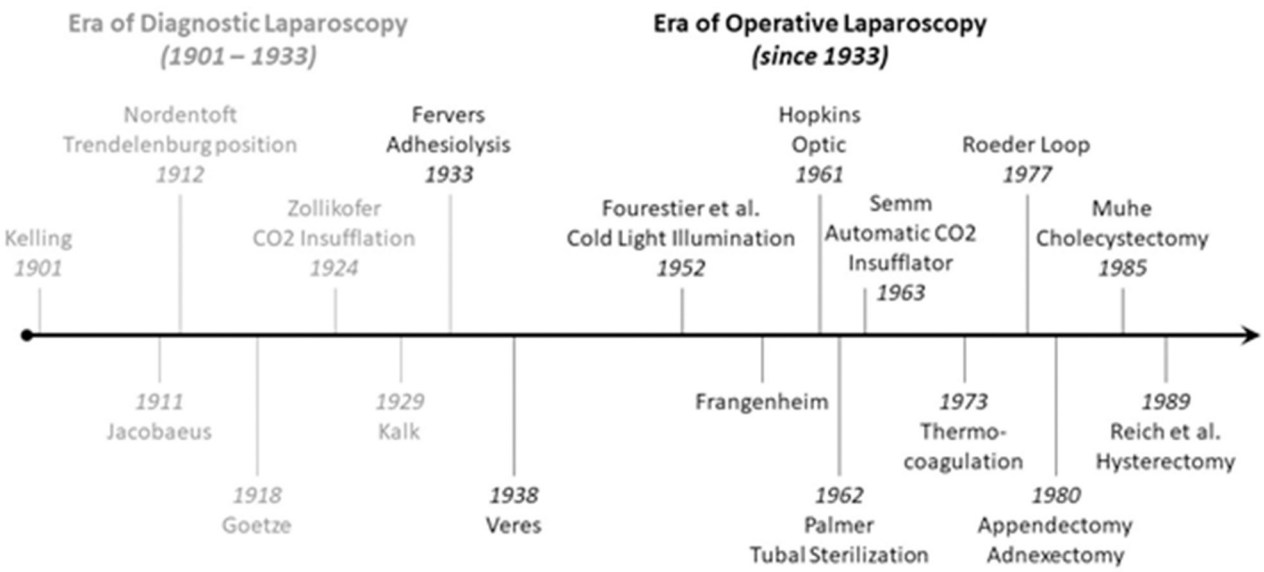

FIGURE 4 | Timeline of the development of laparoscopy.

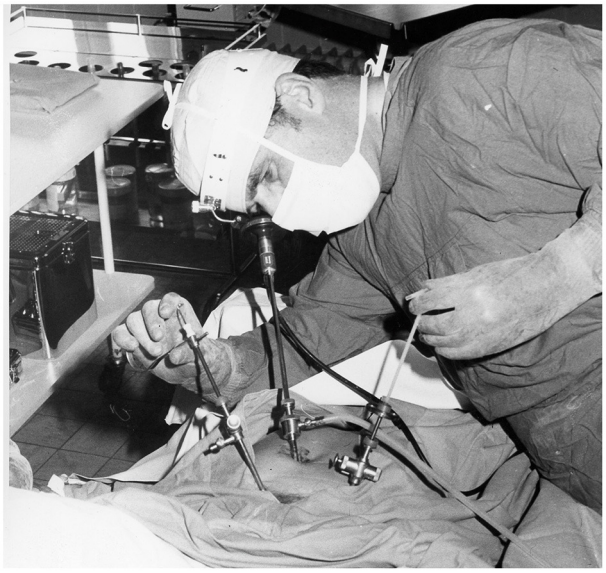

FIGURE 6 | Around 1970 Semm developed the "head ring," a simple device by which he freed his left hand. The optical device need not be held; it hangs on a small hook. Source: Department of Obstetrics and Gynecology, University of Kiel.

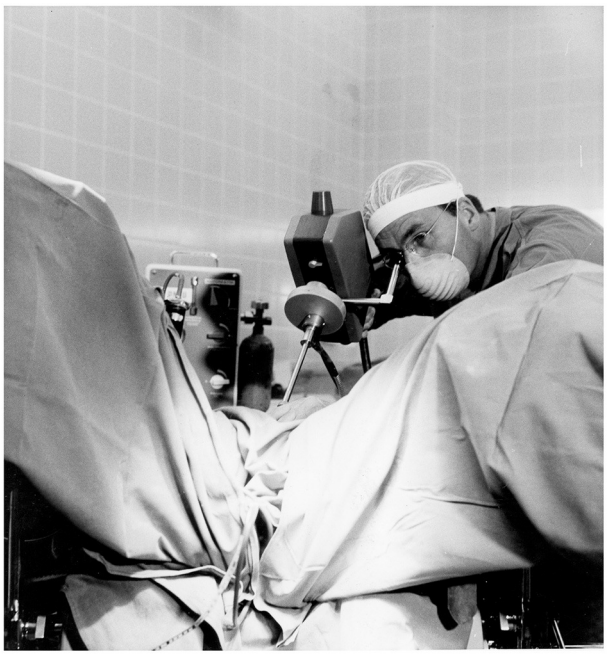

FIGURE 7 | Always with the finger on the pulse of the latest technology. As early as 1970, just a few months after the German tech company Philips launched their first "portable" TV camera, Semm used it in the operating room. Several educational films were produced with the aid of the camera (41–43).

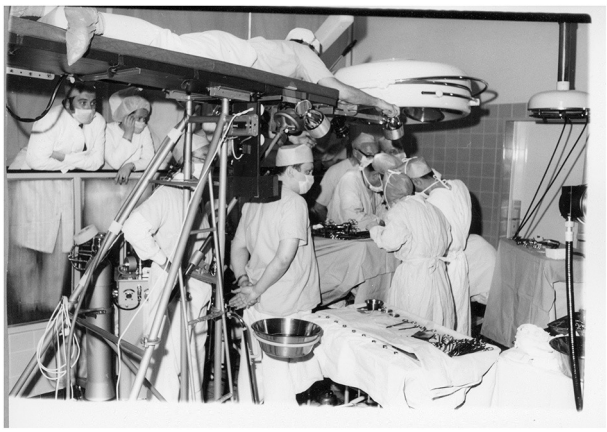

FIGURE 8 | Technical breakthrough: electronic elements in the operating room at the Wertheim week in Kiel, organized by Semm in 1972. The operation was performed by Soichi Sakamoto and Semm and demonstrated by camera broadcast to a large number of national and international guests (camera work by Volker Rimkus, Semm's assistant). Source: Original interview with Volker Rimkus (born in 1939).

FIGURE 9 | 1972 Department of Obstetrics and Gynecology at the University Clinic of Kiel. The new technical options offered by the video camera enabled Semm to demonstrate his operations to a large number of national and international visiting doctors, who followed the operations with great interest. Semm referred to the event as the birth of video pelviscopy [33]. Source: Department of Obstetrics and Gynecology, University Clinic of Kiel.

In 1937, the American J.C. Ruddock reported on more than 500 laparoscopic procedures with biopsies, mainly obtained from the liver. This internist, who published his work in surgical journals, used pincers supplied with electrical power for the purpose of coagulation. Notably, Ruddock was the first to report a substantial number of complications with the technique (26).

A further milestone in the historical development of laparoscopy was achieved by the Hungarian internist and pulmonologist János Veres (1903–1979), who introduced his insufflation needle which had, in fact, been described earlier by Goetze but had slipped into oblivion. Veres developed a special canula with a spring mechanism. Its purpose was to create a pneumothorax in order to treat tuberculosis, which was a widespread disease at the time (27). Even today, the Veres needle is used to create a pneumoperitoneum safely in laparoscopy. Due

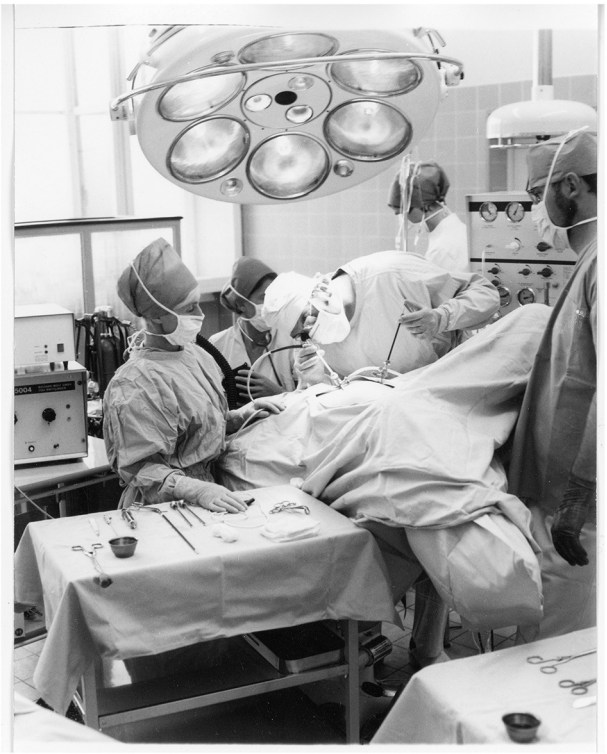

FIGURE 10 | Semm performing a sterilization by laparoscopy. Source: Department of Obstetrics and Gynecology, University of Kiel.

to its spring mechanism, it permits gas insufflation with a low rate of complications and prevents injury to internal organs when being introduced through the abdominal wall (27).

The first minor surgical interventions were performed in the sixties of the twentieth century, primarily by gynecologists. Raoul Palmer (1904–1985), a gynecologist from Paris, made notable achievements in this regard (28). Palmer (**Figure 1**) was mainly concerned with the diagnosis of sterility and its treatment. In 1944 he performed a laparoscopy in Trendelenburg position. He also conducted the first sterilization by laparoscopy. Although an incision site in the upper abdomen in the caudal aspect of the left costal margin is named after Palmer, in 1946 he performed the incision in the navel and preferred this site. Like Kelling, he also referred to the endoscopic procedure as coelioscopy (28).

Since the abdominal access was difficult because of the blind nature of insertion, in 1946 the American Albert Decker (1895–1988) introduced the laparoscope transvaginally through the posterior vaginal vault and named the procedure culdoscopy. However, the diagnostic procedure was inadequate from this perspective and the technique, which was initially rather widely accepted, became less popular in the USA (29).

Pioneers of Operative Endoscopic Surgery

The development of laparoscopy in Germany after the Second World War is primarily linked with the names of Hans Frangenheim (1920–2001) and Kurt Semm (1927–2003) (**Figure 2**). Frangenheim encountered laparoscopy in 1952, when a tumor in the lower abdomen was discovered during an endoscopy of the liver at the Medical Clinic of Cologne, and the subsequent strategy had to be decided. In 1955 he attended a clerkship under Palmer in France and realized that laparoscopy was superior to culdoscopy, which was being used in Germany at the time. He devoted his efforts to the development of new instruments, photographic documentation of endoscopic reports, and the improvement of gas insufflation which was completely uncontrolled until this time. In cooperation with Dräger Company, Frangenheim developed a CO2 insufflator. His monographs, publications and lectures contributed to further dissemination of the method (30, 31).

The Kiel University Department of Obstetrics and Gynecology under Kurt Semm (1927–2003) is regarded as the birthplace of modern laparoscopy. He became the most productive researcher and innovative instrument maker in the field of modern endoscopic surgery (18).

In the 1960s, two decisive developments paved the way for a new era in endoscopy. The British physicist Harold Hopkins (1918–1994) developed the Hopkins optics in 1961 and achieved a further milestone in the field (32). This optical instrument consisted of so-called rod lenses. Its eighty-fold higher light transmission and enlarged field of vision yielded sharper and brighter images. The technique attracted the attention of the German instrument maker Karl Storz (**Figure 2**), who convinced Hopkins to work with him. As early as 1960, Karl Storz Company developed the cold light source, which replaced the bulb at the tip of the endoscope. The advantages of the cold light source were obvious: it provided much better illumination and caused less heat (32). Until 1970, intra-abdominal endoscopy was largely confined to diagnostic procedures. This limitation could be attributed to the fact that there were no means of arresting bleeding after surgical interventions. Semm aimed to use laparoscopy for purposes other than diagnosis alone. In order to distinguish this technique from internistic laparoscopy of the upper abdomen, he named his procedure pelviscopy (4). Being a precision mechanic himself, Semm developed many instruments personally. He had been engaged in endoscopy since 1955. His automatic CO2 insufflator, constructed in 1963, made operations in the abdominal cavity safer and more comfortable. Thermocoagulation was introduced in 1973, followed by the Roeder loop to stop bleeding (33). Semm developed a special suction irrigation device, an electronic insufflator, and the first morcellator in 1977. His spectrum of instruments and methods of hemostasis (endosuture with intra- and extracorporeal knots, as shown in **Figure 3**) enabled surgeons to perform increasingly complex surgical procedures (5). These innovations proved to be crucial prerequisites for the subsequent development of endoscopy.

However, a large number of gynecologists and surgeons criticized Semm for his "keyhole surgery" and believed that, thanks to modern anesthetic methods, laparotomy was no longer a problem. According to these critics, Semm had exaggerated the problem of adhesions which, they believed, could be easily resolved by open laparotomy. Some physicians treated Semm's reports of the new spectrum of endoscopic options (treatment

of tubal pregnancy, adnexectomy, or ovariectomy) with disbelief, and asserted that Semm started an operation as a laparoscopy and ended with a laparotomy (5). Semm met with fierce resistance when he performed the first laparoscopic appendectomy in 1980, because surgeons saw no reason to replace an established surgical method by a technically complicated one (9, 10). The circumstance of a gynecologist showing surgeons how to perform an operation was simply inconceivable. Semm had crossed a limit that was considered impassable until the time. Cognizant of the immense potential of endoscopic surgery not only in gynecology but especially in surgery, Semm pursued his work in laparoscopy with unswerving commitment. He persisted in his efforts to reduce surgical trauma for patients (5, 9).

Two German surgeons, Gotz and Pier, pursued Semm's purpose and established laparoscopic appendectomy on a wide basis. Already in the early 90's, they performed hundreds of appendectomies by this approach and perfected the technique. They even used it in patients with acute appendicitis (5).

In 1985, the German surgeon Erich Mühe (1938–2005) performed the first laparoscopic cholecystectomy using the instruments developed by Semm (34). In 1987, he reported on 97 successful operations performed by this technique (35). Reich et al. described the first laparoscopic-assisted hysterectomy in 1989, while Mouret performed the first cholecystectomy by video laparoscopy in 1991 (36). At the time, the industry realized the importance and potential commercial benefits of this development and became more interested in laparoscopy.

However, there was still vehement opposition. Hans Troidl, then senior surgeon at the University Clinic of Surgery in Kiel reported that, at the 107th Congress of the German Society of Surgery in Berlin in 1990, an article on the first 100 laparoscopic cholecystectomies initially submitted and published by him was suddenly struck off from the official Congress program (from a personal communication with the authors IA and UM).

A video presentation of Semm's laparoscopic appendectomy at a gynecologists' convention in Baltimore in 1988 encouraged McKernan and Saye to perform the first laparoscopic cholecystectomy in the USA. They used Semm's instruments in combination with laser technology (5). Later on, many endoscopists visited the two surgeons in Nashville in order to learn the new technique. The news reached the media in the USA, and the technique was publicized in a talk show on television. This was followed by numerous training courses, which were fully booked within a very short period of time (5).

Figure 4 summarizes the historical steps of development from diagnostic to operative laparoscopy.

Advances in other fields of medicine delayed the subsequent evolution and application of laparoscopy. The development of laparoscopy was ignored by many surgeons in the 1970's and 1980's. The reasons were innovations in anesthesia and intensive medicine, and the new spectrum of medications which enabled surgeons to perform prolonged operations. Endoscopic cholecystectomy and appendectomy were considered daredevil artist's surgeries that offered risky solutions to safely resolved problems. The notion that major medical problems call for major solutions such as abdominal incisions was deeply ingrained in the minds of surgeons. The fundamental concept of laparoscopy was contrary to this notion (5).

Announcement of "Minimally Invasive Surgery"

In contrast to general trends at the time, a group of German surgeons founded the Surgical Task Group for Endoscopy and Ultrasonography in 1976. Five years later, the Society of American Gastrointestinal Endoscopic Surgeons (SAGES) was founded in the USA.

The first issue of the journal Surgical Endoscopy was published in 1987 and the first World Congress of Surgical Endoscopy was held in 1988. The convention was a major success and is regarded as a global breakthrough in laparoscopy (5).

The British urologist John E.A. Wickham (born in 1927) was the first to use the term "minimally invasive surgery" and attracted significant attention when he published his visions about endoscopic procedures in 1987 in the British Journal of Urology (37). Although Wickham was exposed to substantial criticism, his ideas are reflected in the trend of the 1980's, when doctors and patients alike became fascinated with laparoscopic techniques (5).

In 1987 he predicted the paradigm shift in practical surgery that took place a little later: "Surgeons applaud large incisions and denigrate "keyhole surgery." Patients, in contrast, want the smallest wound possible, and we at Britain's first department of minimally invasive surgery are convinced that patients are right" (37).

In the early 1990s, literally overnight endoscopic surgery was welcomed by widespread acceptance and rapid dissemination. This "laparoscopic revolution" was triggered by a sudden demand from patients, and its popularity heightened by avid media interest (38). The change was dramatic especially in cholecystectomy. The unprecedented demand gave rise to new problems: countless surgeons were unfamiliar with the new technique and had to undergo endoscopic training in a short period of time (38, 39).

The problem of imparting the knowledge and skills of endoscopy had been addressed for a long time. A breakthrough was achieved by the so called pelvi trainer (**Figure 5**), developed by Semm in 1985, which became an indispensable tool for learning laparoscopic techniques (40).

Technical Breakthrough With Electronic Video-Endoscopy

The introduction of electronic elements in the operating room (as shown in **Figures 6**–**10**), along with video transmission, aided the breakthrough in operative endoscopy (41–43).

The traditional monocular endoscope does not permit the surgeon to share his vision with others. For a long time, the surgeon guided the optical instrument himself and had only one hand for surgical work (**Figures 6**, **10**). The assistant surgeon had no means of viewing the field of surgery (as shown in **Figure 10**).

The introduction of the endoscopic video camera and image transmission to a monitor transformed the situation. The surgeon could now work with both hands and the assistant could

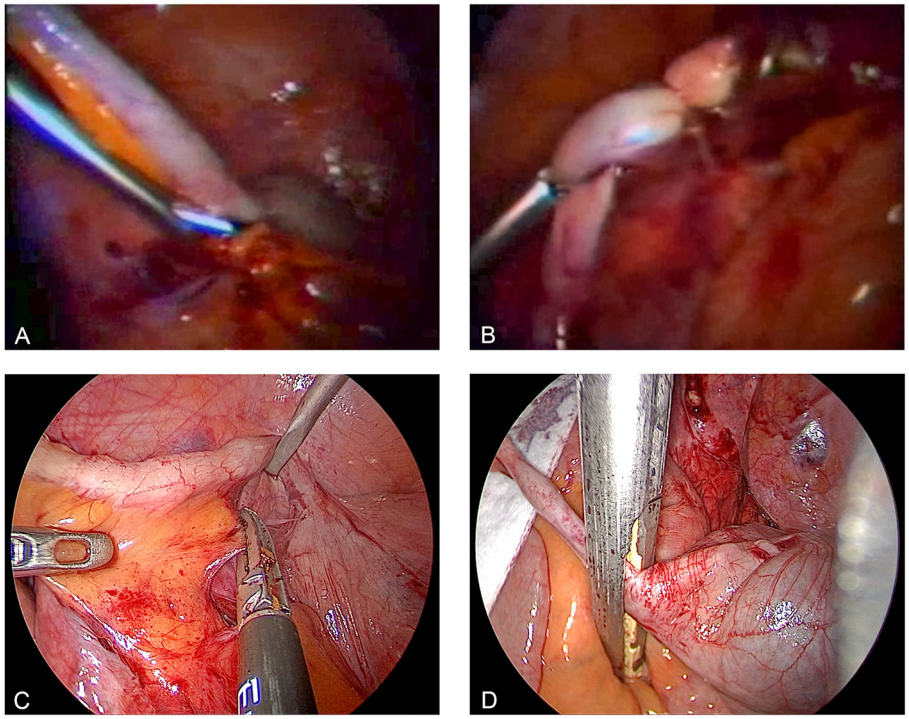

FIGURE 11 | Laparoscopic appendectomy past and present. **(A,B)** are original pictures of the first laparoscopic appendectomy performed by Semm in 1980: skeletization of the appendix was followed by its ligation at the base with a Roeder loop. **(C,D)** show the current standard of surgery with the use of a stapler. The significantly better image quality and advanced instruments are evident. Source: Department of Obstetrics and Gynecology, University of Kiel.

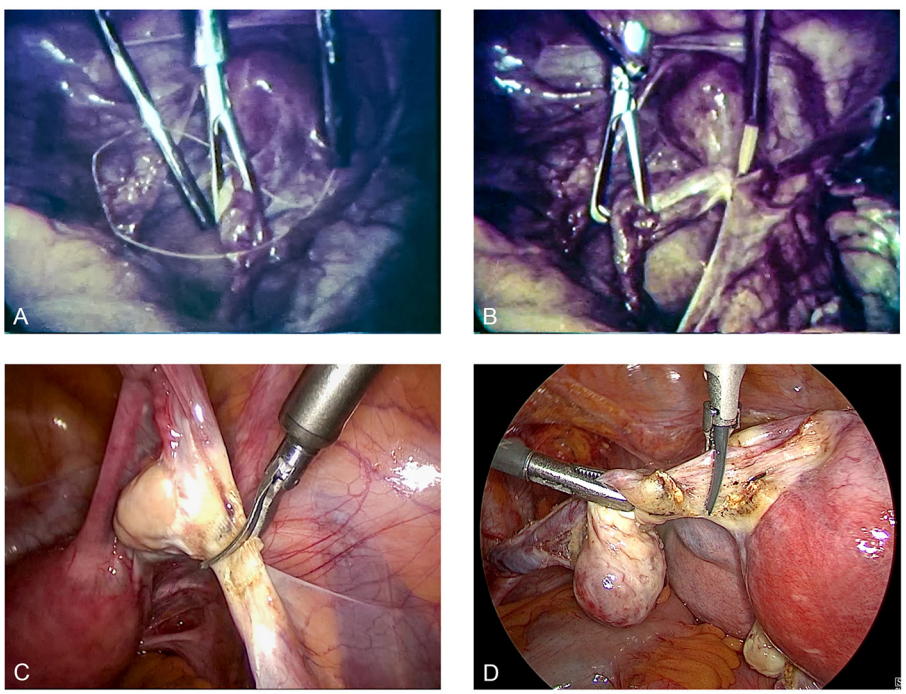

FIGURE 12 | Laparoscopic adnectomy past and present. **(A,B)** are original pictures of a laparoscopic adnectomy performed by Semm using the three-loop method in 1980. **(C,D)** show the current standard of surgery. The markedly better image quality is evident. Source: Department of Obstetrics and Gynecology, University of Kiel.

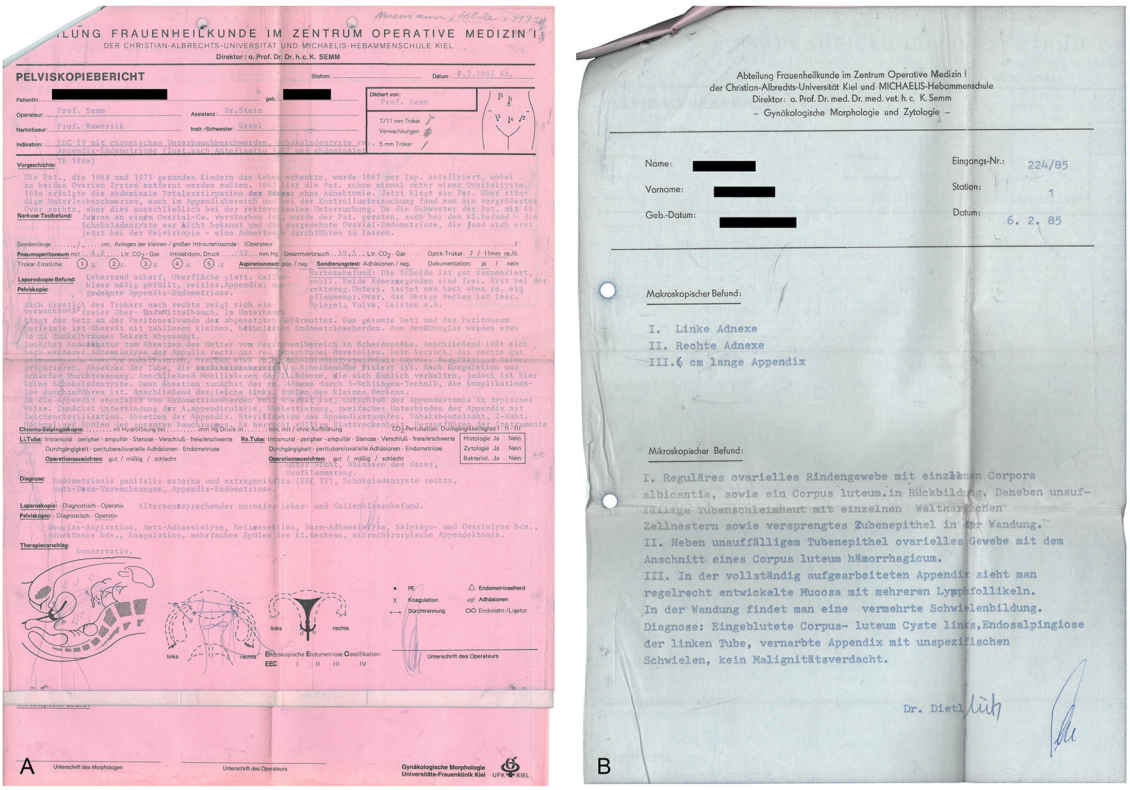

FIGURE 13 | Original operation report by Semm in 1985. **(A)** Pelviscopy report of a patient who had undergone a hysterectomy, had chronic pain in the lower abdomen, suspected endometriosis of the external genitalia and extragenital endometriosis (endometriosis of the right-sided ovary, suspected endometriosis of the appendix). The patient underwent adhesiolysis, adnectomy on both sides by the 3-loop technique, and appendectomy. **(B)** Histological report showing evidence of a hemorrhagic corpus luteum cyst on the left side, endosalpingiosis of the left fallopian tube, and a scarred appendix. Source: Department of Obstetrics and Gynecology, University of Kiel.

follow the operation on the monitor. They could now operate as a team and demonstrate technical options to every observer. However, the first video cameras were heavy, cumbersome, and unsuitable for routine use. Electronic mini-cameras, introduced in 1987, resolved the problem (5).

Instruments and Equipment for Laparoscopy—Past and Present

Palpators were the sole instruments used in endoscopy until 1960. The diagnosis and treatment of female sterility, and later tubal sterilization, were the main procedures performed in gynecological laparoscopy until 1970 (5). Therefore, the first instruments to be developed were scissors and atraumatic grasping forceps for transection of the fallopian tubes. Thermal methods of hemostasis were needed after 1970. The methods of hemostasis developed by Semm (thermocoagulation, Roeder loop, endosuture with intra- and extracorporeal knots) and his extensive range of instruments enabled surgeons to perform increasingly complex operations (5).

Semm, who had completed an apprenticeship as a precision mechanic before entering medical school, found an effective means of putting his discoveries into clinical practice through his family. His father and brother were owners of WISAP, a company that produced medical instruments (9). While others had to wait for years before they could implement their ideas, Semm designs of new devices could be introduced in clinical practice

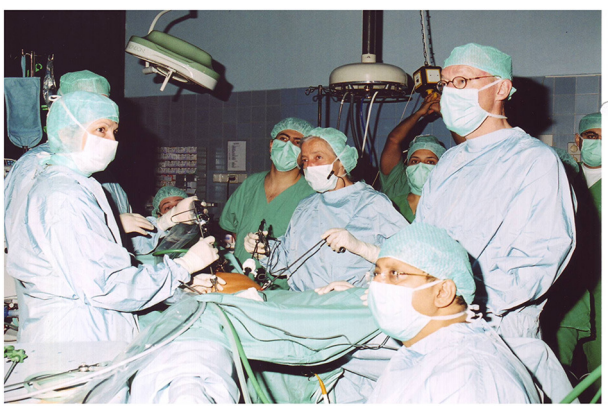

FIGURE 14 | International laparoscopy course at the Endoscopy School of Kiel with Professor Liselotte Mettler. Source: Department of Obstetrics and Gynecology, University of Kiel.

within a short period of time (9). This aroused the envy of many (9). Semm's numerous innovations extended the spectrum of surgical options to a significant extent (such as laparoscopic management of ectopic pregnancies, tubal sterilization by endocoagulation, salpingostomy, oophorectomy, salpingolysis, fimbriolysis, lysis of omental adhesions, bowel suturing, repair of uterine perforations, and myomenucleation) (9). In 1980, Semm and his staff member Liselotte Mettler reported the first endoscopic ovariectomies and adnectomies performed with the aid of the Roeder loop. The same year, Semm performed the first laparoscopic appendectomy which he published in 1983 (5, 9, 10). **Figures 11–13** show original pictures of the first appendectomy and adnectomy performed by Semm in 1980, and original operation reports of the procedures (10, 41). In contrast, the procedures as they are performed today. Technological advancements such as miniaturized video cameras, innovative instruments, HD image quality and 3D technology show where we stand 40 years later. These innovations were driven forward at a rapid pace to the present day by several pioneers of operative laparoscopy and the technical industry.

Semm did not keep his knowledge to himself. Rather, he made it accessible to one and all. In his view, the art of laparoscopic surgery could not be learned by assisting an operation, as was the case for laparotomy. In 1985 he developed the Pelvi trainer, a phantom device for drilling operations (**Figure 5**) (40). The Kiel School of Gynecological Endoscopy was founded in 1990. Semm no longer needed to transport his technique elsewhere; he could make it accessible locally to one and all. A number of national and international courses have been held since this time (as shown in **Figure 14**).

Excursus: Anatomical Illustration—Past and Present

Viewing the transformations in surgery along with innovations in supporting medical specialties such as anesthesiology and intensive medicine, infectious diseases, pathology and others, it is almost disconcerting to note that illustrations of human anatomy, a basis for all medical specialties, were available in similar excellent quality 120 years ago and were by no means inferior to current visual presentations of human anatomy (as shown in **Figure 15**) (44).

Modern Era of Laparoscopy

The introduction of endoscopy in surgical practice is one of the greatest success stories in the history of medicine. This historical overview shows that laparoscopy has developed at an incredible pace in the last two decades and created unprecedented opportunities in gynecology.

Current developments are mainly focused on improving image display and making it more realistic. Furthermore, we have experienced consistent progress in robot-assisted surgery and new surgical accesses such as natural orifice transluminal endoscopic surgery (NOTES) or access via a single trocar (single-port technique). Based on findings in pelvic neurofunctional anatomy and the introduction of laparoscopy in the dissection and visualization of the pelvic nerves Marc Possover introduced the concept of "Neuropelveology" in clinical practice. In 2014 the International Society of Neuropelveology was founded (45).

In an age of increasing specialization in medicine, the interdisciplinary approach is gaining importance and offers opportunities for endoscopic surgery (46). Thanks to the outstanding quality of digital imaging, operations can be shared more easily with surgeons of various specialties. This progress has been further aided by the development of new and user-friendly instruments that can be used in several specialties, and the simultaneous use of two consoles in robot-assisted surgery. Besides, modern operating rooms permit a rapid exchange of surgeons (47). Modern communication systems and telementoring allow the exchange of information over long distances. Thus, diverse specialties or surgeons can communicate intraoperatively without being physically present at the same site (48).

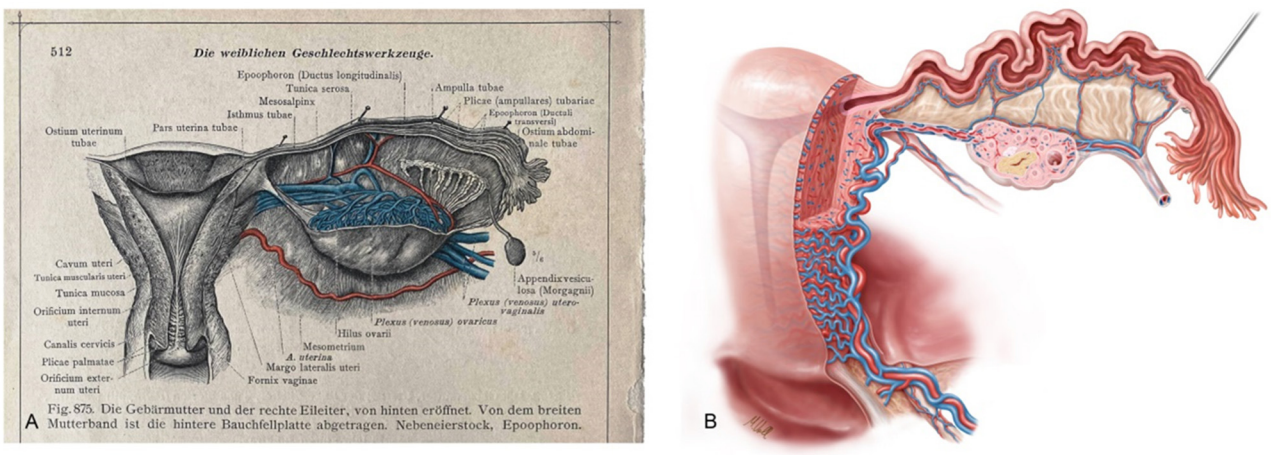

FIGURE 15 | (A) Anatomical illustration of the uterus, adnexa and parametrium in an ancient anatomical atlas (Dr. Carl Toldt, Berlin and Wien 1903 [44]) and **(B)** modern female anatomical illustration generated by Markus Voll.

The disadvantages include the high cost of installation and maintenance in robot-assisted procedures, which usually involve long operating times at least at the beginning and are associated with a renewed learning curve even for experienced laparoscopists. Furthermore, doctors as well as nursing staff must be trained in the use of the robot system (49, 50). Docking and the placement of trocars, and the unfamiliar actions at the console take more time in the initial phase. Notwithstanding the existing disadvantages of robot-assisted surgery, technological developments in this field will lead to further dissemination of miniaturized and economical integrated systems in the foreseeable future even in gynecology, and further enlarge the spectrum of minimally invasive operation techniques (5, 51).

CONCLUSION FOR CLINICAL PRACTICE

We await the coming decades of development in medical technology with a tear in one eye and a smile in the other. With a smile because medicine and patient care will benefit from rapid global technological progress. With a tear because we do not know whether the original essence of our existence, namely exercising our manual skills on human beings, will be abolished in the near future.

AUTHOR CONTRIBUTIONS

IA, DF, UM, LM, JP, NM, MB, GG, and AL contributed equally to the formation, writing, and editing of this manuscript. All authors contributed to the article and approved the submitted version.

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The subject of the article has been published in a similar form in German language (52).

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A Novel Multi-Port Containment System for Laparoscopic Power Morcellation to Prevent Tumoral Spread: A Retrospective Cohort Study

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Objective: To report a novel multi-port containment (NMC) system for laparoscopic power morcellation to prevent tumoral spread and to evaluate its safety, validity, and feasibility.

Methods: This retrospective study included women who underwent laparoscopic myomectomy (LM) between January 2014 and August 2020 at a single academic institution. The NMC system was used in the study group (n = 193); the control group underwent unprotected LM ($n = 1753$).

Results: After 1:1 propensity score matching, no significant differences in the baseline characteristics were observed between 193 matched pairs. Bag damages were detected in two cases in the study group before morcellation, and the NMC systems were replaced. There were no significant differences between the two groups in terms of the complications, total operative time, estimated blood loss, or postoperative hospitalization duration. In the study group, all operations were completed and no system rupture or leakage was observed. The median follow-up times were 21 and 54 months in the study and control groups, respectively. There was no peritoneal tissue spread in the study group. However, three (3/5, 0.6%) and six (6/1,753, 0.3%) patients in the control group experienced malignant and benign peritoneal tissue spread, respectively.

Conclusion: The NMC system for laparoscopic power morcellation is valid, safe, and feasible for preventing a tumor spread.

Keywords: uterine leiomyoma, laparoscopic myomectomy, power morcellation, containment system, uterine sarcoma

INTRODUCTION

Uterine leiomyoma (UL) is the most common tumor of the female reproductive system, with an incidence of >70% (1). Laparoscopic myomectomy (LM) is the most frequent fertility-sparing or uterine-conserving procedure (2, 3). Power morcellation facilitates the efficient fragmentation and removal of tissues *via* small incisions (4). However, unprotective morcellation seriously violates the principle of the no-touch isolation technique and challenges operational safety, thereby becoming a worldwide concern (5, 6).

Laparoscopic power morcellation in the management of uterine malignancy, especially occult uterine sarcomas, may inadvertently cause disease upstaging and negatively affect the prognosis (6–8). In 2014, the U.S. Food and Drug Administration (FDA) reported that the incidence of occult uterine sarcoma was 1 per 352 individuals, and issued a black box warning about power morcellation (9). This was reiterated in 2020 and power morcellation for myomectomy was recommended only if performed with the containment system (10).

However, owing to the lack of compatibility between the containment system and laparoscopic instruments, the leakage rate of the bags is very high (11–13). A prospective multi-center study was paused due to blue dye spillage, mostly from the lateral puncture site, in 9.2% of the cases (12). In addition, bags render morcellation more cumbersome, resulting in increased operative times (14). The aim of this study was to report a novel multi-port containment (NMC) system for laparoscopic power morcellation for preventing tumor spread and to evaluate its safety, validity, and feasibility.

MATERIALS AND METHODS

The flow chart of the study design is presented in **Figure 1**. LM was performed with an NMC system in a total of 193 patients (the study group) from August 1, 2018 to August 1, 2020 at the Gynecology Center of the China-Japan Friendship Hospital in Beijing, China. Considering the stability of the LM technique and the large sample size required for comparison, 1,753 patients treated with unprotected LM from January 1, 2014 to August 1, 2020 were included in the control group. A total of 364 patients were excluded for the following reasons: (1) age > 50 years; (2) largest tumor diameter < 4 cm; (3) history of malignancy; and (4) suspected malignancy. Another 23 patients were lost to follow-up, and were thus, excluded from the control group. All surgeries were performed by the same group of experienced surgeons (B.L., J.L., and H.L.); they were highly trained in minimally invasive procedures.

Demographic, perioperative, and follow-up data were collected and analyzed. The demographic data comprised age, body mass index (BMI), gravidity, parity, hypertension and diabetes status, the American Society of Anesthesiologists (ASA) score, hemoglobin level, major indications of LM (such as menorrhagia), intestinal and urinary tract disorders, presence of abdominal distention or pain, and fertility requirements. Data were also collected on the history of previous abdominal/pelvic surgeries; the sizes, numbers, and locations of the leiomyomas; and the pathological types of the lesions. Perioperative data comprised the integrity of the system after morcellation, intraoperative complications (including visceral, vascular, or nerve injuries; estimated blood loss > 1,000 mL; or serious anesthesia complications), postoperative complications (12), total operative time (defined as the time from incision to closure), estimated blood loss (defined as the surgeon's estimate recorded in the operative record), and postoperative hospitalization duration. All patients were followed up with ultrasound or magnetic resonance imaging at 1 month, 6 months, and 1 year after the operation.

All surgeries were performed by senior surgeons who followed the same standardized procedures for each intervention; the patients were placed under general anesthesia in a semi-lithotomy position. A standard four-port operative laparoscope was introduced for direct visual entry. During each surgical intervention, a careful and systematic inspection of the uterus, ovaries, and entire pelvis was performed. In the control group, standard intra-abdominal uncontained power morcellation was performed using a reusable, uterine power morcellator (KANGJI medical) (15). The NMC system was used for the study group.

The main components of the NMC system are shown in **Figure 2** and include a detachable trocar (trocar base and trocar sheath) and a retrieval bag (soft bag body, hard sheath on the bag, and sealing cap).

The key steps of the surgical procedure involving the NMC system are illustrated in **Figure 3** and are also depicted in the **Supplementary Video 1**. The first stage was placement, and the steps involved are outlined hereafter: (a) the bag was placed in the abdominal cavity through the right lower 20-mm introduction sheath, (b) the myoma was resected into the bag via its large opening, (c) the edges around the opening of the bag were pulled out through the introduction sheath, (d) the hard sheaths on the bag were pulled from the body through the corresponding trocar incisions, (e) the sealing caps were replaced with the trocar bases, (f) the abdominal cavity was de-sufflated, and simultaneously, a pseudo-pneumoperitoneum (14 mmHg) was established by inflating the bag via the umbilical trocar. Thereafter, power morcellation was performed.

The next stage was extraction, and the steps involved are outlined hereafter: (a) after morcellation, the trocar bases were replaced with the sealing caps and sent back into the abdominal cavity, (b) the bag was de-sufflated, and the abdominal cavity was re-insufflated, and (c) the bag was removed through the introduction sheath.

After LM, the abdomen and pelvis were carefully examined for signs of tissue spillage. Surgeons visually examined the integrity of the system. The system was filled with 1,000 mL of methylene blue solution to identify potential disruptions. Precautions were outlined such that in case a system tear or leakage occurred at any time prior to or during the morcellation, the procedure would be halted and a new system would be utilized.

All statistical analyses were performed using SPSS version 31.0 (IBM Corp., USA). Continuous data are summarized as means and standard deviations (SDs). The *t*-test was used for comparing continuous variables and the χ^2 test or the Fisher's exact test was used for comparing the categorical variables between the

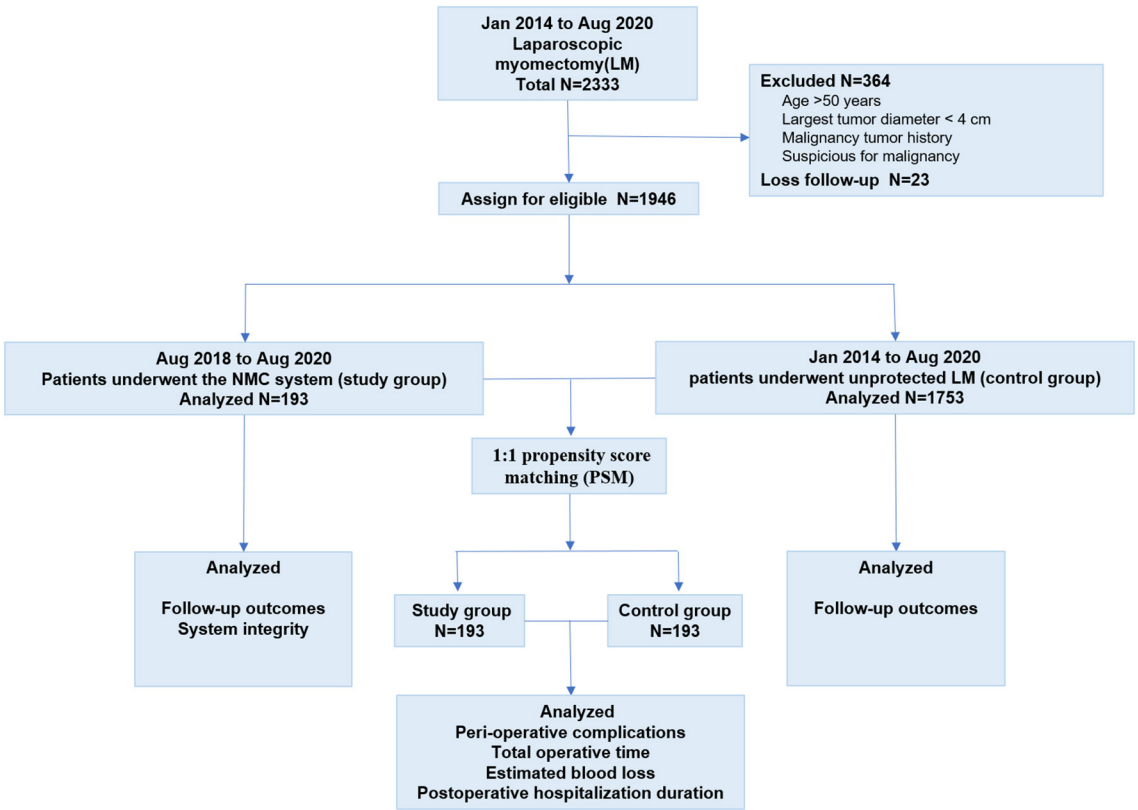

FIGURE 1 | Study design.

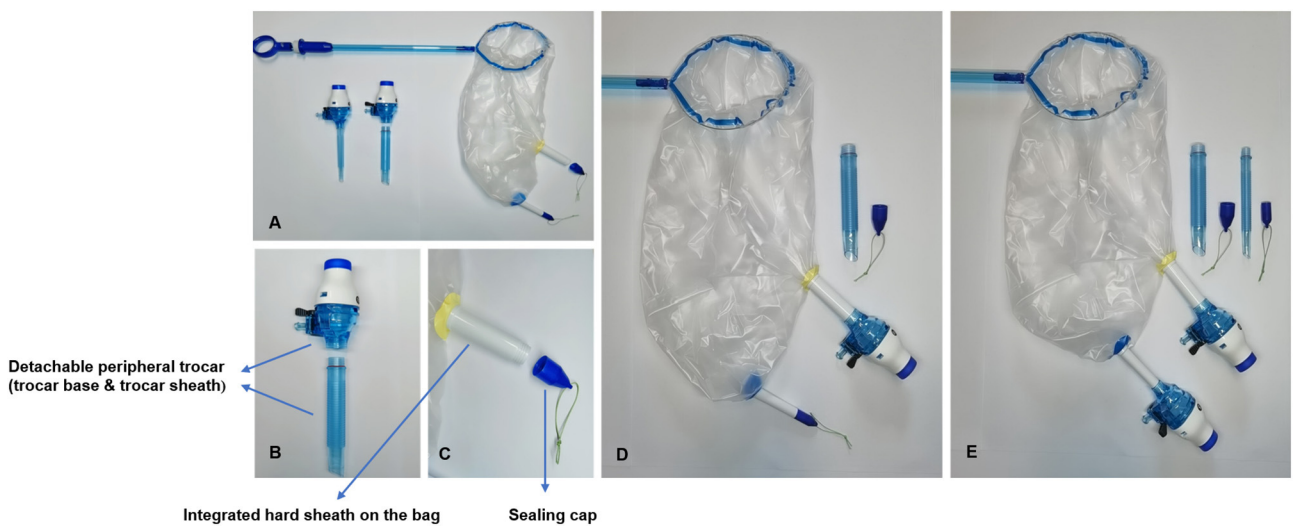

FIGURE 2 | Main components of the novel multi-port containment (NMC) system. **(A)** The main components of the NMC system include the detachable peripheral trocar and the retrieval bag. **(B)** Detachable peripheral trocar (trocar base and trocar sheath). **(C)** Hard sheath on the bag and sealing cap. **(D,E)** Transposing sealing caps and trocar bases by threaded structures.

unmatched groups. Propensity score matching (PSM) was used to minimize bias; it has been widely used in previous studies as well (16). Based on previous reports and experience, the age; BMI; gravidity and parity; preoperative diabetes and hypertension status; hemoglobin level; ASA score; main surgical indications; history of abdominal/pelvic surgery; and the tumor size, number,

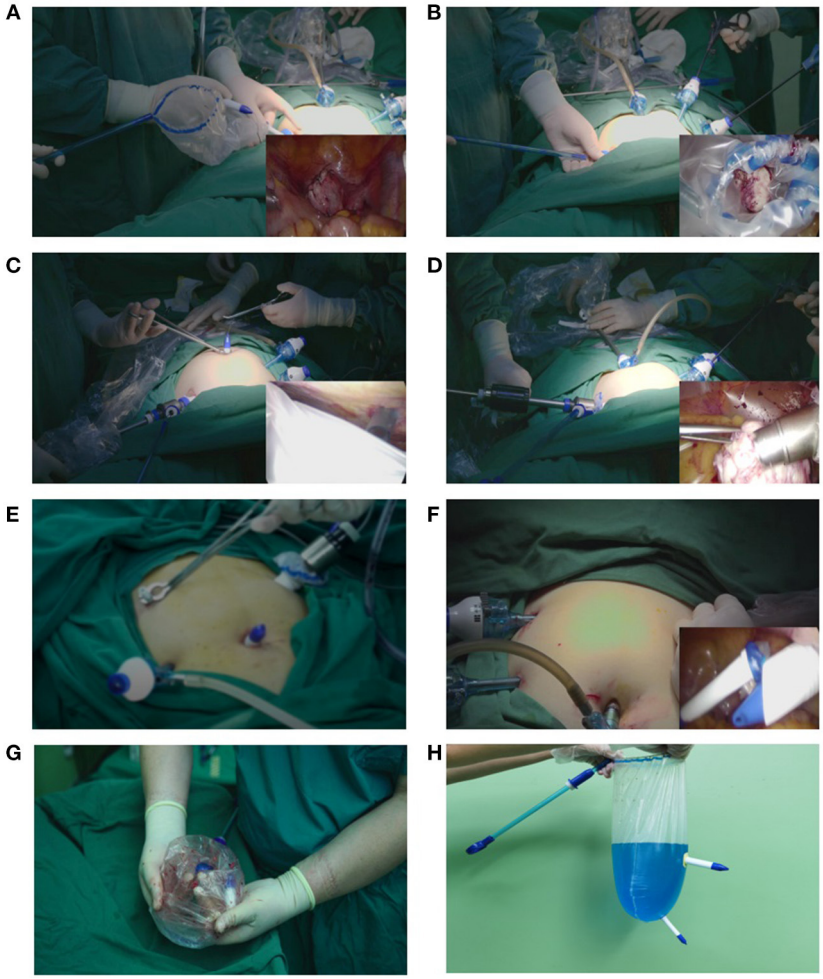

FIGURE 3 | Placement and extraction of the novel multi-port containment (NMC) system. **(A)** The bag is placed into the abdominal cavity through the right lower 20-mm introduction sheath. **(B)** The myoma is resected into the bag via its large opening. **(C)** The sealing caps on the hard sheaths are unscrewed and replaced with trocar bases. **(D)** The abdominal cavity is de-sufflated, and simultaneously, a pseudo-pneumoperitoneum is established by inflating the bag via the umbilical trocar. Thereafter, power morcellation is performed. **(E)** After morcellation, the trocar bases are unscrewed and replaced with the corresponding sealing caps. **(F)** The bag is removed through the introduction sheath. **(G)** Tissue and fluid remnants after morcellation in the NMC system. **(H)** 1,000-mL methylene blue solution is used to identify eventual system integrity.

and location were considered to be important factors associated with the perioperative outcomes in the two groups. We calculated a propensity score for each patient through logistic regression modeling; thereafter, patients from the study and control groups were matched at a ratio of 1:1, with the caliper width set as 0.02 for the SD. The standardized mean difference was estimated before and after matching to evaluate the balance. Patient demographic data were adjusted to almost the same levels after matching. For proportional outcome comparisons between the two groups after PSM, the paired *t*-test was used for continuous variables and the McNemar test was used for binary variables. Two-sided p-values < 0.05 were considered to indicate statistical significance. The analysis was conducted in August 2021.

This study was approved by the institutional review board of the China-Japan Friendship Hospital. All patients were fully informed of the operation; they agreed to undergo it and consented to the further utilization of the data collected before and after the operation. Before the operation, all patients were informed in detail about the operative procedures, potential risks, and benefits of the intervention. The patients had the right to choose whether to undergo treatment using the NMC system, mainly based on their desires. Written informed consent was obtained from all the patients.

RESULTS

The baseline characteristics of the patients are displayed in **Table 1**. No significant intergroup differences in most of the baseline characteristics, except for gravidity, average diameter of the largest tumor, and main surgical indications, were observed. After PSM, 386 women were successfully matched

TABLE 1 | Patient characteristics before and after propensity score matching.

Characteristic	Propensity score matching, no. (%)					
	Before			After		
	Study group ($n = 193$)	Control group ($n = 1753$)	*P*-value	Study group ($n = 193$)	Control group ($n = 193$)	*P*-value
Age, mean (SD), y	39.2 (6.4)	39.2 (7.0)	0.993	39.2 (7.0)	38.7 (6.6)	0.428
BMI			0.134			0.698
<19	17 (8.8)	141 (8.0)		17 (8.8)	21 (10.9)	
19–24	117 (60.6)	946 (54.0)		117 (60.6)	119 (61.7)	
>24	59 (30.6)	666 (38.0)		59 (30.6)	53 (27.5)	
Gravidity, mean (SD)	1.4 (1.4)	1.8 (1.5)	<0.001	1.4 (1.4)	1.6 (1.5)	0.292
Parity, mean (SD)	0.6 (0.6)	0.7 (0.7)	0.034	0.6 (0.6)	0.7 (0.6)	0.654
ASA score			0.060			0.335
1	161 (83.4)	1,555 (88.7)		161 (83.4)	158 (81.9)	
2	32 (16.6)	190 (10.8)		32 (16.6)	35 (18.1)	
≥3	0 (0)	8 (0.5)		0	0	
Diabetes			0.099			1.000
Yes	4 (2.1)	84 (4.5)		4 (2.1)	3 (1.6)	
No	189 (97.9)	1,669 (95.2)		189 (97.9)	190 (98.4)	
Hypertension			1.000			0.724
Yes	3 (1.6)	31 (1.8)		3 (1.6)	5 (2.6)	
No	190 (98.4)	1,722 (98.2)		190 (98.4)	188 (97.4)	
Hemoglobin level			0.630			0.554
Normal	169 (87.6)	1,560 (89.0)		169 (87.6)	164 (85.0)	
Abnormal	24 (12.4)	193 (11.0)		24 (12.4)	29 (15.0)	
Major indications			0.006			0.555
Menorrhagia	675 (38.5)	675 (38.5)		88 (45.6)	100 (51.8)	
Intestinal and urinary tract disorders	174 (9.9)	174 (9.9)		30 (15.5)	21 (10.9)	
Abdominal distention or pain	114 (6.5)	114 (6.5)		13 (6.7)	13 (6.7)	
Fertility requirements	666 (38.0)	666 (38.0)		54 (28.0)	54 (28.0)	
Others	124 (7.1)	124 (7.1)		8 (4.1)	5 (2.6)	
History of abdominal/pelvic surgery			0.376			0.498
No	135 (69.9)	1,169 (66.7)		135 (69.9)	142 (73.6)	
Yes	58 (30.1)	584 (33.3)		58 (30.1)	51 (26.4)	
Myomectomy	8	75		8	7	
Cesarean section	43	384		43	37	
Others	14	178		14	12	
The average diameter of the largest tumor, mean (SD), cm	7 (1.9)	6.7 (2.1)	0.001	7 (1.9)	6.8 (2.0)	0.147
Location of the tumor			0.590			1.000
Uterus	176 (91.2)	1,626 (92.8)		176 (91.2)	176 (91.2)	
Cervical or uterus ligaments	17 (8.8)	123 (7.0)		17 (8.8)	17 (8.8)	
Others	0 (0)	4 (0.2)		0 (0)	0 (0)	
Number of the tumor	2.7 (2.5)	2.5 (2.2)	0.521	2.7 (2.5)	2.8 (2.5)	0.618

BMI, body mass index; Normal hemoglobin level is ≥ 110 g/L.

such that the previously mentioned baseline differences were no longer present.

The perioperative outcomes of the two groups are displayed in **Table 2**. All operations were completed in the study group. In two cases, bag damages were detected before morcellation and the NMC systems were changed. Following PSM, no intraoperative complications were noted in the two groups. Furthermore, no significant differences in the postoperative complications were noted between the two groups ($p = 1.000$; **Table 3**). There was no significant difference in the mean total operative time between the study and control groups (119.9 ± 46.4 vs. 120.2 ± 44.2 min, $p = 0.953$). The difference in the estimated blood loss per patient was not statistically significant between the study and control groups (73.7 ± 102.7 mL vs. 65.7 ± 76.2 mL, $p = 0.621$). Additionally, there was no significant difference in the postoperative hospitalization duration between the study and control groups (3.8 ± 1.3 vs. 4.0 ± 1.4, $p = 0.442$; **Table 2**).

There were no significant differences in the initial pathological types between the two groups ($p = 0.414$; **Table 4**). Unexpected malignant uterine leiomyosarcoma (ULSM) was diagnosed in

TABLE 2 | Perioperative outcomes of the two groups.

Characteristic	Propensity score matching, no. (%)					
	Before			After		
	Study group (n = 193)	Control group (n = 1,753)	*P*-value	Study group (n = 193)	Control group (n = 193)	*P*-value
Leakage	0	–	–	0	–	–
Intra-op. complications	0	4	–	0	0	–
Post-op. complications	9 (4.7)	99 (5.6)	0.625	9 (4.7)	10 (5.1)	1.000
Total operative time, mean (SD), min	119.9 (46.4)	116.6 (46.7)	0.349	119.9 (46.4)	120.2 (44.2)	0.953
Estimated blood loss, mean (SD), ml	73.7 (102.6)	66.2 (91.8)	0.271	73.7 (102.7)	65.7 (76.2)	0.621
Postoperative hospitalization duration, mean (SD), d	3.8 (1.3)	3.6 (1.3)	0.004	3.8 (1.3)	4.0 (1.4)	0.442

TABLE 3 | Peri-operation complications of the two groups.

	Propensity score matching, no. (%)					
	Before			After		
	Study group (n = 193)	Control group (n = 1,753)	*P*-value	Study group (n = 193)	Control group (n = 193)	*P*-value
Intra-op. complications	n = 0	n = 4 (0.2) Bladder injury 1 AWV injury 1 EBL > 1,000 mL 2	–	n = 0	n = 0	–
Post-op. complications	n = 9 (4.7) Incisional seroma 1 Incisional infection 1 Urinary tract infection 2 Hematuria 1 Uroschesis 2 Abdominal dressing allergy 2	n = 99 (5.6) Blood transfusion 5 Phlebothrombosis 1 Pelvic infection 2 Incisional seroma 12 Incisional infection 15 Subcutaneous emphysema 8 Urinary tract infection 17 Hematuria 11 Uroschesis 15 Abdominal dressing allergy 13	0.625	n = 9 (4.7) Incisional seroma 1 Incisional infection 1 Urinary tract infection 2 Hematuria 1 Uroschesis 2 Abdominal dressing allergy 2	n = 10 (5.1) Incisional seroma 2 Incisional infection 1 Urinary tract infection 1 Hematuria 1 Uroschesis 2 Abdominal dressing allergy 3	1.000

EBL, estimated blood loss; AWV, abdominal wall vascular.

one patient (1/193, 0.5%) in the study group. In the control group, five patients (5/1,753, 0.3%) developed malignancy after LM; this included one endometrial stromal sarcoma and four ULSMs. Reoperations for the unexpected sarcomas included laparoscopic hysterectomy and bilateral salpingectomy (LH + BS) or laparoscopic hysterectomy and bilateral salpingo-oophorectomy (LH + BSO) (**Table 5**).

The median follow-up times in the study and control groups were 21 months (range: 12–36 months) and 54 months (range: 12–92 months), respectively. No peritoneal tissue spread was found in the study group. However, 2–6 months after LM, three patients (3/5, 0.6%) in the control group experienced pathologically confirmed sarcoma peritoneal spread. Furthermore, six patients (6/1,753, 0.3%) developed a benign peritoneal tissue spread [the lesions included parasitic leiomyoma and disseminated peritoneal leiomyomatosis (DPL)] due to the recurrence of myomas, abdominal pain, or other reasons. The interval to subsequent surgery ranged from 31 to 73 months (**Table 6**).

TABLE 4 | Initial pathology types of the two groups.

	Pathology types	Study group (n = 193) No. (%)	Control group (n = 1,753) No. (%)	*P*-vaule
Initial pathological types	UL	143 (74.1)	1,259 (71.8)	0.414
	Special types of UL[a]	49 (25.4)	489 (27.9)	
	Uterine sarcoma	1 (0.5)	5 (0.3)	

UL, uterine leiomyoma.

[a]*Special types uterine leiomyoma including atypical leiomyomas, cell-rich leiomyomas, and leiomyomas with uncertain malignant potential, et al.*

DISCUSSION

The use of containment systems in power morcellation is accepted worldwide to thwart the spread of occult malignant tumors (5, 6). However, owing to the poor compatibility between the extraction bag and the surgical instrument, the bag has a

TABLE 5 | Patients with unexpected uterine sarcoma during laparoscopic surgeries for uterine leiomyoma.

Groups	Patients	Age	Pathology	FIGO stage	Supplementary treatment	Peritoneal dissemination (Time to the first operation)	Follow-up time (months)	Survival state
Study group	1	26	ULMS	Ia	LH + BS	No	24	Survival
Control group	1	32	ULMS	Ia	LH + BSO	No	62	Survival
	2	36	ESS	Ib	LH + BSO	Yes (2 months)	25	Die
	3	41	ULMS	Ia	LH + BSO	No	72	Survival
	4	41	ULMS	Ia	LH + BSO	Yes (5 months)	73	Survival
	5	43	ULMS	Ia	LH + BSO	Yes (6 months)	71	Survival

FIGO, The International Federation of Gynecology and Obstetrics; ULMS, uterine leiomyosarcoma; ESS, endometrial stromal sarcoma; LH + BS, laparoscopic hysterectomy; bilateral salpingectomy; LH + BSO, laparoscopic hysterectomy, bilateral salpingo-oophorectomy.

TABLE 6 | Power morcellation-related reoperation of benign pathologies in the control group.

Control group	Patients	Age (years)	Initial pathology	Interval to subsequent surgery (months)	Site
Parasitic leiomyoma	1	20	Leiomyoma	31	Pelvic leiomyoma
	2	35	Leiomyoma	33	Pelvic leiomyoma
	3	41	Leiomyoma	66	Pelvic leiomyoma
	4	37	Cell-rich leiomyoma	54	Trocar site of the previous LM
DPL	5	33	STUMP	36	Peritoneum, Omentum,
	6	36	Leiomyoma	73	Peritoneum, Omentum, Mesocolon

LM, laparoscopic myomectomy; DPL, disseminated peritoneal leiomyomatosis.

high leakage rate and is not easy to operate. This limits the development of minimally invasive surgery (11–14). Therefore, in this study, we reported an NMC system with the aim of realizing the integration of the containment bag and laparoscopic trocars to form a completely sealed containment barrier that prevents the spillage of liquids and tissue from the time the uterine tissue is morcellated and encapsulated in the system.

Several protected techniques by using endobag systems for UL power morcellation have been described in the literatures (17–27). Although these technologies can play a protective role, there are still three major shortcomings. First, the soft auxiliary sleeve is easily twisted and punctured when the surgical instruments enter the bag through a small incision. Second, the end of the auxiliary sleeve is sealed by knotting or suture ligation during removal through the abdominal wall incision; this is inadequate for preventing the sealing area from being contaminated by the tissue. Furthermore, when the bag is removed through the incision, an excessive pressure is generated inside the bag; this puts the sealed area at the highest risk of leakage. Moreover, it is inconvenient to operate by a single port or without the help of an assistant; this does not conform to the traditional laparoscopic operating habits and may increase the difficulty and risk of operation. In addition, using endobag inserted through the posterior colpotomy to remove the specimen is also an effective and feasible alternative technique, and has better a cosmetic effect (28–30). Nevertheless, transvaginal procedures cannot be performed in patients without a sexual history. Furthermore, it is extremely difficult to apply in patients with a narrow vaginal capacity, an obliterated cul-de-sac, or in whom larger myomas require removal (30).

To solve these problems, the system makes use of a hard sheath and sealing cap; these are connected through a reliable and stable threaded interface, thus providing good protection against the spread of tumors. The auxiliary sleeve of the system is composed of a hard material that effectively prevents the twisting or puncturing of the bag. In addition, a sealing cap is used to seal the hard sheath, which can maintain the integrity of the system during the extraction process. The uterine tissue in the bag is completely covered by the sealing cap and does not come in contact with the abdominal wall incision; compared with suture ligation or knotting, the threaded connection can provide tighter and more pressure-resistant protection to the end of the auxiliary sleeve.

In our study, bag damage occurred in two cases in the study group; however, in both cases, the damage was discovered before morcellation, and the NMC systems were replaced. The postoperative methylene blue solution test confirmed that there was no leakage. These two cases of damage occurred in the first 30 cases, and the damaged parts were near the small hard sheath. We considered that this may be due to a torsion between the rigid sheath and the bag body. We also considered that the laparoscopic instrument may have been introduced when not sufficiently adjusted, which may have caused the bag to puncture. In subsequent operations, full attention was paid to the procedure, and all the operations were performed under direct laparoscopic view; therefore, no damage occurred.

On analyzing the follow-up data in the control group, we identified three patients with uterine sarcomas who suffered intraperitoneal dissemination soon after LM (2–6 months); the spread rate was 0.6% (3/5). This result is consistent with the results of previous studies (31, 32). Unprotected morcellation is detrimental to the patient. In case of a malignant sarcoma, it will cause disease upstaging and negatively affect the prognosis. Only one patient in the study group had a ULSM; it has been followed up for 24 months with no evidence of dissemination. In addition to malignancy, there is a risk of benign tissue spread after unprotected morcellation (5, 18, 33, 34). Four cases were observed in the control group and none in the study group. Although there were certain discrepancies in the sample scale and follow-up time between the two groups, because the NMC system has an airtight protective effect and there was no damage or leakage during the operation, we believe that the probability of disseminated implantation is extremely low. Of course, a longer follow-up time is needed for further verification, especially of dissemination of benign tissues.

Finally, to ease manipulation, we used the multi-port rigid sheaths as auxiliary ports, because they can match with the multi-port laparoscope to facilitate the operation with the help of an assistant.

Some studies have reported that the application of the endobag system could be time-consuming due to bag manipulation (27). Based on our findings, the total operative time did not differ significantly between the study and control groups. The reason may be that although the placement and extraction of the system spend more time, the time in searching for tissue fragments and performing repeat irrigation after morcellation can be saved, and the multi-port rigid sheath makes the operation easier.

There were some limitations in our study. The main limitations were the bias associated with patient selection and the retrospective nature of the study. Therefore, to provide stronger evidence, further prospective, multicenter, large-sample clinical studies (NCT 04392674) will be performed. Besides, the control group did not receive any protection during morcellation; thus, there was a risk of tissue dissemination. Although the U.S. FDA proposed a prohibition of power morcellation in 2014; in 2020, it updated the guidelines again to point out the need for morcellation containment system (9, 10). In fact, it was not until 2020 that China proposed the consensus on the implementation of laparoscopic power morcellation for UL (35). During this period, there were some disputes (36). Furthermore, in China, there are still great differences in the economic levels. Many protective devices have not been included in the reimbursement of basic medical insurance; this exerts additional economic burden on the patients. Therefore, some patients still take a chance to choose uncontained morcellation despite knowing the relevant risks; however, the number of patients who make such a choice has reduced significantly. In recent years, Chinese gynecologist have been making continuous efforts to ensure the safety of LM. Furthermore, apart from us, other research groups in China, are also investigating some self-made protective bags during morcellation. However, in general, we are still in the exploratory stage about the containment systems. We believe that the use of containment systems will prevent the risk of tumoral spread caused by power morcellation.

In conclusion, the NMC system is compatible with traditional laparoscopy and can easily comminute fully enclosed fibroids in the abdominal cavity. It is safe, effective, and feasible for the dissemination of tumors under laparoscopy.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of the China-Japan Friendship Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WW, WF, YD, and MX: statistical analysis. BL, JL, DF, HL, HY, and FZ: obtained funding. JL, BL, FZ, HY, QC, CR, and YY: administrative, technical, or material support. WW, JL, and BL: supervision. All authors: critical revision of the manuscript for important intellectual content.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.803950/full#supplementary-material

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Single-Port Laparoscopic Surgery for Adnexal Mass Removal During Pregnancy: The Initial Experience of a Single Institute

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Objective: Single-port laparoscopy has become a feasible and safe approach for the management of benign adnexal masses during pregnancy. To our knowledge, there are few reports on the feasibility and safety of single-port laparoscopy for adnexal mass removal during pregnancy. Our study reports the use of single-port laparoscopy in adnexal mass removal during pregnancy in our hospital.

Methods: We included 10 cases of single-port laparoscopic surgery for adnexal mass removal during pregnancy in the West China Second University Hospital between January 2017 and March 2020. Median values were found using SPSS20. When the *p*-value was < 0.05, the median and interquartile range were used. All patients provided informed consent.

Results: The following median values were recorded: surgical time, 112.50 min; blood loss, 25 ml; postoperative hospital stay, 3 days; postoperative pain [visual analog scale (VAS)] at 6 h, 3; and postoperative pain (VAS) at 24 h, 2. Our study reported no postoperative spontaneous abortions. There was one preterm birth.

Conclusion: Single-port laparoscopy appears to be safe for both the mother and the fetus.

Keywords: single-port laparoscopy, adnexal mass, pregnancy, obstetric outcome, ovarian mass

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INTRODUCTION

Conventional laparoscopy has been widely used as a gold standard surgical method for adnexal mass removal. It is associated with shorter hospital stays, less operative pain, and fewer intraoperative complications when compared with laparotomy. Between 1:500 and 1:635, women require non-obstetric surgery during pregnancy (1). The most common gynecological non-obstetric surgery is adnexal mass removal, with an incidence rate between 0.1 and 2.4% (2). Single-port laparoscopic surgery (SPLS) has become a feasible and safe approach for the management of benign adnexal masses when compared with conventional laparoscopy (3). With the development of surgical experience in laparoscopic technology, it has been used more in pregnant patients. However, to our knowledge, there are few reports on the feasibility and safety of SPLS used in adnexal mass removal during pregnancy. Given the lack of consensus on adnexal mass treatment

during pregnancy, we aimed to compile evidence regarding the safety and efficacy of SPLS as a treatment. Our study reports the use of SPLS in adnexal mass removal during pregnancy in our hospital.

MATERIALS AND METHODS

Subjects

We included 10 cases of SPLS for adnexal mass removal during pregnancy in the West China Second University Hospital between January 2017 and March 2020. The inclusion criteria were as follows: (1) adnexal torsion or rupture was suspected during surgery and (2) the adnexal mass was continually increasing in size during the second trimester of pregnancy and was > 6 cm in diameter.

Operative Techniques

First, we made a 2–3 cm umbilical incision longitudinally. We then inserted the single-port wound retractor into the incision and the port cap was fixed to the wound retractor. The single-port cap contained a gas inlet and four access ports (Kangji Medical). The other laparoscopic instruments were the same as those conventionally used, such as 30°, 10 mm laparoscopes that are placed into the pelvic cavity through the 10 mm port. Then, a pneumoperitoneum was established using CO_2 insufflation of up to 10–15 mmHg, and the abdominal pressure was maintained at around 12 mmHg during surgery. The entire surgical procedure of ovarian cystectomy and suturing of the ovarian tissue within the abdomen was carried out through the single-port. The ovarian tissue was sutured with 2–0 absorbable suture materials, and topical hemostats, such as oxidized cellulose and bipolar hemostat forceps, were used when necessary to reduce the risk of bleeding and to shorten the surgical time if suturing was difficult. Finally, the cyst was retrieved through the umbilical incision and placed in a bag before the umbilical incision was sutured.

Larger adnexal masses were removed using the single-port assisted extracorporeal method. In the single-port assisted extracorporeal method surgical procedure, after puncture and aspiration of the content of the ovarian mass, the cyst was extracted from the abdominal cavity through an umbilical incision. Ovarian cystectomy and suturing of the ovarian tissue were then performed outside of the abdomen (**Figure 1**).

Data Collection and Statistical Analysis

Basic patient data was recorded. This included age, body mass index (BMI), surgical history, parity, method of conception, gestational week, maximum diameter of the ovarian mass, location of the ovarian tumors, and tumor pathology. The perioperative parameters included the diagnosis, such as the cause of the surgery, duration of the surgery, blood loss, postoperative hospital stay, axillary trocar insertion, intraoperative complications such as blood vessel injury, ileus injury, and postoperative complications such as ileus, fever, and wound infection. Postoperative pain was assessed at 6 and 24 h. All patients were contacted to determine the mode of delivery and the gestational week of delivery. Data on the duration of surgery, blood loss, postoperative hospital stay, postoperative pain [visual analog scale (VAS)] at 6 h, and postoperative pain (VAS) at 24 h were analyzed using SPSS20. When the p-value was < 0.05, the median and interquartile range were used.

RESULTS

A total of 10 cases of SPLS for adnexal mass removal during pregnancy were included in our study. **Table 1** describes the basic characteristics of the included patients. Three of the ten procedures were performed because of torsion of the ovarian mass. The rest of the procedures were performed because of persistent enlarged ovarian masses which were >6 cm in the second trimester of pregnancy.

Table 2 presents the perioperative data of the patients. The median surgical time was 112.50 min (interquartile range, 88.75, 185). The median blood loss value was 25 ml (interquartile range, 20, 57.5). The median postoperative hospital stay was 3 days (interquartile range, 3, 4). The median postoperative pain score (VAS) at 6 h was 3 (interquartile range, 2, 3). The median postoperative pain score (VAS) at 24 h was 2 (interquartile range, 1.75, 2). The final histological pathology is included in **Table 2**. Mature teratomas accounted for 40% of the included cases. Hemorrhagic corpus luteal cysts were found in 30% of patients. Mucinous cystadenomas accounted for 20% of cases and only one borderline ovarian serous papillary cystadenoma occurred in the study.

Table 3 reports the obstetric outcomes of the patients. Seven patients delivered after a full-term pregnancy. One patient delivered at 34 + 4 gestational weeks, four patients delivered naturally, and six had a cesarean section delivery.

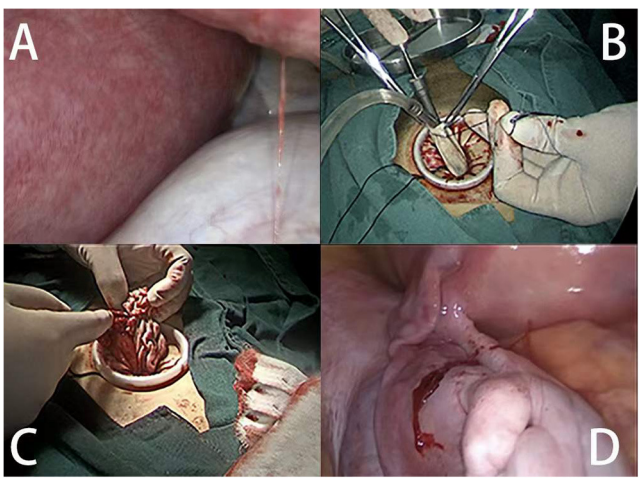

FIGURE 1 | Extracorporeal cystectomy procedure. **(A)** The intraoperative view shows the enlarged uterus and left ovarian mass. **(B)** The puncture and aspiration of the contents of the ovarian mass. **(C)** Cystectomy was performed and sutured extracorporeally. **(D)** The ovarian tissue was returned to the abdomen.

TABLE 1 | Demographic characteristics of the patients.

Case	Age	BMI	Number of previous surgeries	Maximum diameter of the ovarian cyst(cm)	Parity	Gestational week	Method of conception	Location of the ovarian mass	Postoperative diagnosis
Case 1	25	20.3	0	10	G2P0+1	16 + 1	Natural	Left	Torsion of left ovarian mass
Case 2	26	21.6	0	8	G1P0	16 + 4	Natural	Right	Right ovarian mass
Case 3	31	25.7	0	6	G2P0+1	13 + 2	Natural	Right	Right ovarian mass
Case 4	24	18.4	0	10	G1P0	17 + 6	Natural	Bilateral	Bilateral ovarian mass
Case 5	33	21.5	0	11	G2P0+1	14	Natural	Left	Torsion of left ovarian mass
Case 6	32	24.2	0	10	G1P0	18	IVF-ET	Bilateral	Bilateral ovarian mass
Case 7	29	20.9	0	6	G1P0	8 + 2	Natural	Right	Right ovarian mass
Case 8	28	21.6	0	6	G1P0	18 + 2	Natural	Right	Torsion of right ovarian mass
Case 9	35	24.8	0	25	G1P0	13 + 2	Natural	Left	Left ovarian mass
Case 10	32	27.1	0	12	G3P1+1	15 + 5	Natural	Right	Right ovarian mass

DISCUSSION

In the past, the laparoscopic approach to treat adnexal masses in the second and third trimesters of pregnancy has been discouraged. The main concerns were the risk of uterine perforation when using a Veres needle, the impact of intraabdominal pressure and CO_2 on the feto-maternal circulation, longer surgical times compared to laparotomy, and potential harm from the use of monopolar current. Based on these concerns, open surgical techniques have been preferred during pregnancy. Pearl et al. (4) commissioned the guideline for laparoscopy in pregnancy which recommends that (1) End-tidal CO2 ($ETCO_2$) be used as a surrogate marker for maternal arterial CO_2 monitoring, (2) CO_2 insufflation be performed to 10–15 mmHg, and (3) that the abdominal operating pressure of 12 mmHg be observed to maintain feto-maternal perfusion and optimal utero-placental blood flow. Additionally, bipolar hemostasis has been reported to be safe to use in the course of laparoscopic surgery performed during pregnancy (5). Further studies have since reported maternal and fetal safety using a laparoscopic surgical approach in pregnant patients (5, 6). Laparoscopic surgery in pregnant women has also been associated with faster recovery, shorter hospital stays, and fewer wound infections compared with laparotomy (7). Single-port laparoscopy also has the advantages of conventional laparoscopy without the risk of Veres needle injury and with less postoperative incision pain, shorter hospital stays, and ease of specimen extraction through the umbilical incision (8).

We reported 10 cases of adnexal mass removal during pregnancy using SPLS and the obstetric outcomes for each patient were optimal. We have also summarized the literature about the single port approach during pregnancy in **Table 4** (8–16). To our knowledge, only seven studies have reported the use of SPLS for adnexal mass removal during pregnancy (8–14). Jiang et al. (8) reported 15 cases of cystectomy during pregnancy with no instances of missed abortion or preterm birth. Lee et al. (9) reported 14 women with intrauterine pregnancies who underwent SPLS for adnexal disease during pregnancy with good obstetric outcomes. Takeda et al. (10) reported 29 cases of adnexal mass removal during pregnancy, four of which resulted in preterm birth. Scheib et al., Kim et al., Dursun et al., and Xiao et al. (11–14) detailed two, one, nine, and six case reports, respectively, where SPLS was performed on an adnexal mass during pregnancy, and the obstetric outcomes were also good.

According to the American College of Obstetrics and Gynecology committee (17), performing non-urgent laparoscopic surgery in the second trimester is the best option for adnexal mass removal during pregnancy. In women with persistent masses in pregnancy, the reported malignancy rate is 3.6 to 6.8% and the rate of torsion of adnexal masses during pregnancy is 10% (2). Persistently growing ovarian masses >6 cm in diameter in the second trimester can be considered for removal *via* elective surgery in cases of emergencies and malignancies (17). Diagnostic laparoscopy in the management of adnexal masses during pregnancy is safe unless clinical severity warrants laparotomy or malignancy is strongly suspected (4). In our study, we performed three emergency surgeries and seven elective surgeries.

Chong et al. (18) reported using a single-port assisted extracorporeal approach for the removal of an ovarian cyst that

TABLE 2 | Perioperative characteristics of the patients.

Case	Histological pathology	Surgery time (min)	Surgical blood loss (ml)	Postoperative Hospitalstay (days)	Ancillary trocar insertion	Intraoperative complication	Postoperative complication	Postoperativepain (VAS) 6h	Postoperativepain (VAS) 24h
Case 1	Hemorrhagic corpus luteal cyst	90	30	3	No	No	No	3	2
Case 2	Mature teratoma	100	20	4	No	No	No	1	1
Case 3	Borderline ovarian serous papillary cystadenoma	185	20	3	No	No	No	2	2
Case 4	Mature teratoma	200	80	3	One	No	No	3	2
Case 5	Mature teratoma	185	20	6	One	No	No	7	4
Case 6	Hemorrhagic corpus luteal cyst	120	100	3	No	No	Delayed wound healing	3	2
Case 7	Hemorrhagic corpus luteal cyst	105	30	4	No	No	No	2	2
Case 8	Mature teratoma	120	10	3	No	No	No	3	0
Case 9	Mucinous cystadenoma	83	50	3	No	No	No	3	2
Case 10	Mucinous cystadenoma	85	20	4	No	No	No	2	2

TABLE 3 | Obstetric outcome of the patients.

Case	Gestational age at delivery	Delivery method
Case 1	37 + 6	Natural labor
Case 2	40	Natural labor
Case 3	39 + 1	Cesarean delivery
Case 4	39	Natural labor
Case 5	41	Cesarean delivery
Case 6	34 + 4	Natural labor
Case 7	38 + 3	Cesarean delivery
Case 8	40 + 2	Cesarean delivery
Case 9	39	Cesarean delivery
Case 10	40 + 3	Cesarean delivery

measured > 8 cm in diameter on preoperative imaging. Kim et al. (12) first reported the safety of this method in adnexal mass during pregnancy. We adopted a single-port assisted extracorporeal approach for Case 9. The remaining patients underwent single-port laparoscopy. Ancillary trocar insertion was performed in two patients.

A meta-analysis reported by Liu et al. (19) showed that using laparoscopy for ovarian cyst removal is associated with better maternal and obstetric outcomes when compared with laparotomy. Three studies have reported on the safety and feasibility of single-port laparoscopy for adnexal masses when compared to conventional laparoscopy (3, 20, 21). Wang et al., Lee et al. (3, 20) compared the perioperative outcomes of single-port laparoscopy and conventional laparoscopy in adnexal mass removals and reported no difference in the median operation time, the median decreased level of hemoglobin from preoperative to postoperative day, or the median duration of postoperative hospital stay. Furthermore, Yim et al. (21) reported no difference in postoperative pain scores, operative time, perioperative complications, intraoperative blood loss, or duration of hospital stay between single-port laparoscopy and conventional laparoscopy in adnexal disease. However, only two reports have compared the use of single-port laparoscopy for ovarian mass removal during pregnancy with the use of conventional laparoscopy, but they both concluded that the techniques had comparable perioperative surgical and pregnancy outcomes (8, 10). We report a median surgical time of 112.50 min, a median blood loss of 25 ml, a median postoperative hospital stay of 3 days, a median postoperative pain (VAS) score of 3 at 6 h, and a median postoperative pain (VAS) score of 2 at 24 h. These results are similar to those detailed by Liu et al. (19) in their report on the perioperative data of laparoscopy used in adnexal masses during pregnancy. Our study reported no postoperative spontaneous abortions and one preterm birth. SPLS seems to be a safe alternative to conventional laparoscopy in treating patients with adnexal masses that require removal during pregnancy. However, there are still some shortcomings and challenges of SPLS compared to conventional laparoscopy during pregnancy. The ability to maneuver instruments in one port is limited and the enlarged uterus influences the view and

TABLE 4 | Published literature of single port laparoscopy during pregnancy.

References	Country	Disease during pregnancy	Cases	Surgical complications	Obstetric outcome
Jiang et al. (8)	China	Acute abdomen	26	None	1 abortion, 4 preterm births (did not mention the gestational age)
Lee et al. (9)	Korea	Adnexal surgery	14	None	1 preterm birth (24 + 5 week) and 1abortion
Takeda et al. (10)	Japan	Adnexal masses	29	None	4 preterm births (did not mention the gestational age)
Scheib et al. (11)	USA	Adnexal Masses	9	None	1 Preterm birth (36 weeks)
Kim et al. (12)	Korea	Ovarian mass	1	None	Not available
Dursun et al. (13)	Turkey	Adnexal mass	2	None	1 preterm birth (32 weeks)
Xiao et al. (14)	China	Gynecological disease	13	None	4 preterm births (35-36+2 weeks)
Koh et al. (15)	Korea	Acute appendicitis	2	None	Not available
Cho et al. (16)	Korea	Acute appendicitis	12	2 superficial surgical site infections and 1 post-operative ileus.	1 abortion

operating space. As a result, the British Society for Gynecological Endoscopy (BSGE) recommends that laparoscopic surgery during pregnancy be performed by advanced laparoscopic surgeons with appropriate training and competencies (4).

There are two possible areas of future improvement for this technique. Minilaparoscopy uses 2–5 mm diameter laparoscopic instruments that can improve the cosmetic outcomes of surgery (22, 23). Minilaparoscopic single-site surgery is a new surgical procedure that combines the advantage of minilaparoscopic and single-site surgery. Casarin et al. (24) reported on this procedure to perform bilateral salpingo-oophorectomy. It is possible that this technique can be applied to the treatment of adnexal mass during pregnancy. In addition, it has been suggested that Endo Bags be used to extract suspected malignant masses to prevent spillage and the chance of spillage is rarely existed (25). In single-port laparoscopy, the cyst can be placed in a bag after cystectomy and retracted through the umbilical incision. However, if the cyst is ruptured during the cystectomy, the spillage cannot be avoided. In this case, the ovarian mass can be placed in the Endo Bag before the cystectomy is performed to reduce the spillage as suggested by Laganà et al. (26).

CONCLUSION

The limitation of our study was the small number of patients included; therefore, we did not compare our findings with those of traditional laparoscopy performed in our hospital. We intend to include more cases and conduct large randomized trials with long-term follow-up in the future. However, based on the data we included, SPLS appears to be safe for the mother and fetus.

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 authors.

ETHICS STATEMENT

The study was approved by the Ethics Committee of the West China Second University Hospital and informed consent was taken from all the patients. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LH and YC were responsible for the conception of the study and manuscript drafting. AZ, QW, and LH contributed to the revision and final approval of the manuscript. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Left External Iliac Vein Injury During Laparoscopic Pelvic Lymphadenectomy for Early-Stage Ovarian Cancer: Our Experience and Review of Literature

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Laparoscopic surgical staging is the standard treatment of early-stage ovarian tumors with similar survival outcomes if compared with laparotomic procedures. In this article, we report a case regarding an incidental external iliac vein injury during a pelvic lymphadenectomy for fertility sparing treatment of early-stage ovarian cancer with a video showing the laparoscopic repair without any consequence or side effect. A 36 year-old obese woman with Body Mass Index 30 kg/m^2 referred at our hospital with an histological diagnosis of high grade ovarian serous carcinoma after a left laparoscopic salpingo-oophorectomy performed in another hospital. After an hysteroscopy with endometrial biopsy, a laparoscopic surgical staging with a pelvic and aortic lymphadenectomy with lymph-node dissection until the left renal vein, omentectomy, and appendectomy were performed. A thermal injury to the left external iliac vein occurred using the bipolar forceps during lymphadenectomy and was repaired after an immediate clamping of the site using endoclinch and the suction irrigator probe. The laceration on the iliac vein was successfully repaired using 10 mm laparoscopic titanium clips; after a follow-up of 42 months no recurrence was detected. In conclusion, laparoscopy is a safe and effective therapeutic option for fertility sparing treatment patients with early stage ovarian carcinoma with a significantly low morbidity and postoperative hospitalization, but it should be reserved for oncologic surgeons trained in advanced laparoscopic procedures and repair of vascular injuries potentially associated with high mortality rate.

Keywords: injury, iliac vein, laparoscopy, lymphadenectomy, repair, ovarian cancer

INTRODUCTION

Vascular interventions are frequently performed during gynecological oncological procedures for injury of pelvic blood vessels. Vascular repairs during gynecologic procedures are associated with an high morbidity and mortality and are associated to intraoperative vascular injury (1, 2).

Pelvic and aortic lymphadenectomy have a prognostic and therapeutic significance and are often performed during gynecological oncological procedures (1–3) operating in proximity to multiple vascular structures.

In a recent prospective study Uccella et al. (2) assessed safety and feasibility of the sentinel lymph node (SLN) technique with indocyanine green to identify the presence of lymph node metastases in patients with early stage epithelial ovarian cancer, although they observed that the detection of SLN in early epithelial ovarian cancer is low when patients are submitted to delayed-staging surgery. However, they concluded that SLN procedure is safe and feasible and has the potential to provide reliable and useful information on lymph nodal status in the majority of patients with a lower morbidity and hospitalization.

Given the high mortality associated with vascular repairs, strategies for increasing the availability of gynecological surgeons trained in vascular surgery should be adopted (2).

These complications mostly involve iliac veins (2, 3) for their anatomical variability and a deep positions with risks of serious intraoperative hemorrhage of about 2.21–4.44% (4–6).

In this article, we report a case regarding an incidental external iliac vein injury during a pelvic lymphadenectomy for fertility sparing treatment of early-stage ovarian cancer with a video showing the laparoscopic repair performed without any consequence or side effect.

MATERIALS AND METHODS

A 36 year-old obese woman with Body Mass Index 30 kg/m^2 referred at our hospital with an histological diagnosis of high grade ovarian serous carcinoma after a left laparoscopic salpingo-oophorectomy performed in another hospital.

After an hysteroscopy with endometrial biopsy, a laparoscopic surgical staging with pelvic and aortic lymph-node dissection until the left renal vein, omentectomy and appendectomy was performed.

The pelvic lymphadenectomy started developing the right paravesical and pararectal spaces. The round ligament was coagulated and transected and the peritoneal layers of the broad ligament were opened.

Dissection of the paravesical space was completed by introducing the endoclinch and the bipolar forceps (BiClamp, 210 ERBE VIO System, Tübingen, Germany) in the space laterally to the internal iliac artery (obliterated umbilical artery) and external and common iliac lymph nodes were removed.

The obturator nerve and vessels were isolated and skeletonized and, finally, superficial, and deep obturator lymph nodes were dissected and removed.

During the left pelvic lymphadenectomy, a thermal injury at the medial surface of the left external iliac vein occurred using the bipolar forceps (**Figure 1**).

After an immediate clamping of the injury site using the endoclinch and the suction irrigator probe, the insufflation pressure was increased to 20 mm Hg to reduce bleeding (1, 2). After obtaining a better view by insinuating the suction irrigator probe and drawing the blood, we decided to try a laparoscopic management of the complication.

All the procedures for unexpected surgical vascular injury were activated: after releasing the tension of the Endoclinch the entity and the site of vascular lesion were recognized and detected.

The laceration on the left external iliac vein was successfully repaired using 10 mm laparoscopic titanium clips and the operative time for the left external iliac vein repair was 3 min.

Laparoscopic vessel repair was performed successfully without intracorporeal suture; to prevent thromboembolism, intravenous heparin was administered during the surgical procedure.

The patient was regularly discharged 4 days after laparoscopic procedure without blood transfusion with an hemoglobin value that was 11 g/dL.

Low molecular–weight heparin 4,000 U subcutaneously once daily was administered during hospitalization. No sign of thromboembolism was detected; no metastases were detected by intraoperative and definitive pathologic examination; after a follow-up of 42 months no recurrence was detected.

DISCUSSION

Vascular injuries can occur at entry during gynecological oncological procedures using a Veress needle or at the introduction of trocars and surgeons may suspect these damages when there is any evidence of bleeding or hematoma that cannot be explained (7).

External iliac vessel injury at the beginning of a laparoscopy is frequently due to the position of the aorta and vena cava near the umbilicus; frequently, this risk is highest in thinner patients due to the proximity of the vessels to the skin (1, 2).

Although data from randomized controlled trials has shown that laparoscopic hysterectomy results in reduced operative morbidity, shorter hospital stays, and similar oncologic outcomes when compared with laparotomy, this approach may be unsuccessful in patients with obesity because of technical challenges, limited anatomical exposure due to fat deposits around iliac vessels during lymphadenectomy, and cardiopulmonary compromise while in the Trendelenburg position (3, 4).

Vascular damages in gynecology are rare (0.2/1,000) but are associated with a 6–13% of mortality.

The most frequent sites of hemorrhage are iliac vessels, inferior vena cava, and abdominal aorta.

Frequently, electrosurgery during laparoscopy may cause vascular trauma and thermal injuries: in fact injury to iliac vessels due to thermal spread are frequently reported during

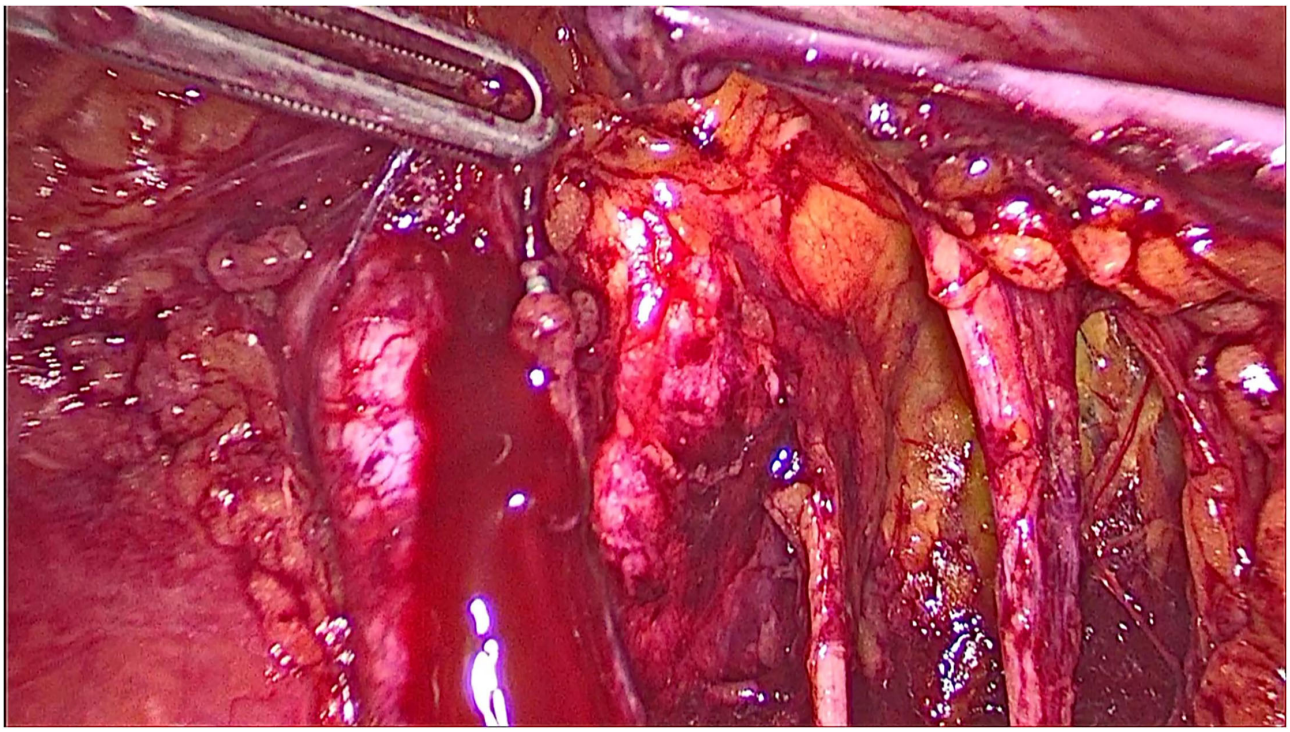

FIGURE 1 | A thermal injury at the medial surface of the left external iliac vein occurred while using the bipolar forceps during left pelvic lymphadenectomy.

laparoscopic and robotic lymph node dissection and are due to failure of the insulation around the scissors (8).

Managing of these complications includes immediate recognition and localization of the injury because vascular injuries are rare but can be fatal and may require midline laparotomy and vascular surgeons (9).

The vascular iatrogenic repairs during extensive oncologic laparoscopic procedures are increasing in frequency (5–7).

Clinical evaluation of severity of the injury should be immediately done: in cases of damage to the aorta, iliac vessels or IVC (inferior vena cava), a laparotomic repair should be performed.

Injuries to aortic branch like inferior mesenteric artery that is clearly visualized may be repaired laparoscopically. However, in case of aortic branch vessel damage, skeletonization could be difficult and there is a risk of concomitant visceral injury.

Control of the bleeding by applying a direct pressure on the injury site should be considered and it will nearly always suffice.

If the site of hemorrhage cannot be visualized, abdominal packing should be done: in this case a conversion from laparoscopic to open surgery with a midline laparotomy should be considered.

Most vascular injuries will occur in the pelvis and, after pack removal out of the pelvis for definitive management, it is important to determine the extent of injury.

Common iliac artery or distal aorta are best repaired with primary suture by a vascular surgeon. These injury sites should be compressed until a vascular surgeon is available.

Repair of internal iliac artery can be performed by sutures and ligaclip because there is a great collateral blood vascularization.

Venous pelvic injuries are the most difficult to manage: in the first instance the bleeding site should be carefully packed and, after a temporarily closing of the abdomen, the patient should be re-operated the next day for pack removal and re-assessment.

If packing alone is not enough and the damage includes the sacral venous plexus, internal iliac vein or collateral veins then hemorrhage occluder pins can be directly applied to the hemorrhage site (8–10).

In a recent report Levin et al. investigated the incidence of vascular injury in patients who underwent open, laparoscopic and vaginal gynecologic surgery.

In their multicenter study including 201,224 surgical procedures they observed that vascular repairs were rare and occurred during laparotomic hysterectomies performed for malignant in patients with chronic anticoagulation, ASA class 3 or class 4 (0.2% of open, 0.04% of minimally invasive, and 0.03% of vaginal operations) (11).

In another multicenter study, of 482 gynecologic laparoscopies for benign or malignant disease performed in a USA center between 1996 and 2000, 1,165 laparoscopic hysterectomies for benign disease in Finland between 1993 and 1994, and 25,764 gynecologic laparoscopies for benign or malignant disease in the Netherlands, a 1.5, 1.2, and 0.25% of vascular injury was observed, respectively (10, 11).

A recent systematic review by King et al. on 1,097 patients reported the rate of vascular injuries during gynecologic

laparoscopic procedures for benign disease. One hundred and seventy-nine vascular injuries were reported with a percentage of 0.09%. The inferior epigastric vessels were the most commonly injured and the majority of injuries occurred during abdominal entry. Most injuries were recognized intraoperatively. Only two of the 179 major vascular injuries resulted in death with a mortality rate of 0.001%.

They concluded that the incidence of major vascular injury during gynecologic laparoscopy is very low, and that laparoscopy is a safe surgical technique if performed for benign gynecologic disease (11–13).

In recent studies regarding patients who underwent laparoscopic gynecologic surgery a correlation between lower BMI and increased injuries rate was observed in thinner patients.

In fact, in patients with lower BMI a shorter distance between the skin and retroperitoneal vessels was observed as well as an increased proximity of the aortic bifurcation to the level of the umbilicus that minimize the safe distance with an higher risk of vascular injury at introduction of the Verses needle and the trocar.

Long-term multicenter studies analyzing the association between vascular injury and morbidity or mortality in gynecologic patients are not available (12, 13).

The feasibility, safety, and efficacy of laparoscopic treatment of gynecologic malignancies has been reported by several articles in the last decades (3, 4) with a lower postoperative morbidity.

In fact, staging procedures including hysterectomy, pelvic and Para aortic lymph-node dissection, omentectomy, and peritoneal biopsy are actually completed by laparoscopy (14, 15).

In our study, the hemorrhage was controlled with endoscopic clips applied distally and proximally to the lesion, with the clip applier/remover (Aesculap, Braun, Germany) introduced into the abdomen through the surgeon trocar.

In fact, endoscopic clips are safe and effective therapeutic tools that ensure a great control of hemorrhage.

Laparoscopic treatment of vascular injuries is an effective and safe procedure: to better control the hemorrhage we suggest using immediately, in case of vascular injury, the endoclinch forceps applied directly to the lesion and to isolate the vessel that have to be repaired (16–18).

In selected cases before removing the endoclinch forceps, a laparoscopic bulldog clamp can be placed proximally, and another clamp should be used distally for a better repair and an improved suture.

During last decades several articles confirmed the role of laparoscopic and robotic pelvic lymphadenectomy in the treatment of gynecologic cancers (18, 19).

Current guidelines for complete surgical staging in early-stage ovarian cancer recommend systematic lumbo-aortic and pelvic lymphadenectomy, despite their controversial therapeutic value. Sentinel lymph node (SLN) detection with indocyanine green in early ovarian cancer is a feasible technique and could provide useful information on nodal status, avoiding future lymphadenectomy in the majority of patients. SLN biopsy in ovarian cancer is not yet the standard approach, and is currently under investigation. A recent report by Turco et al. confirmed the feasibility of laparotomy approach for SLN detection in voluminous ovarian cancer (6), although a recent prospective study by Uccella et al. observed that the detection of SLN in early epithelial ovarian cancer is low when patients are submitted to delayed-staging surgery but SLN procedure could avoid systematic lymphadenectomy in the majority of patients (2, 6).

However, strategies for increasing the availability of gynecological surgeons trained in vascular surgery should be adopted (4, 5, 20, 21).

In conclusion, laparoscopy is a safe and effective procedure for treatment of fertility sparing treatment patients with early stage ovarian carcinoma with a lower morbidity and hospital stay and a reported pelvic vessel injury rate during pelvic lymphadenectomy of about 1%.

Repair of this complications should be reserved for gynecologic surgeons trained in advanced laparoscopic procedures and repair of vascular damages potentially associated with an high mortality rate.

Strategies for prevention and treatment, including continuous training on this gynecological emergency situation should be adopted to increase the availability of gynecologic surgeons trained in vascular surgery.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

RT, LN, MiD, ES, and FS were a major contributor in writing the manuscript. SA, MaD, SP, SU, and GB were in charge of the final approval of the version to be published. RT performed the surgery. All authors analyzed, interpreted the patient data according to the histological examination and the literature review, and read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.843641/full#supplementary-material

A video reported an incidental external iliac vein injury during a pelvic lymphadenectomy for early-stage ovarian cancer that was laparoscopically repaired without any problem.

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BRIEF RESEARCH REPORT
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Treatment of Placenta Increta With High-Intensity Focused Ultrasound Ablation and Leaving the Placenta *in situ*: A Multicenter Comparative Study

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Objective: To explore the feasibility of simple high-intensity focused ultrasound (HIFU) ablation for placenta increta.

Methods: Ninety-five patients after a vaginal delivery were enrolled in this retrospective cohort study, 53 patients were treated with simple HIFU ablation, and 42 patients were treated with HIFU followed by uterine curettage.

Results: All 95 patients were successfully treated with a single-session HIFU procedure, and in the control group, the necrotic placental tissue was removed with curettage. Vaginal hemorrhage did not occur in either group. The duration of bloody lochia was 25.9 ± 8.6 days in the sHIFU group and 24.2 ± 8.8 days in the control group ($P > 0.05$). The median serum human chorionic gonadotropin (HCG) level was 3,222 mIU/mL and 2,838 mIU/mL in the sHIFU and control groups, respectively, which decreased and returned to normal within 30 days, and the differences were not significantly on comparing the blood HCG level in the two groups at 7, 15, and 30 days after HIFU (all $P > 0.05$). Decreased menstrual volume occurred in 85.71% of patients in the control group, which was higher than that in the sHIFU group (23.08%) ($\chi^2 = 6.839$, $P < 0.001$). During 2–8 years of follow-up, six pregnancies occurred in the sHIFU group without any recurrence of placenta increta, three pregnancies occurred in the control group, and one patient developed a repeat placenta increta.

Conclusion: Simple HIFU treatment is safe and effective for postpartum placenta increta and leaving the placenta *in situ*. It is a promising option for patients who wish to preserve their fertility and conceive.

Keywords: placenta increta, high-intensity focused ultrasound (HIFU), focused ultrasound therapy, leaving the placenta *in situ*, placenta accreta spectrum, abnormally invasive placentation

INTRODUCTION

Placenta accreta spectrum (PAS) refers to the range of pathologic adherence of the placenta, including placenta increta, placenta percreta, and placenta accreta (1). Placenta increta is defined as invasion of the placenta into the myometrium, but not beyond (2). Abnormally invasive placentation (AIP) is observed clinically when the placenta cannot be separated from the uterus (3). The MRI features considered indicative of invasive placenta previa are as follows (4–6): (1) myometrial thinning: the myometrium thins and the typical trilaminar appearance is undetectable; (2) interrupted myometrium: the myometrium is interrupted abruptly at the site of focal placenta bulging; and (3) loss of the placental-myometrial interface: the thin hypointense layer between the placenta and myometrium disappears. When an abnormally invasive placenta develops, the placenta may not be completely separated from the uterus at the time of delivery, resulting in potentially life-threatening massive intrapartum or postpartum hemorrhage and associated morbidities, such as multisystem organ failure, disseminated intravascular coagulation, and even death (2).

Leaving the placenta *in situ* after delivery of the fetus has been utilized as a treatment option in multiple studies, but it is generally used in conjunction with other conservative modalities (2). The recent International Federation of Gynecology and Obstetrics (FIGO) consensus guidelines have recommended "leaving the placenta *in situ*" as a suitable option with close follow-up in hospitals with adequate expertise (7). Infection and hemorrhage and reoperative interventions are associated with high morbidity rates during observation and can even be life-threatening for the mother. Therefore, if the placental blood supply can be blocked in the clinical strategy of "leaving the placenta *in situ*," it may be an effective idea to reduce the maternal morbidity. The 2018 FIGO placenta accreta disease guidelines clearly indicate the advantages of high-intensity focused ultrasound (HIFU) for the treatment of PAS (7).

High-intensity focused ultrasound is an *in vitro* low-intensity ultrasound focused on the target area *in vivo*, which forms a high-energy density focal point and causes rapid heating of the tissue in the focal area and coagulative necrosis of the target area within a short period of time, and thus, it achieves the purpose of treating the disease. At present, HIFU has been widely used in clinical practice to block the blood supply of uterine fibroids to induce coagulative necrosis. In a study including 12 patients with PAS after vaginal delivery treated with HIFU, one case could clear off the coagulated necrotic placental tissue and the remaining patients had a mean time to residual placental degeneration of 36.9 days. HIFU treatment did not increase the risk of infection or bleeding, and none of the patients required hysterectomy (8). However, there is still a lack of clinical evidence on whether placenta increta can be treated with HIFU ablation alone and leaving the placenta *in situ*. The aim of this study was to confirm the feasibility, safety, and efficacy of HIFU treatment alone in the treatment of placenta increta by a combined comparative study of HIFU treatment alone and HIFU treatment followed by curettage.

MATERIALS AND METHODS

Patients

From 2013 to 2020, 95 women with postpartum placenta increta were treated in the First People's Hospital of Neijiang City, Suining Central Hospital and Chongqing Haifu Hospital, and were enrolled in this retrospective cohort study. Inclusion criteria were as follows: (1) vaginal delivery, incomplete delivery of the placenta, and close adhesion of the placenta to the uterine muscle wall that could not be detached on palpation during freehand placenta removal. (2) Vital signs were stable and there were no signs of active hemorrhage. (3) The diagnosis of placenta increta was confirmed by MRI. (4) Intention to be treated with HIFU and signature on the written informed consent form. Exclusion criteria were as follows: (1) penetrating placenta increta; (2) occurrence of major bleeding (bleeding volume $\geq$500 mL); (3) residual placenta is large and extends to cervix or vagina; (4) current infection with body temperature $\geq$38.5°C. The study was approved by the ethics committee of the hospital (IRB approval number: 2020027). The Chinese Clinical Trial Registry (a non-profit organization, established according to both the WHO International Clinical Trials Register Platform Standard and the Ottawa Group Standard) provided full approval for the study protocol, recruitment materials, and consent form (Registration No. ChiCTR2200056055).[1]

High-Intensity Focused Ultrasound Ablation

Ultrasound-guided HIFU was performed using a Focused Ultrasound Tumor Therapeutic System (Model-JC200, Chongqing Haifu Medical Technology Co., Ltd., Chongqing, China). The procedure of HIFU ablation has also been described in a previous publication (7). In summary, all patients were asked to consume only liquid food for 1 day, followed by a 6-h fasting period. An enema was performed on the morning of the treatment day. The hair on the abdominal wall from the umbilicus to the level of the upper margin of the pubic symphysis was shaved and degreased using 75% ethanol solution. The patient was positioned prone on the treatment table of the HIFU system with the abdominal wall in contact with degassed water over the transducer. The treatment plan was created automatically under ultrasonography guidance: the residual placenta increta was divided into slices of a thickness of 5 mm, acoustic power of 350–400 W was used, and HIFU treatment was terminated when guided ultrasonography showed a grayscale increase change in the target tissue or the signal of blood flow to the placental tissues disappeared. Contrast-enhanced ultrasound was also used to evaluate blood perfusion in the placental tissues (**Supplementary Material**). Patients were given low doses of fentanyl citrate injection (first 1 μg/kg) and midazolam (first 0.03 mg/kg, total combined dose $\leq$0.15 mg/kg) *via* the intravenous (IV) route during the procedure. The patient's response was observed while the sonication was being performed, so that the patient was at the sedation level 3–4 Ramsay scale.

[1] www.chictr.org.cn

Non-perfused Volume rate (NPVR) was measured on enhanced MRI after HIFU treatment. Monitoring and evaluation images are shown in **Figure 1**.

Management After High-Intensity Focused Ultrasound

After HIFU treatment, patients were informed about two management options. Allowing the placenta to be kept *in situ* to wait for absorption and expulsion, or curettage with removal of necrotic lesions after HIFU ablation and possible reduction of the postoperative observation time, but there was a risk of uterine perforation and hemorrhage. Patients who voluntarily chose to undergo curettage served as the control group. Curettage was performed by a team of experienced gynecologists from each hospital under ultrasound imaging guidance within 5 days after the HIFU procedure.

Follow-Up

Serum human chorionic gonadotropin (HCG) levels were rechecked on day 7, day 15, and day 30 after HIFU until return of normal levels. The time and volume of vaginal bleeding, the time and menstrual volume, and pregnancy achievement were assessed by a telephone interview.

Statistical Methods

The statistical software SPSS 26.0 was used for statistical description. The categorical variables were expressed as frequencies and percentages, and continuous variables were expressed as medians (interquartile range, IQR). The intergroup comparison of the count data was performed by the Chi-square test or Fisher's exact probability method. The Mann–Whitney U test was used for comparison of the measurement data between groups. Generalized estimating equations were used for intergroup comparisons of repeated measures at a test level of 0.05. Differences were considered statistically significant at $P < 0.05$.

RESULTS

Ninety-five patients were enrolled in this study. There were 53 patients in the sHIFU group; the median age was 29.0 years (IQR: 24.0–32.0 years); 12 women were primipara, 41 had a history of delivery and 21 cases underwent cesarean section; 32 females delivered at 28 weeks or more; the implanted placenta size (longest diameter) was 6.0 cm (IQR: 4.0–7.0 cm) and the area was 15.1 cm^2 (IQR: 9.6–26.3 cm^2) (longest diameter × vertical diameter of the longest diameter), and the placenta increta depth was 4.0 cm (IQR: 2.6–4.5 cm). In the control group, there were 42 patients, the median age was 28.0 years (IQR: 25.0–32.0 years); 5 women were primipara and 37 were multiparas, including 23 cases that underwent cesarean section; 18 females delivered at 28 weeks or more; the implanted placenta size was 7.0 cm (IQR: 5.2–9.0 cm) and the area was 31.3 cm^2 (IQR: 15.8–51.8 cm^2), and the placenta increta depth was 4.5 cm (IQR: 3.6–4.9 cm). Details are presented in **Table 1**.

Results of High-Intensity Focused Ultrasound Treatment

All 53 patients in the sHIFU group and 42 patients in the control group completed HIFU treatment as per the treatment plan, and all patients appeared to have a non-perfused area within the implanted placenta, as shown in **Figure 2**. Patients complained of discomfort, such as pain and abdominal distension in the sacrococcygeal region and treatment area during HIFU treatment, which was tolerable. No complications, such as skin burns and lower limb paralysis, occurred after treatment. The median power of HIFU treatment was 400.0 W (IQR: 395.0–400.0 W), treatment time was 70.0 min (IQR: 59.0–92.2 min), and sonication time was 700.0 s (IQR: 550.0–950.0 s). The median NPVR of the implanted placenta was 83.0% (IQR: 75.0–87.0%) in the sHIFU group and 81.0% (IQR: 74.8–88.3%) in the control group, and the difference between the two groups was not significant ($Z = 0.098$, $P = 0.922$).

Tissue Expulsion and Vaginal Bleeding After Treatment

Forty-two patients were treated with curettage 1–5 days after HIFU, and necrotic tissue was expelled in 100% of the cases without any complications, such as uterine perforation. All 53 cases in the sHIFU group discharged necrotic tissues, while 41 cases in the control group experienced intermittent discharge of necrotic tissues after the curettage procedure. None of these 95 patients developed heavy bleeding after treatment, and only a few cases have a small volume of old blood vaginal discharge. The duration of bloody lochia was 24.0 days (IQR: 19.0–31.0 days) in the sHIFU group and 25.0 days (IQR: 16.0–31.0 days) in the control group, with no significant difference between the two groups ($Z = 0.803$, $P = 0.422$).

Changes in Serum Human Chorionic Gonadotropin After Treatment

Serum HCG levels decreased sharply after treatment in both groups, and serum HCG levels in both groups returned to normal within 30 days after treatment. There was no statistically significant difference between the HCG level in the sHIFU group and the control group at 7, 15, and 30 days postoperatively ($P > 0.05$), as listed in **Table 2**. The "interaction of grouping factors and time" was also not statistically significant ($P > 0.05$); i.e., there was no difference in the time trend of serum HCG between the two groups, as shown in **Table 2**.

Menstrual Resumption and Pregnancy Achievement

After HIFU treatment, menstruation resumed within 3 months in all 95 patients, and it took 62.0 days (IQR: 54.0–72.0 days) in the sHIFU group and 70.0 days (IQR: 6,254.0–82.0 days) in the control group; there was a significant difference between the two groups ($Z = 2.685$, $P = 0.007$). A total of 85.7% of patients in the control group experienced reduced menstrual volume, which was significantly higher than that in the sHIFU group (23.1%), with a significant difference ($\chi^2 = 6.839$, $P = 0.000$).

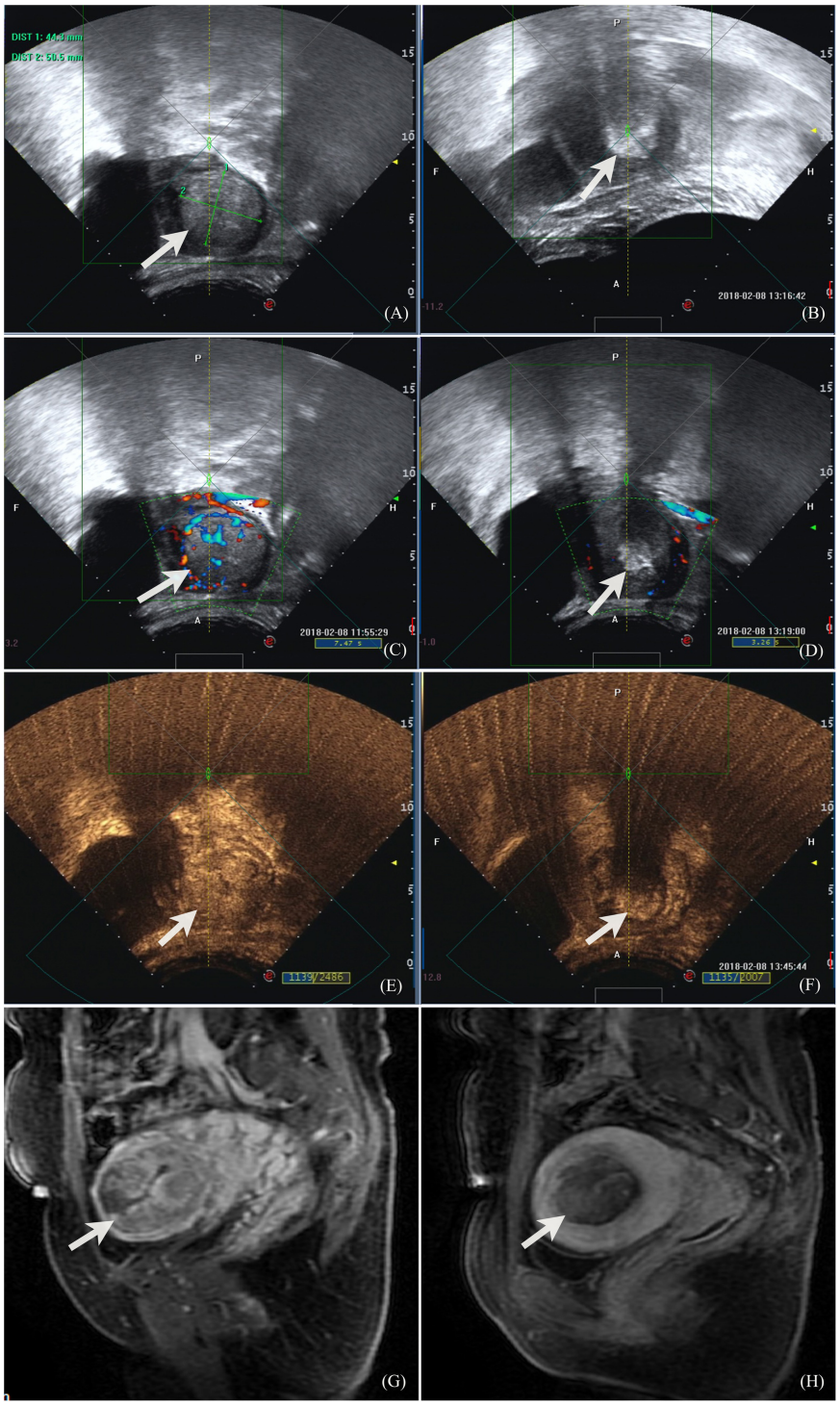

FIGURE 1 | Ultrasound and MR images of a 32-year-old patient with placenta increta. **(A)** Before HIFU ablation, monitoring ultrasound showed placenta invasion on the fundus-posterior wall of the uterus, about 50.5 × 44.3 mm, with thin myometrium surrounding; **(B)** during the procedure of HIFU ablation, the monitoring images showed that the target area was clumped with enhanced echo; **(C)** color Doppler flow imaging showed abundant blood flow signals both in the lesion and surrounding before HIFU ablation; **(D)** color Doppler flow imaging showed that the grayscale increased in the lesion and no blood flow signal was observed, also peripheral blood flow signal decreased and disappeared after HIFU ablation; **(E)** contrast-enhanced ultrasound showed that there was abundant blood perfusion in the lesion before HIFU ablation, and there were lacunar areas with less blood flow; **(F)** contrast-enhanced ultrasound showed that after HIFU ablation, the lesions were covered by grayscale increased images, and the posterior acoustic attenuation was observed. There was no blood perfusion in the lesions, and the boundary between the lesions and the surrounding uterine myometrium was clear; **(G)** contrast enhanced MR image showed that abnormal signal lesion enhanced in the intrauterine before HIFU and thin myometrium in the fundus of uterus; **(H)** contrast enhanced MR image 1 day after HIFU showed that the lesion in the uterine cavity was ablated with no blood perfusion.

TABLE 1 | Comparison of clinical characteristics of patients in two groups.

	sHIFU group (*n* = 53)	Control group (*n* = 42)	*P*-value
Age (years)*	29.0 (24.0–32.0)	28.0 (25.0–32.0)	0.916
Number of gravidities*	3.0 (3.0–5.0)	3.0 (2.0–5.0)	0.753
Number of parturitions*	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.641
History of cesarean section (*n*, %)	21 (39.6%)	23 (54.8%)	0.154
Gestational week (*n*, %)			0.102
<28 Weeks	21 (39.6%)	24 (57.1%)	
≥28 Weeks	32 (60.4%)	18 (42.9%)	
Placenta increta size[1] (cm)*	6.0 (4.0–7.0)	7.0 (5.2–9.0)	0.042
Placenta increta area[2] (cm^2)*	15.1 (9.6–26.3)	31.3 (15.8–51.8)	0.001
Placenta increta depth (cm)*	4.0 (2.6–4.5)	4.5 (3.6–4.9)	0.003
Serum HCG (mIU/mL)*	2,550.0 (996.5–5,523.0)	1,895.2 (217.6–5,321.0)	0.152
Sonication time (sec)*	660.0 (538.0–890.0)	710.0 (585.0–1,024.0)	0.438
Power (W)*	398.0 (394.0–400.0)	400.0 (396.0–400.0)	0.068
NPVR (%)*	83.0 (75.0–87.0)	81.0 (74.8–88.3)	0.922
Duration of bloody lochia (days)*	24.0 (19.0–31.0)	25.0 (16.0–31.0)	0.422
Tissue expulsion (days)*	9.0 (5.0–14.0)	3.0 (3.0–6.0)	<0.001
Menstrual resumption (days)*	62.0 (54.0–72.0)	70.0 (62.0–82.0)	0.007
Treatment time (min)*	71.0 (60.0–90.0)	66.0 (55.0–95.0)	0.860

HCG, human chorionic gonadotropin; NPVR, non-perfused volume ratio.
**Data are expressed as median (interquartile range).*
[1]The longest diameter of the implanted placenta.
[2]The area of the implanted placenta = 1/4 π multiplied by the longest diameter times the vertical diameter of the longest diameter.

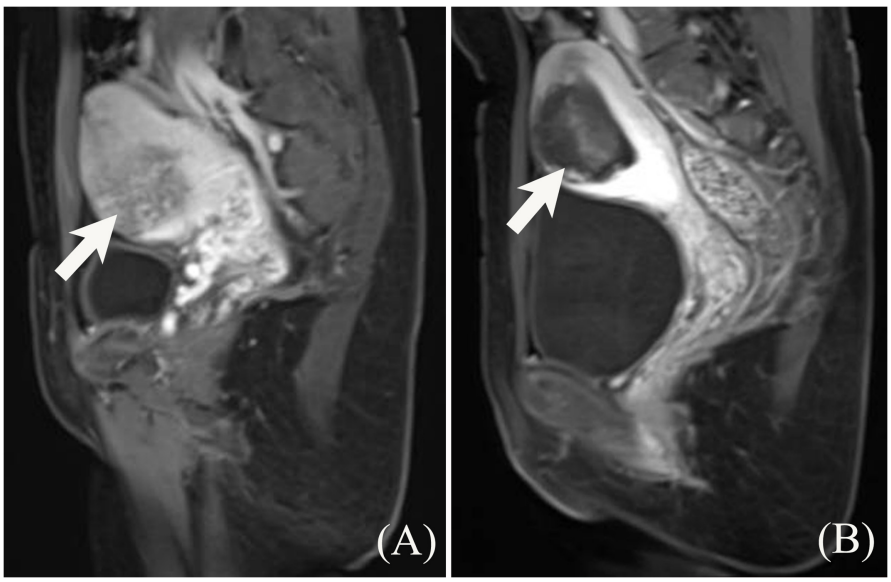

FIGURE 2 | Contrast enhanced MRI of A 23-year-old woman with placenta increta before and after HIFU treatment. **(A)** The depth of placenta invasion was 3.7 cm, close to the uterine serous surface, and uniform enhancement of the implanted placenta with perfusion slightly below the myometrium. **(B)** After HIFU treatment, contrast enhanced MRI shows no perfusion of the placental tissue.

During 2–8 years of follow-up, six pregnancies in the sHIFU group and three pregnancies in the control group were delivered at full term, and eight cases experienced uneventful delivery of the placenta after delivery. In the sHIFU group, five cases delivered *via* cesarean section and one case underwent a vaginal delivery. In the control group, three cases delivered *via* cesarean section, and in one case, the placenta was incompletely detached and partially implanted for about 3 × 3 cm, bleeding on the detached surface was active with suturing, and then the bleeding was successfully stopped.

TABLE 2 | Comparison of the serum HCG level changes before and after treatment (mIU/mL).

	Before treatment	After treatment		
		7 days	15 days	30 days
sHIFU group	2,550.0 (996.5–5,523.0)	288.0 (100.0–633.0)	78.0 (46.0–298.0)	<1.20 (<1.20, <1.20)
Control group	1,895.2 (217.6–5,321.0)	191.9 (44.8,- 5.5)	79.5 (22.5–214.6)	<1.20 (<1.20, <1.20)
Z-value	−1.432	−1.544	−1.225	−1.000
P-value	0.152	0.122	0.182	1.000

Data are expressed as median (interquartile range).

DISCUSSION

Placenta accreta occurs in approximately 1:1,000 deliveries with a reported range from 0.04% rising up to 0.9% (9, 10). According to a large population-based pregnancy cohort study, the incidence of PAS reach up to 2.1% (11). Placenta increta accounted for 29.8% of PAS patients undergoing surgical management (12). Currently, there are clinical differences in the management of placenta increta (7, 13). For placenta increta combined with uncontrollable hemorrhage that endangers maternal life, hysterectomy remains the primary treatment (14). Hysterectomy deprives the patients of their fertility and normal menstrual cycles, and some studies have suggested that hysterectomy leads to premature ovarian failure and early onset of perimenopausal symptoms in women. "Leaving the placenta *in situ*" can successfully preserve the uterus and avoid hysterectomy in the majority of patients without any major bleeding, but there is still a risk of infection and bleeding, and whether residual placenta mechanization will affect later pregnancy is still a clinical concern. Focused ultrasound therapy is a non-invasive treatment technique that has been widely used in the clinical treatment of many diseases in recent years, and it has achieved satisfactory clinical outcomes (15–19). The HIFU ablation technique is used for the treatment of placenta increta, which is based on the strategy of "leaving the placenta *in situ*," where HIFU ablation causes *in situ* necrosis of the residual placental tissue, vascular blockage, peeling off of the necrotic tissue, and reduction in the number of medical operations, such as curettage. HIFU alone is feasible option for the treatment of patients who develop non-major bleeding postpartum placenta increta with *in situ* leaving of the placenta, and the return of menstruation and pregnancy achievement in some patients after treatment reveal its unique advantages.

The studies reported that HIFU combined with hysteroscopic resection is an effective and safe method for the management of placenta accreta (20, 21). But less is more. HIFU alone is more beneficial 53 patients were included in this study for HIFU ablation alone and 42 patients were treated with HIFU ablation followed by curettage; no significant differences were observed between the two groups in terms of patient age, gestational week and serum HCG. After HIFU ablation, the implanted placental lesion was necrotic *in situ*, and the lesion was not enhancing, as assessed by an enhanced MRI, leaving the placenta *in situ*, and avoiding the risk of re-injury of the uterus during curettage procedure. Disruption of the integrity of the uterine endometrium and smooth muscle layers of the myometrium is the main cause of placental invasion (22). Therefore, reducing intrauterine surgery is an important measure to avoid the occurrence of placental implantation in second pregnancy.

In this study, although the placental size and placental implantation depth were statistically greater in the control group than in the sHIFU group ($P < 0.05$), all HIFU ablations achieved technical success with a median NPVR $\geq$80%. The key to the clinical benefit of the HIFU ablation technique is to obtain a high NPVR, with target tissue structure and blood supply being the major influencing factors. Keserci et al. (23) reported that enhanced MRI evaluation of adenomyosis with blood perfusion intensity below the myometrium obtained a mean NPVR of 89.2%, which was significantly higher than the NPVR of 42.9% in the group with blood perfusion equal to that above the myometrium. The placenta is an organ for material exchange between the mother and the fetus. There are two sets of blood circulation in the placenta, maternal and fetal blood circulation. When a fetus is delivered, the maternal-fetal material exchange is discontinued, and the placenta is detached from the mother. When the implanted placenta cannot be detached, the placental decidua basalis can still obtain blood supply from the myometrium, but most of the blood vessels in the placenta are occluded and some tissues become necrotic and degenerated; therefore, most of the residual placenta can be easily ablated and a high NPVR can be obtained. It needs to be further investigated whether the effect of ablation can be predicted by imaging means, such as enhanced MRI.

Although the safety of HIFU for uterine fibroids and adenomyosis has been extensively studied and reviewed (24–26), its safety still needs to be considered in terms of case selection, preoperative preparation, intraoperative monitoring, and dose control (27). Firstly, placental implantation is very deep and there is a risk of damage to the ectopic bowel during HIFU ablation; hence, patients with placenta penetration were excluded from case selection in this study. Specific treatment strategies need to be considered for placenta penetration.

Secondly, near-field acoustic channel scarring is also an important factor affecting the safety assessment of HIFU ablation (27). Ultrasound-guided HIFU ablation systems, with cryogenic circulating degassed water as the coupling medium and a continuous cooling effect on the acoustic channel skin, have a high safety profile in patients with abdominal surgery-related scarring (28). Some scholars have used scar patches in MRgHIFU treatment to avoid damage to the scar when high NPVR is

obtained (29). Due to different imaging principles, it needs to be further studied whether scar patches are suitable for USgHIFU. Thirdly, for placental implantation, the susceptibility of residual placenta to infection is a matter of concern and should therefore be taken into account while screening cases, and further consultation is needed in case of abnormalities by monitoring the temperature. Fulminant exacerbation of infection due to HIFU ablation should be avoided since it may be life-threatening for the patient. Finally, death of patients reported in the literature, although rare, raises a higher level of warning for the clinical application of HIFU technology (27). In patients with placental implantation, the physiological situation is significantly different from that in non-pregnant women, and it is necessary to determine whether there are any problems related to vascular injury. In this early stage of HIFU technology application, attention needs to be paid to the possibility of uncertain risks in cases with pathological pregnancies, such as gestational hypertension disorder. Future studies should evaluate the safety of this technique in the context of obstetric conditions.

During the observation period, major bleeding did not occur in patients who underwent clearing and non-clearing of the uterus, and no obstetric complications, such as Asherman syndrome, were observed. A small amount of necrotic tissue was discharged vaginally, accompanied by only a small volume of old blood discharge. There were no statistically significant differences in the time to vaginal bloody lochia, time to HCG decline, and time for conversion to negative ($P > 0.05$). Therefore, leaving the placenta *in situ* after HIFU for treating postpartum placenta increta is a feasible and safe option, which has comparable efficacy to HIFU combined with curettage.

Individualized management is performed in young women with fertility preservation requirements (30). Menstrual recovery is an important outcome. In this study, patients had menstrual cycle resumption within 3 months after HIFU ablation leaving the placenta *in situ* and had a significantly lower incidence of menstrual volume decreased than in the HIFU combined with curettage group. Further study is needed to assess whether curettage induced the injury to the endometrium or affects the endometrial microenvironment. There is a lack of histological evidence on how the myometrium recovers in patients treated with leaving the placenta *in situ* after HIFU with the necrotic placental tissue expels spontaneously. However, on a long-term follow-up, nine women achieved a second pregnancy; eight women had an uneventful delivery of the placenta without any recurrence of placenta increta, and one case developed partial placenta increta along with the second pregnancy, and the uterus could still be preserved after intraoperative management by cesarean section. This finding suggests that the structure and physiological function of the myometrium and endometrium can be restored after HIFU ablation.

However, the present study has some limitations. The first limitation is the failure to establish the pathological diagnosis of implanted placenta and histological outcome evidence of myometrial and endometrial repair. Secondly, the small number of cases and design of the retrospective study may have resulted in patient selection biases, such as statistical differences in placenta size and depth of placental implantation; hence, the impact of patient selection on clinical application still needs to be considered, and they necessitate further validation of its clinical application in a prospective randomized controlled study. Further randomized controlled studies are needed to confirm whether the single-session HIFU treatment strategy of placental leaving *in situ* is superior to leaving the placenta *in situ* without any intervention in terms of the conception rate, pregnancy safety, and placenta accreta during postoperative pregnancy achievement, and whether this treatment strategy is superior to HIFU combined with curettage. In addition, patients who developed any major bleeding were excluded from this study, and it needs to be further explored whether effective hemostasis can be achieved by using the HIFU technique.

CONCLUSION

In summary, single-session HIFU is safe and effective in treating postpartum placenta increta *in situ*. HIFU alone opens a new era of leaving the placenta *in situ* treatment of placenta increta and is a promising option for those who wish to preserve their fertility and experience pregnancy.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Neijiang First People's Hospital Clinical Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XG and JC contributed to the conception and design of the study, performed the statistical analysis, and wrote and revised the manuscript. XG, XH, MY, GH, XX, and JC were responsible for data acquisition and interpretation. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.871528/full#supplementary-material

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ORIGINAL RESEARCH
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Safety and Feasibility of Vaginal Delivery in Full-Term Pregnancy After Transvaginal-Natural Orifice Transluminal Endoscopic Surgery: A Case Series

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Study Objective: The aim was to investigate the outcome of vaginal delivery of full-term pregnancies in patients after transvaginal-natural orifice transluminal endoscopic surgery (vNOTES) treatment for gynecological disorders.

Design: A case series report.

Setting: A medical university hospital.

Patients: 12 cases of successful delivery after transvaginal-natural orifice transluminal endoscopic surgery.

Interventions: Long-term follow-up of patients with fertility needs after transvaginal-natural orifice transluminal endoscopic surgery.

Measurements and Main Results: From 2018 to 2021, 163 cases of gynecological diseases were treated by vNOTES. One hundred forty-seven patients were followed up, with a follow-up rate of 90.1%. The average follow-up time was 28 (15–47) months, including 66 cases with fertility requirements. Among these 66 patients, 12 patients successfully got pregnant and completed delivery, including 10 cases of vaginal delivery and 2 cases of cesarean section, with no adverse pregnancy outcomes associated with vNOTES arising.

Conclusion: Vaginal delivery of a full-term pregnancy after transvaginal-natural orifice transluminal endoscopic surgery appears to be safe and feasible and would not be one of the bases for elective cesarean delivery.

Keywords: transvaginal-natural orifice transluminal endoscopic surgery, Minimally invasive gynecology techniques, transvaginal delivery, full-term pregnancy, Childbirth ability

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INTRODUCTION

vNOTES is an emerging minimally invasive technique that enables surgical access to the peritoneal cavity through the vagina, a natural body orifice. In recent years, with the rapid development of minimally invasive gynecology and the concept of accelerated recovery surgery, combined with the unique advantages of scarless skin and fast recovery, vNOTES has made not only a splash in the field of gynecology (1) but also became an emerging surgical modality in general surgery (2, 3) and urology (4, 5).

Although the therapeutic efficacy and safety of vNOTES in the treatment of a variety of benign and malignant gynecological diseases have been demonstrated (6–8), there is still a lack of research on its long-term postoperative effects, such as the safety of vaginal delivery in full-term pregnancies and the impact on sexual life. In this study, we investigated the impact of vNOTES on vaginal delivery of full-term pregnancies after surgery in patients by retrospectively analyzing a case series.

MATERIALS AND METHODS

Patients

This study retrospectively collected 163 patients with gynecological diseases treated by vNOTES in the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University from 2018 to 2021. 147 patients were followed up, with a follow-up rate of 90.1%. The average follow-up time was 28 (15–47) months. Among the 66 patients with fertility requirements, 12 cases were successfully pregnant and completed delivery, including 10 cases of vaginal delivery and 2 cases of cesarean section. See **Supplementary Appendix S1 and Appendix S2** for case data.

Surgical Technique

The patient requires vaginal cleansing one day before the procedure. Anterior vaginal vault approach: cervical forceps or Allis forceps the anterior cervical lip and pull downward, make a transverse incision slightly below the cervical portion of the bladder attachment, bluntly separate the vesicovaginal space, free the bulging bladder, separate the cervical ligament of the bladder and push the bladder upward to the retroperitoneum of the bladder and open the retroperitoneum of the bladder and uterus into the pelvis; posterior vaginal vault approach: cervical forceps or Allis forceps the rear cervical lip and pull upward to expose the posterior vaginal vault. A transverse incision of approximately 2–3 cm is made 1.5–2.0 cm below the cervix to separate the rectal space and enter the pelvis bluntly. The pneumoperitoneum was established by inserting a particular HangT Port (Beijing HangTian KaDi Technology R&D Institute, Beijing, China) vaginal access (**Figure 1**). A standard 10-mm rigid 30° laparoscope was used through 1 trocar, whereas 2 endoscopic instruments were used through the other two trocars (**Figure 2**); through the surgical platform, access to remove the lesion peritoneal and vaginal vault incisions were closed with a running Vicryl 2 suture. All procedures were performed by a chief surgeon with extensive experience in vNOTES surgery.

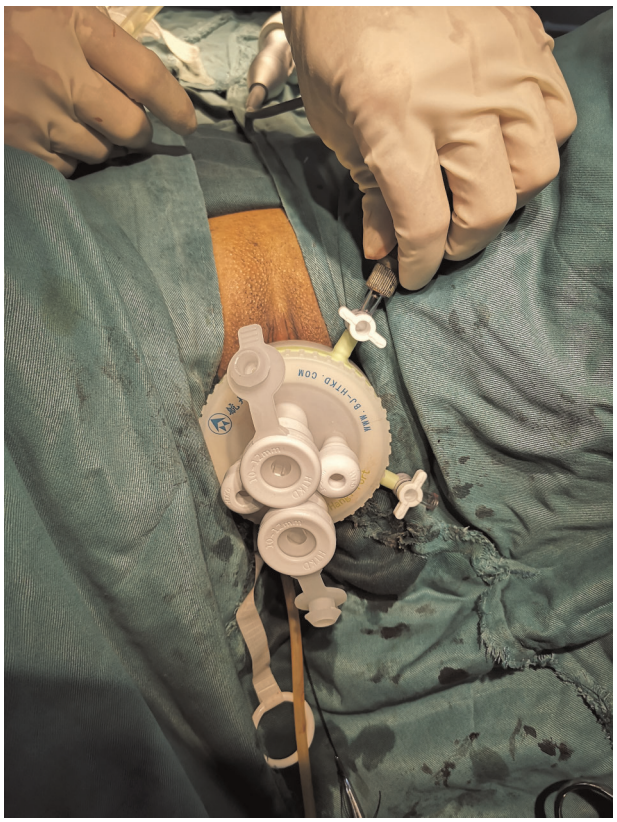

FIGURE 1 | Establish vaginal access.

Outcomes

Baseline characteristics of patients included age, body mass index (BMI), obstetric history, and history of previous pelvic surgery. Surgical correlates included time of surgery, location of the surgical incision, surgical approach, postoperative pathological diagnosis, need for conversion to laparoscopy or cesarean, and surgical complications as indicated by Clavien-Dindo classification. All patients were followed up at one week, 1, 3, and 6 months postoperatively and annually postoperatively. Assessment of the healing of the surgical incision, non-healing or delayed healing of the incision, abnormal sensation of the incision (pain, itching), rupture or fluid flow from the incision, narrowing or shortening of the vagina, and adhesion of the vault are noted as poor healing of the incision. Detailed obstetric and delivery data were recorded for all patients, such as the gestational week of delivery, pregnancy and delivery complications, the time interval from the first day after vNOTES to the next delivery, perineal incision rate, and grading of perineal rupture. After delivery of the placenta and three days after delivery, the

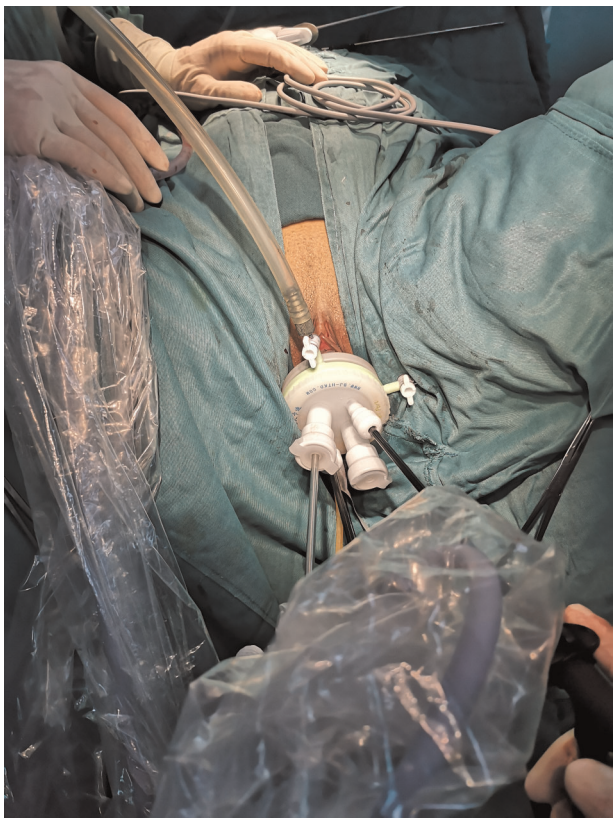

FIGURE 2 | Schematic diagram of laparoscopic operation devices.

vaginal vault is exposed using a speculum or vaginal puller to check for tears or bleeding from the surgical scar. All data were tallied by one physician and examined by two others.

Statistical Methodology

Percentages, mean, and standard deviation were performed. Statistical analysis was carried out with IBM-Microsoft SPSS version 26.0.

RESULTS

Patient Characteristics

During the study period, a total of 12 patients completed their pregnancies and delivered successfully, and the characteristics of all patients are shown in **Table 1**.

Surgical Outcome

In this study, all 12 vNOTES patients had successful surgical completion. These included mature ovarian teratoma ($n = 6$), tubal ectopic pregnancy ($n = 5$), an ovarian cyst ($n = 1$); the mean operative time was 128.4 min and the longest operative time was 190 min; the operative incisions included anterior vaginal fornix incision ($n = 6$), posterior vaginal fornix incision ($n = 6$), and no additional vaginal wall injury due to surgical manipulation was observed in all patients; according to Clavien-Dindo classification, there were two postoperative complications, one postoperative incisional infection, which healed well after incisional dressing change (Grade 1 complication); one postoperative fever due to abdominal infection (Grade 2 complication), which improved after antibiotic treatment. The surgical incision healing was reviewed at 1 week, 1 month, 3 months, and 6 months after surgery. One of the 12 patients had poor surgical incision healing due to infection. After cleaning and dressing change, the incision healed well within one week after the operation, and the patient delivered successfully through vagina in the follow-up (See **Table 2**).

TABLE 1 | Characteristics of 12 patients who delivered after vNOTES.

Characteristics	Total ($n = 12$)
Mean age ± SD, y	30.16 ± 6.22
Preoperative BMI ± SD, kg/m²	20.71 ± 3.74
Fertility history, *n* (%)	
$n = 0$	4 (33)
$n = 1$	8 (67)
$n \geq 2$	0
Previous surgical history, *n* (%)	
Artificial abortion	2 (16)
Laparoscopic myomectomy	1 (8)
Cesarean	0
Others	0

SD, standard deviation; BMI, body mass index.

TABLE 2 | Surgical data and postoperative review results of 12 patients.

	Total ($n = 12$)
Diagnosis, *n* (%)	
Ovarian teratomas	6 (50)
Tubal ectopic pregnancy	5 (42)
Oophoritic cyst	1 (8)
Operation time ± SD, min	128.4 ± 37.7
Surgical incision location, *n* (%)	
Anterior vaginal fornix	6 (50)
Posterior vaginal fornix	6 (50)
Laparoscopy or laparotomy, *n*	0
Clavien-Dindo classification, *n*	
1	1
2	1
≥3	0
Incision healing, *n*	
Good healing	11
Poor healing	1

Poor healing is defined as nonunion or delayed healing of the incision, abnormal sensation of the incision (pain, itching), incision rupture or fluid flow, vaginal stenosis or shortening, and dome adhesion.

Pregnancy and Delivery Outcomes

Among the 66 patients with reproductive needs, 46(69.7%) cases were successfully pregnant, but 6 (13%) cases had an abortion, and 3(50%) cases were successfully pregnant after abortion. At present, there are 31(67.4%) patients during pregnancy. Twelve cases of pregnancy and delivery were successful, conception modes were classified as natural ($n = 11$), and assisted reproduction ($n = 1$), and all patients were examined during pregnancy according to the maternity program. Complications of pregnancy included gestational diabetes ($n = 2$), gestational obesity ($n = 1$), gestational hypothyroidism ($n = 1$), gestational mild anemia ($n = 1$), cord encirclement ($n = 3$), and premature rupture of membranes ($n = 2$). The 12 cases of successful delivery were vaginal delivery ($n = 10$) and cesarean delivery ($n = 2$). One cesarean delivery was due to a twin pregnancy, and the fetal position did not allow for vaginal delivery. The other was due to a previous history of obstructed labor. The patient refused the attempt of vaginal delivery. Ten vaginal deliveries were full-term pregnancies, singleton in the first position, normal deliveries ($n = 8$), obstructed deliveries ($n = 2$), and one obstructed delivery due to a previous history of obstructed labor. The other case was cervical edema during pregnancy, which was not significantly associated with the vNOTES procedure. No bleeding or tearing of the vNOTES surgical scar was detected after delivery of the placenta and on the third postpartum day. Six patients with perineal rupture were all with first-degree perineal rupture, which was not significantly associated with the vNOTES procedure. No bleeding or tearing of the vNOTES surgical scar was detected after delivery of the placenta and on the third postpartum day. The mean interval from the first postoperative day to the next delivery was approximately 21.8 months, with the shortest being 11.1 months. (See **Table 3**)

TABLE 3 | Obstetric delivery outcomes of 10 patients undergoing vaginal delivery.

	Total ($n = 10$)
Mean gestational age of delivery, wks	39^{+6}
Interval time ± SD, mos	21.89 ± 2.5
Induced labor mode, *n* (%)	
Natural induction of labor	6 (60)
Assisted induction of labor	4 (40)
Oxytocin induced labor	4
Balloon induced labor	2
Mode of delivery, *n* (%)	
Natural childbirth	8 (80)
Vacuum assisted	2 (20)
Obstetric forceps assisted	0
Anesthesia mode, *n* (%)	
None	7 (70)
Epidural anesthesia	3 (30)
Labor time ± SD, (h)	4.58 ± 0.62
First stage of labor	3.94 ± 0.38
Second stage of labor	0.52 ± 0.24
Third stage of labor	0.10 ± 0.008
Intrapartum hemorrhage ± SD, ml	175.0 ± 8.33
Neonatus	
Biparietal diameter ± SD, cm	9.31 ± 0.1
Head circumference ± SD, cm	33.04 ± 0.52
Abdominal circumference ± SD, cm	34.28 ± 0.51
Weight ± SD, g	3497 ± 118.3
Perineum, *n* (%)	
Complete perineum	2 (20)
Episiotomy	2 (20)
Perineal tear	6 (60)
Spontaneous labor, *n*	8
Dystocia, *n*	2

wks, weeks; mos, months; h, hour; m, milliliter; g, gram.

DISCUSSION

vNOTES is a minimally invasive surgical technique for treating disease after endoscopic access to the pelvic and abdominal cavity via the vagina, a natural cavity. It is the most used and developed surgical technique for trans-natural cavity surgery. vNOTES was widely used to treat benign gynecological diseases after Lee reported using vNOTES for tubal resection for tubal pregnancy in 2012 (9). In vNOTES, the intraoperative blood transfusion and hospital days are comparable to trans umbilical single-port laparoscopic surgery. Still, vNOTES has more advantages in postoperative pain relief, reduction of incisional fat liquefaction, and cosmetic results (6–8). In recent years, vNOTES has been gradually explored in gynecologic malignancies (10). Due to the significant advantage of no scar on the abdominal wall, vNOTES has been favored by many young women of reproductive age. In China's open third-child policy, promoting fertility and reducing the cesarean section rate has been favored become a priority (11, 12). Therefore, we are concerned about the possible long-term effects of vNOTES on vaginal delivery in term pregnancies. It has been reported that full-term delivery can lead to rupture of the vaginal vault (13), but whether vNOTES will receive long-term benefits on vaginal delivery of full-term pregnancy and female sexual function has been less reported (14, 15).

The location of the incision depends mainly on the location of the lesion. Although the vNOTES approach of the posterior vaginal fornix is enough to complete the surgical treatment of most diseases in general surgery, urology, and gynecological surgery, due to the natural barrier of the uterus, the posterior vaginal fornix approach is still a difficult challenge for the lesions of the anterior wall of the uterus and the front of the pelvic cavity, and the incision of the anterior vaginal fornix can well solve this difficulty. For examples, anterior wall myomas and cesarean scar pregnancies are suitable for the anterior vaginal vault approach. In contrast,

most adnexal diseases, posterior uterine wall myomas (16), and pelvic lymph node dissection (17) are more suitable for posterior vaginal vault incisions. Simultaneously, the posterior vault is more extensible, and the surgical specimen is easier to obtain intact than the anterior vault. In our study, we found that in many patients, especially those with endometriosis, the incidence of posterior pelvic adhesions is higher than that in the front of the pelvic cavity. Posterior vaginal fornix adhesions or the closure of the uterine rectum depression often led to the failure of the establishment of posterior vaginal fornix approach in vNOTES surgery and the conversion to laparoscopic surgery or rectal injury. In this study, ten vaginal deliveries included anterior vaginal vault incisions ($n = 5$) and posterior vaginal vault incisions ($n = 5$), and none of them had surgical scar tears during delivery. The current research data show that the anterior vaginal fornix incision and the posterior vaginal fornix incision have no relevant impact on the vaginal delivery of full-term pregnancy. With further follow-up, we will obtain more data to confirm this view. Vaginal preparation 1 day before surgery can effectively reduce the number of bacteria in the vagina and reduce the risk of intraoperative infection (18), and surgical incision healing is unlikely to result in abnormal incision sensation (pain, itching), incision rupture, or fluid flow, or vault adhesions that could affect the patient's sexual life and ability to give birth. In addition, the surgical operation may damage the vaginal wall, or the suture may cause vaginal narrowing or shortening, which may affect the patient's sexual function after surgery and thus reduce the probability of natural conception. At present, there are few research reports in this field (14).

The vNOTES produce an old surgical scar between the anterior and posterior vault of the cervix, which lacks extensibility relative to healthy tissue and may become a factor that delays the progress of labor or causes scar tearing during vaginal delivery—becoming an indication for the choice of cesarean delivery? In this study, 10 patients delivered vaginally were full-term pregnancies, and 2 were delivered by cesarean section, with a mean cesarean section rate of 16.6%, which is lower than the cesarean section rate of 39.2% in the region; the mean neonatal weight was 3,497 g, and the maximum neonatal weight was 4,220 g. No slow progression of labor or tearing of the scar was observed during delivery, which may suggest that vNOTES surgery does not full-term affect the way full-term pregnancy is delivered vaginally. The shortest postoperative interval between the patient's surgery and full-term delivery was 11.1 months, with a mean time of 21.8 months. It may still be a topic for discussion about how long it takes after vNOTES to qualify for transvaginal delivery.

Younger patient age is a distinctive feature of the vNOTES surgery population with high estrogen production and estrogen's ability to increase collagen deposition, increase wound strength, and promote healing of the vaginal vault surgical incision; low estrogen may increase inflammation production, prolong healing time, and affect wound healing relative to older age groups (19–21), and for those older than 45 years of age advanced maternal age, the safety of vaginal delivery after vNOTES for full-term pregnancies was not explored.

Study Limitations

The retrospective case report of the small sample is an essential limitation of this study and there was no systematic sexual function assessment for all patients with fertility requirements after vNOTES.

CONCLUSION

In this retrospective case series, all women who successfully conceived and delivered did not have adverse birth outcomes significantly associated with vNOTES; based on our data, vNOTES appears to be safe and feasible for vaginal delivery after a full-term pregnancy, does not become a basis for elective cesarean delivery, and has important implications for the promotion of vNOTES. Multicenter, randomized controlled studies are needed to confirm the long-term benefits of vNOTES for vaginal delivery and sexuality.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

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

SZ: Conception and Design of Study. ZD: Data Collection. JL: Data Analysis and Interpretation. ZQ, RS, JC, BX: Responsible Surgeon or Imager. HW: Statistical Analysis. MB: Manuscript Preparation. WW: Patient Recruitment. All authors contributed to the article and approved the submitted version.

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IRB EXEMPTION

The institutional review board (IRB) of The Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University exempted the study. It was a retrospective case series with anonymous data and written informed consent.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/article/10.3389/fsurg.2022.888281/full#supplementary-material.

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OPINION
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Fertility-Sparing Treatment for Young Patients with Early-Stage Cervical Cancer: A Dawn of a New Era

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Keywords: cervical cancer, fertility preservation, fertility-sparing surgery, radical trachelectomy, less radical surgery

INTRODUCTION

In the last decades, the incidence and mortality rate of cervical cancer in high-income countries have decreased due to the implementation of organized screening programs and recent advancements in diagnosis and prognosis (1). Potential candidates for surgical resection are women with locoregional tumors. Given the excellent 5-year survival rates for early-stage cervical cancer, surpassing 90%, and that up to 40% of these patients are of reproductive age, the need for fertility-sparing surgery (FSS) is mandatory (2). In the literature, many approaches are described, but in the last decade, the debate has been focused on radical and more conservative surgical approaches.

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Vaginal Radical Trachelectomy

Vaginal radical trachelectomy (VRT), combined with laparoscopic pelvic lymphadenectomy, was introduced by Professor Daniel Dargent, back in 1987. The procedure begins with the incision of the vagina and the dissection of the bladder and ureters away from the cervix. Identification and, usually, preservation of the uterine arteries is succeeded through the dissection of the Douglas pouch and the resection of proximal parametria, bilaterally. The minimum tissue needed to be preserved from the uterine isthmus is between 0.5 and 1 cm, and the resection of the specimen includes approximately 1–2 cm of the vagina (3, 4). The specimen is then sent for a frozen section to ensure negative margins, with 5–10 mm being the recommendation in the literature (5, 6). Also, subsequent curettage of the fundus has been reported for the exclusion of remaining residual disease, especially in adenocarcinomas. In case that negative proximal margin in conjunction with the preservation of adequate cervical tissue (5–10 mm) cannot be obtained, radical hysterectomy is recommended (3, 7).

Abdominal Radical Trachelectomy

Abdominal radical trachelectomy (ART) was introduced by Smith et al. in 1997. The approach to the abdomen is succeeded through a low transverse or vertical abdominal incision, and it is similar to the surgical approach for abdominal radical hysterectomy. Uterine arteries can be preserved or ligated due to the ovarian vasculature that preserves the uterine blood supply.

ART is the standard approach for patients with stage IB1 tumors, as stated by the ESGO/ESTRO/ESP Guidelines (8). However, the main disadvantages include higher blood loss, increased transfusion rates, greater incidence of wound infections, and prolonged hospital stay. The radicality of the parametrial resection in ART is more extensive, compared to the vaginal approach, and the oncologic outcomes are comparable to those after radical hysterectomy, with a recurrence rate of approximately 3.9% (9).

Minimal Invasive Surgery-Radical Trachelectomy

Minimal invasive surgery-radical trachelectomy (MIS-RT) includes either robotic or laparoscopic radical trachelectomy (RRT or LRT, respectively), and its main target is to accomplish radical parametrial resection as ART without the adverse effects of open surgery. The advantages of the MIS-RT approach are decreased blood loss, lower rates of wound dehiscence, and shorter hospital stay without significant prolongation in operative time compared to ART (10, 11).

The oncologic outcomes of MIS-RT are similar to those of VRT and ART, with a combined recurrence rate of 4.2% and a death rate of <1%; however, the data remain unclear, especially regarding the lesion size, due to the small size of samples in MIS-RT studies (12). However, after the publication of the LACC trial, the minimal invasive approach for young patients with cervical cancer is not recommended, and each treatment should be tailored (10, 13).

Less Radical Fertility-Sparing Surgery in Early-Stage Cervical Cancer

Although the gold standard for early-stage cervical cancer is radical hysterectomy, related complications regarding principally to the parametrial resection lead to decreased quality of life. The main negative effects include sexual dysfunction, bladder and rectal dysfunction, and fistula formation (14, 15). Furthermore, the rates of parametrial spread have been observed to be <1% in a selected group of patients with negative pelvic lymph nodes, tumor stage IB1, and a depth of invasion of <10 mm (16). The combination of increased possibility for severe complications with findings that show no significant improvement in oncologic outcomes from radical procedures has led to a more conservative surgical approach for early-stage disease. The less radical surgical management includes cervical conization and simple trachelectomy with sentinel lymph node mapping or complete pelvic lymphadenectomy.

Cervical conization refers to the excision of a cylindrical wedge or a cone-shaped resection of the uterine cervix, including the transformation zone. The NCCN guidelines recommend cone biopsy with negative margins in stage IA1 with negative LVSI; however, for stage IA1 with positive LVSI or stage IA2, the recommendations are cone biopsy or radical trachelectomy with pelvic node dissection or the consideration of sentinel lymph node mapping. The management of St IA1 with cone biopsy has been found to have no difference in the 5-year survival rate compared to hysterectomy (17). Simple trachelectomy is defined as the removal of the cervix, leaving the adjacent paracervical tissues *in situ*. It should be combined with lymph node dissection or sentinel lymph node mapping, and it serves as an alternative option for lesions <2 cm and negative pelvic lymph nodes (18).

Neoadjuvant Chemotherapy and Conservative Management of Early-Stage Cervical Cancer

Neoadjuvant chemotherapy (NACT) poses an alternative approach for bulky tumors larger than 2 cm (19, 20). The philosophy of NACT is to reduce the tumor volume, which could lead to an FSS. There are little data in the literature showing the effectiveness of NACT followed by radical hysterectomy in reducing the size of the lesion in cervical cancer. The responses to NACT can be defined using the pathological outcomes on the trachelectomy\cone specimen as complete response, optimal partial response in cases where residual disease is less than 3 mm, and suboptimal partial response for those with residual disease greater than 3 mm. Globally, the response rate to NACT is reported to be approximately 70%, but the implementation of NACT includes some vague and confusing issues (21). Although NACT can potentially convert a positive node to a negative and proceed with the FSS option, outcomes from studies show a higher recurrence rate and identify node positivity as a negative prognostic factor for FSS (22).

Postsurgical Follow-Up

Patients after any kind of FSS are arbitrarily counseled for a postponement of pregnancy for 6–12 months to allow the detection of possible recurrent or persistent disease (8). Follow-up visits consist of pelvic examination, Pap smear, and colposcopy, combined with pelvic imaging through transvaginal sonography or MRI. The intervals of surveillance are intended to be every 3–6 months for the first 2–3 years and thereafter every 6–12 months for >2–4 years after surgery due to late recurrences (12). Finally, clearance hysterectomy is not recommended after the completion of childbearing (8).

DISCUSSION

Since 2014, the NCCN has recommended radical trachelectomy as a fertility-sparing treatment for young women with early-stage cervical cancer. Eligible patients for such surgical procedures are women younger than 40 years of age, with stage IA1 with LVSI, IA2, IB1 with lesions <2 cm, and some selected FIGO stage IB2 patients. Also, as an indicator for FSS, selection should be considered the infertility history and the adequate evaluation by a fertility specialist (23, 24). This workup can be completed within 8 weeks from the diagnosis, without impacting survival (25). Negative factors for FSS are bulky tumors (<4 cm) and lesions with high-risk histologic types, such as neuroendocrine tumors and gastric-type adenocarcinomas, due to the highest relapse rates. However,

few data are currently available in the literature on bulky St IB2 tumors and the safety of FSS. Therefore, tailored treatment is necessary for these patients (6, 26).

Preoperative evaluation should concern tumor size and depth of invasion. The combination of clinical examination with pelvic magnetic resonance imaging (MRI) is integral, prior to FSS, in order to estimate the tumor size, depth of invasion, and extension of the disease. Also, the addition of computerized tomography (CT) with or without the use of positron emission tomography (PET/CT) can help to evaluate lymphadenopathy and distant metastasis (2, 3). In some cases, cervical conization is used in addition to punch biopsies because it offers a more valuable and accurate estimation of histology, lymphovascular space invasion (LVSI), and tumor size (27).

Regarding the surgical approach, the open abdominal incision can be avoided by VRT, leading to lower complication rates. On the other hand, there is a need for specialized surgical skills in vaginal radical procedures, which are not universally common. Moreover, the use of VRT in tumors greater than 2 cm is limited due to the compromised oncologic outcomes and increased complication rates (18, 28).

The oncologic outcomes of VRT for early-stage cervical cancer in recurrences, 5-year recurrence-free survival, and 5-year overall survival are comparable to that of radical hysterectomy, with optimal prognosis, while death from the disease is 1.7% (12). The reported combined pregnancy rate is 49.4%, and complications from the procedure itself, such as cervical stenosis or female sexual dysfunction, may lead to reduced fertilization (29). For these reasons, preoperative counseling is necessary. Pregnancies after VRT are considered high-risk for preterm delivery and preterm premature rupture of membranes. Therefore, these women should be advised for extensive prenatal monitoring and planned delivery through a cesarean section. The live birth rate in these pregnancies is approximately 65% (12).

When referring to the abdominal approach, multiple studies have shown a greater recurrence rate for lesions >2 cm with ART, but death from disease is reported at <2% (9, 12). The pregnancy rate ranges between 13% and 67%, the combined live birth rate is 44%, and the severe preterm delivery occurs in up to 50% of the total pregnancies, establishing them as high-risk pregnancies (9).

Patients that are candidates for the laparoscopic or robotic approach should be counseled about the advantages compared with open surgery and for the possible higher recurrence risk and the unclear data regarding the MIS-RT approach. Patients with tumors >2 cm are not candidates for the MIS-RT FSS approach. The combined pregnancy rate is 36.2% and the live birth rate is 57.1%, which are comparable to those for radical procedures (9).

Furthermore, regarding NACT, a phase II multicentric study demonstrated that weekly topotecan, with cisplatin, is effective with acceptable toxicity (30). After the implementation of NACT in patients with complete or optimal partial response, large conization or simple trachelectomy seems to be an adequate option since the probability of occult parametrial disease is very low, while in suboptimal chemo responders, radical surgery is mandatory (21).

Patients should be informed about the possible adverse effects of chemotherapy agents on ovarian reserve and the possible premature menopause. However, favorable obstetrical outcomes that have resulted from NACT are related to fewer gonadotoxic agents and shorter chemotherapy cycles (19).

The hot topic of current treatment is, however, less radical surgery. Studies have shown that the risk of recurrence after conization or simple trachelectomy with lymph node sampling is approximately 4.2%, and the significance of lymph node evaluation is essential for the maintenance of oncologic safety after the nonradical fertility-sparing management. The pregnancy outcomes are superior to radical management, with a pregnancy rate of 55.1% and a live birth rate of 71% (12, 31).

Results of the ConCerv trial demonstrated that less radical surgery with conization and simple hysterectomy is a feasible approach for patients with early-stage cervical cancer. The positive lymph nodes rate was 5%, and the rate of residual disease in the hysterectomy group, following conization, was 2.5% (32). Provided that the ongoing SHAPE and GOG-278 prospective trials will present similar results to the ConCerv trial, we will have a more thorough opinion regarding the potential change in the standard of care for early-stage cervical cancer.

To conclude, fertility-sparing treatment for young patients with early-stage cervical cancer demands a tailored approach that is ever-evolving. New trends lead to less radical surgery, targeting optimizing the quality of life without compromising oncologic safety. If the results of the much-anticipated SHAPE and GOG-278 clinical trials match those of the ConCerv trial, then perhaps we will witness a paradigm shift to a more conservative surgical approach for these patients.

AUTHOR CONTRIBUTIONS

CP and A-MK wrote the manuscript, NT and CP edited the manuscript, and DH and AR approved the manuscript. All authors contributed to the article and approved the submitted version.

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Laparoscopic Lateral Suspension (LLS) for the Treatment of Apical Prolapse: A New Gold Standard?

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Nowadays, the gold standard to treat apical pelvic organ prolapse (POP) is laparoscopic sacrocolpopexy (LSCP). However, LSCP is a difficult procedure associated with rare but potentially severe complications. Promontory dissection may expose to potential life-threatening intraoperative vascular injuries, and sacral roots or hypogastric nerve damage. There are also a few case reports of spondylodiscitis with consecutive lumbar vertebra bone erosion. Laparoscopic lateral suspension (LLS) with mesh is an alternative technique for apical POP repair. It lowers perioperative risks by avoiding sacral promontory preparation. Recent studies show similar anatomical and functional outcomes to LSCP, with the advantage of better preserving the vaginal axis. Moreover, LLS is well suited for hysteropexy which is important as an increasing number of women prefer uterine preservation during POP surgery. In this article, we discuss both techniques, and we share our opinion on a novel perspective in the treatment of apical POP with uterine preservation.

Keywords: pelvic organ prolapse, apical prolapse, sacrocolpopexy, lateral suspension, hysteropexy

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INTRODUCTION

Pelvic organ prolapse (POP) is a condition affecting up to 40% of an outpatient setting and causes impaired body image and decreased quality of life (1–3). Most women suffer in silence and shame (4, 5). By the age of 85, 19% of women will have undergone a surgical cure for their prolapse (6). POP are hernias of the pelvic floor involving three compartments: anterior-related to the bladder, apical-related to the uterus, and posterior-related to the rectum. The gold standard to treat apical prolapse is sacrocolpopexy (SCP) (7). However, SCP is a difficult procedure with potentially severe complications. Promontory dissection exposes to potential life-threatening vascular injuries, spondylodiscitis, hypogastric nerve impairment (resulting in bladder or bowel dysfunction), or sacral roots damage (8–11). This step of the procedure may be challenging, especially in obese patients. Therefore, there is interest for alternative pelvic floor repair procedures which would

Abbreviations: POP, pelvic organ prolapse; ASCP, Abdominal sacralcolpopexy; LSCP, Laparoscopic sacrocolpopexy; RALSCP, Robotically assisted laparoscopic sacrocolpopexy; LLS, Laparoscopic lateral suspension; RALLS, Robotically assisted laparoscopic lateral suspension; SUI, Stress urinary incontinence.

guarantee the same anatomical and functional outcomes with less perioperative risks. Laparoscopic lateral suspension (LLS) with mesh is an alternative approach for apical POP repair avoiding promontory dissection, thereby lowering perioperative risks. Recent series show comparable results (**Table 1**). Moreover, LLS is well suited for hysteropexy which is an important feature as many women prefer uterine preservation during POP surgery (12, 13). The objective of this article is to show the advantages of LLS over LSCP and set a new gold standard for apical POP with uterine preservation.

BACKGROUND AND HISTORY

Sacrocolpopexy (SCP)

Historically, SCP was developed to treat recurrent vaginal vault prolapse. It was performed abdominally at the end of the 1950s, adapted to laparoscopy in the 1990s, and performed with robotic assistance since 2004 (14–17). It is nowadays the gold standard to treat apical POP (7). In case of apical POP in women without previous hysterectomy, surgeons often performed the procedure with associated hysterectomy. Studies showed that the rate of mesh exposure was nearly six times lower when the uterus was preserved, and progressively, total hysterectomy was replaced by supracervical hysterectomy to reduce this risk (18). To meet the expectations of women who increasingly prefer to keep their uterus, a symbol of femininity (12, 13), the technique started to be performed with uterine preservation (19).

Evolution of the Technique

Sacral colpopexy was initially developed by interposing a prosthesis between the apex of the vagina and the sacrum. In order to maintain a physiological orientation of the vagina, some authors have fixed the prosthesis directly at level S3-S4 (20). After experiencing threatening haemorrhages, the prostheses were fixed a little higher on the promontory, where the middle sacral artery was well identified and damage avoided (8). In order to limit the risk of the prosthesis detaching from the vagina, it was gradually placed along the entire length of the rectovaginal septum and the vesico-vaginal septum to limit the risk of subsequent cystocele (9). Author agrees that today, in the event of significant prolapse of anterior and posterior compartment, a mesh should be placed deep in the vesico-vaginal and in the recto-vaginal septum until the levator ani muscles (21). However, there remains a certain heterogeneity of practices in various centres.

Outcomes and Safety of SCP

Results of SCP, whether abdominal, laparoscopic, or robotic, all show very high cure rate during short term follow-up with good results at a longer term. In a large review dated 2004 including abdominal (ASCP) and laparoscopic sacrocolpopexy (LSCP), Ingrid Nygaard described success rates between 78 and 100 percent for follow-ups from six months to three years (9). In a more recent review of LSCP and robotic sacrocolpoepxy (RSCP), Richard Lee described success rates of around 90% for both techniques with an average follow-up of 26 months (22). In a review analysing the longer-term results of ASCP, Ingrid Nygaard described reduced success rates of around 70%–75% with a 7-year follow-up (23). Sarlos and al in a LSCP study including 101 patients described an objective success rate at one year of 98% which decreased to 83.8% at five years (24, 25). The 2016 Cochrane review describes better results for SCP compared to the vaginal route in the treatment of apical prolapse. However, the differences in absolute values are relatively modest, since success rates for SCP are estimated at 93% in the short term, versus 86% for vaginal procedures. Reoperation for recurrence was of 4% in SCP and only between 5 and 18 percent for vaginal procedures (7).

Although LSCP has been performed for nearly 30 years and is considered the gold standard for apical prolapse, it remains less widely used than the vaginal route (26). The main reason for

TABLE 1 | LLS and RALLS main studies.

Study	N	Mean follow-up (months)	Objective[a] success rate (%)	Subjective[b] success rate (%)	Reoperation for recurrence (%)	Laparotomy conversion (%)	Perioperative complications (%)	Mesh erosion (%)
LLS Dubuisson 2011	218	17.8	86.2	NA	4.6	0	1.8[c]	6
LLS Martinello 2019	48	24	>80	NA	6.3	0	0	0
Chatzioannidou 2021 standardized LLS	88	40	87.3	96.2	5.1	0	0	0
Simoncini et al. 2016- RALLS (82)	40	1	100	NA	NA	0	0	2.5
LLS (60) and RALLS (60) Mereu et al 2019	120	24	94.2	89	6.4	0	0	0.8
RALLS Dällenbach et al 2021	54	33	83.3	77.2	9.3	0	0	0

[a]Objective success defined by the anatomical correction of the prolapse during the clinical examination.
[b]Subjective success defined as the patient satisfaction measured by PGI-I (Patient Global Impression of Improvement for urogenital prolapse).
[c]1 bladder perforation, 1 abdominal wall hematoma, 1 bowel obstruction due to trocar hernia, one umbilical trocar hernia.

disaffection for this technique is the perceived difficulty of this procedure compared to the ease of vaginal techniques. Claerhout in Belgium evaluated the learning curve of LSCP and found that it takes around 60 procedures to ensure anatomical success and limit the risk of complications. Operative time decreased rapidly after the first 30 procedures and reached a steady state after 90 procedures (27). Alex Mowat described in an article that a structured program could reduce this learning curve (28). The advent of robotic surgery facilitated the realization of laparoscopic sutures, and could help reduce this learning curve. However, studies on this subject report relatively similar numbers of 50 to 75 operations required before mastering the technique (29, 30).

Complications of SCP are rare but potentially severe. Ingrid Nygaard's comprehensive review described not only bladder (3.1%) and rectal wounds (1.6%) but above all haemorrhages or transfusions in 4.4% of cases. Mesh erosion rate was 3.4%. This review included many open ASCP which could explain the increase in bleeding complications (9). More recent studies using the minimally invasive route described, in addition to bladder and rectal wounds and haemorrhagic complications, the conversion to laparotomy in nearly 4% of cases (24, 31). Reoperation rate for mesh erosion were also close to 3% in these studies. In one of the largest series of LSCP published today comprising 1,238 procedures, the Clermont-Ferrand team described 2.7% of severe complications including hematomas, peritonitis and complications related to prostheses (32).

In Richard Lee's review, there was also a case of spondylodiscitis, which is a complication occasionally described after SCP and which can be destructive to the surrounding bone (22). There are several case reports of this complication in the medical literature (33, 34). In the same review by Lee, the rate of de novo stress urinary incontinence was between 0 and 30% after SCP, averaging around 9% (22).

Laparoscopic Lateral Suspension (LLS)

LLS is not a new technique. It was developed by laparotomy in the 1960s by Kapandji (35), and like SCP was adapted to laparoscopy by Cornier in 1994 (36), then developed by Dubuisson in the 2000s (37–41). The technique was first performed with robotic assistance in 2014 by ourselves, with improvements authorized by robotic ergonomics allowing less scars compared to the laparoscopic technique (42). Since the first description of the technique, the difference with SCP lies in the fact that LLS was a prosthetic suspension of the uterine isthmus (hysteropexy) in contrast to the suspension of the vaginal vault for SCP. However, in the first Dubuisson series, subtotal hysterectomy was also frequently performed. In a French randomized trial on 50 patients published in 1983 by comparing ASCP with lateral suspension according to Kapandji's technique, the results obtained for lateral suspension were better in terms of prolapse and urinary incontinence (43). Paradoxically, SCP has been the preferred and most widespread technique over the past 40 years and is accepted as the gold standard today.

Evolution of the Technique

Kapandji's initial description was a colpo-isthmo-cystopexy using a transverse band that he attached to the aponeurosis of the oblique muscle opposite the anterior and superior iliac spine. The strip used was 2 cm wide Crinoruban® (polyamide) or Teflon® (Polytetrafluoroethylene), or sometimes skin, and was attached to the posterior wall of the bladder, to the vaginal fascia, and to the uterine isthmus by Tergal® (polyester) threads. The fixation of the aponeurosis of the oblique muscle was done by a point of Catgut n°1. The technique associated a section and tensioning of the round ligaments plicated forwards, and a Douglassoraphy with plication of the uterosacral ligaments (35).

In 1994, Cornier and Madelanat described for the first time a laparoscopic hysteropexy according to Kapandji in 7 patients (36). The technique was similar, but with fixation of a Mersilene® (polyester) prosthesis comprising of a 2×2 cm anterior tongue, and 3 cm wide and 10 cm long lateral arms, fixed to the iliac spines. Unlike Kapandji's original technique, they simply fixed the strip to the vagina and the uterine isthmus, without fixing it to the posterior wall of the bladder. The anterior tongue was secured by transfixing vaginal stitches tied in the vagina with nylon 00. It was also associated with a Douglassoraphy and plication of the uterosacral ligaments by a vaginal transfixing thread of nylon 00. The prosthesis was then fixed by a nylon thread to the aponeurosis of the oblique muscle at the level of the iliac spines.

The technique was then further developed and described by Dubuisson by modifying the shape of the prostheses with an anterior tab 6 cm long and 4 cm wide, attached to the vesico-vaginal fascia, with fixation entirely by laparoscopy. He initially used two lateral suspension prostheses, one anterior and one posterior, with two pairs of lateral arms fixed a little higher, about 5 cm above the anterior superior iliac spine, giving an even more physiological vaginal angulation (37, 38). He then developed the technique by placing a single anterior prosthesis with a 6×4 tab in the vesico-uterine space, associated either with a posterior prolapse cure by the vaginal route (posterior colporraphy), or with the placement of a posterior prosthetic tension free patch (39–41). He initially fixed the lateral arms to the abdominal fascia and progressively abandoned it creating a tension free sub peritoneal passage. He fixed the lateral arms to the peritoneum with absorbable tackers (AbsorbaTack™fixation device by Medtronic, Minneapolis,MN, USA). He subsequently used a prosthesis of polyester (Mersilene® by Ethicon), then of polypropylene (Gynecare Gynemesh®) and finally developed a prosthesis of macroporous polypropyene covered with titanium (TiLOOP® "Prof Dubuisson"® 9×41.5 cm, 65 g/m^2, pfm medical, Germany). The prosthesis was fixed to the vesico-vaginal fascia and to the isthmus uteri with non-absorbable threads of Ethibon ® (polyester sutures) and sometimes with synthetic glues (Glubran®). We have further standardized the Dubuisson technique and published two series of laparoscopic and robotic techniques using only absorbable sutures to fix the Ti-LOOP prosthesis to the

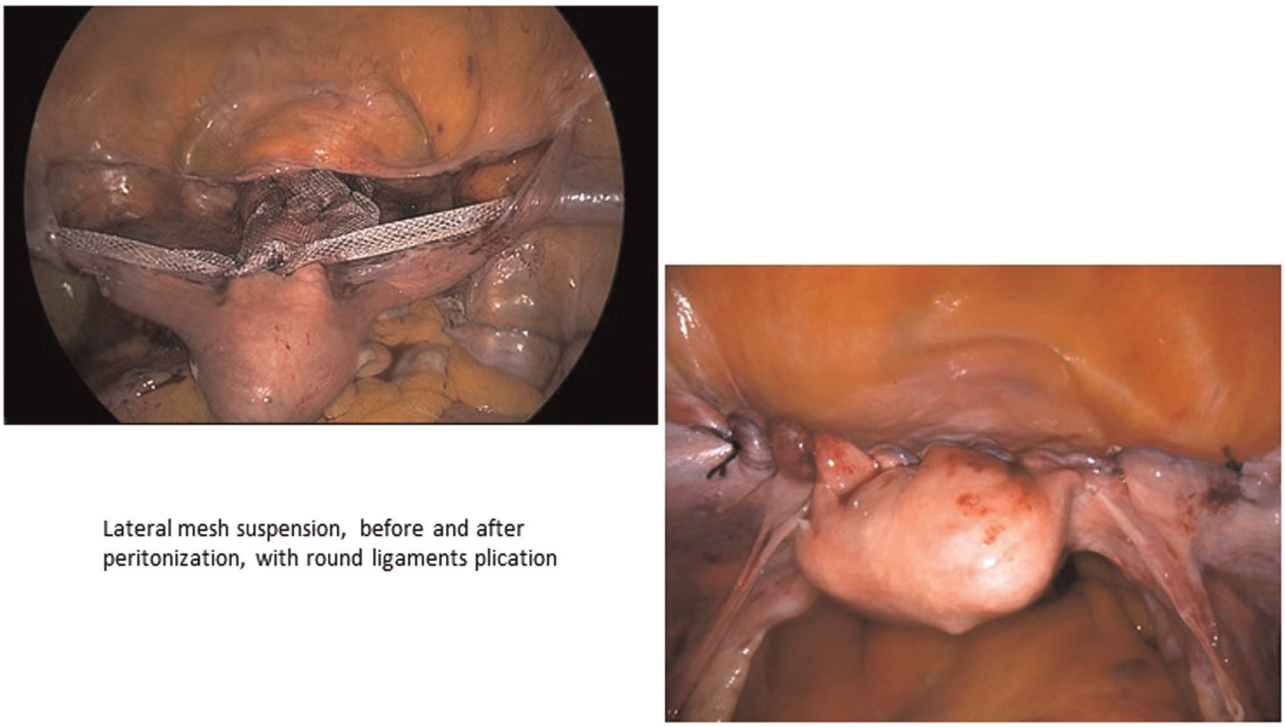

FIGURE 1 | Lateral mesh suspension, before and after peritonization, with round ligaments plication.

vaginal fascia (**Figure 1**). In case of associated rectocele, the treatment of the posterior compartment was done vaginally only when required (44, 45). These further developments reduced the vaginal mesh erosion rate to zero without impairing effectiveness. We believe it is unnecessary to use non absorbable polyester sutures to fix the mesh to the vesico-vaginal fascia as the subsequent fibrosis fixes the mesh. Non absorbable sutures may sometimes transfix the vaginal wall and carry bacteria to the mesh material enhancing the risk of erosion.

Outcomes and Safety of LLS

Results of the main studies are summarized in **Table 1**. They are very similar to the ones of SCP, with around 90% of success at short term follow-up and over 80% of success at 3 years. Thus far longer follow-up studies are unavailable to compare with SCP. An important feature in all the LLS series is the absence of major perioperative complications, in particular no severe bleeding and no conversion to laparotomy. In our experience, the learning curve is also shorter compared to SCP, but we have no comparative study to prove it. We believe 10–15 cases to be enough for mastering the technique for a trained surgeon in laparoscopic suturing. Some protagonists of SCP criticize the prosthetic lateral suspension for not treating the posterior compartment well. However, the global rate of recurrence is very low and comparable to SCP. We agree that in women for whom the posterior compartment was not treated initially, some developed posterior rectocele. However, this number remains low, and few women (between 2 and 7%) required a second surgery for this problem (39, 44–46). The mesh erosion rates were around 5% for Dubuisson's initial series, and between 0 and 2.5% in recent reports, which is comparable to the ones described for SCP (**Table 1**). As previously stated, it was zero in studies using Ti-LOOP® macroporous titanised mesh with only absorbable sutures to fix the mesh on the vesico-vaginal fascia. We have analysed risk factors for mesh erosion in a previous study, and showed the importance of customizing use of mesh material (47). As discussed, avoiding non absorbable suture to fix the mesh to the vesico-vaginal fascia may also decrease the risk of mesh erosion by limiting access of bacteria to the prosthesis.

POP DISTRIBUTION

Prolapse surgery should ideally correct all the pelvic floor defects. Many surgeons have aimed to do this, but in reality pelvic floor alterations are so complex that most of our surgical techniques are defect compensation approaches rather than actual repair**.** Knowing the distribution of defects can allow us to better adapt our repair techniques. We have shown in a series of 326 patients representing of a cohort of 1,811 women consulting for surgical correction of genital prolapse over a period of 20 years, that the anterior compartment is most frequently affected and often in association with the middle compartment (48). In this study

we also showed that a previous hysterectomy increased the risk of developing posterior compartment prolapse. This is probably due to the section of the uterosacral ligaments (De Lancey level 1) which participates in the support of the posterior compartment (49). Other authors found similar distributions between the compartments, with a higher proportion of prolapse of the posterior compartment (50). If we consider their populations in detail, we realize that a significant proportion of women had undergone prior hysterectomy, which is consistent with our observations. If the defects of the anterior and apical compartment are most often associated, prosthetic lateral suspension is the treatment of choice as it concomitantly compensates for these two defects.

HYSTEROPRESERVATION DURING POP SURGERY

Historically, POP surgical procedure with native tissue repair included a vaginal hysterectomy. As we have seen before, SCP was initially validated for vaginal vault prolapse. Most SCP procedures nowadays still include a hysterectomy, and supracervical hysterectomy is preferred to limit the risk of erosion. However, an increasing number of women prefer uterine preservation as it represents a symbol of femininity (12, 13). Moreover, hysterectomy is probably an unnecessary act during POP surgery, and may increase the risk of posterior compartment prolapse (48). Recent studies also show a benefit of uterine preservation by reducing operating time and blood loss without affecting outcome (18, 51). Another advantage of hysteropreservation is to avoid uterine morcellation which lengthens the operating time, increases the risks, and can in some cases disseminate abnormal uterine tissue. Therefore, we believe hysterectomy should only be performed in case of genital prolapse with an underlying uterine pathology. LLS was developed for hysteropexy and is well suited for uterine conservation. The lateral suspension follows the natural ligament suspension of the uterus thus providing a more physiological orientation of the vaginal axis (52) than during SCP, which deflects it to the right and a little backwards.

POSTERIOR MESH AND RISK OF EROSION

The Cochrane review shows that the posterior compartment is best treated vaginally without a prosthesis with a simple posterior colporraphy (53). We showed previously that introduction of prosthetic material in the rectovaginal septum causes a fivefold risk of prosthetic erosion (47). This observation was corroborate by other authors (38, 54). We hypothesized that it might be due to a different vascular supply of the posterior vaginal wall, or due to dissection close to the vaginal wall thereby avoiding rectal injury. These elements have to be taken into account when performing a pelvic floor repair and choosing SCP, during which an anterior and posterior prosthesis is generally placed. From our point of view, it would suffice to place an anterior mesh and treat the posterior compartment vaginally, which is the case with LLS in most centres nowadays. As discussed, genital prolapses most often affect the anterior and middle compartment, so it does not seem necessary to concomitantly treat the posterior compartment. Some authors will argue that a preventive correction is useful to limit the risk of recurrence. This must be weighed against the risk of complications related to prostheses in the posterior compartment. If the rectocele is not clinically significant, we choose a shared decision approach to correct it later only if it becomes symptomatic. Indeed, cures for rectoceles can sometimes be accompanied by dyspareunia (55). Since prolapse surgery is above all a functional surgery, the goal is to relieve the symptoms without necessarily seeking for perfect anatomical correction. In our experience, the need to correct a rectocele at a later stage remains infrequent and if required, the cure provided by the vaginal route is simple and rapid.

PELVIC ORGAN PROLAPSE (POP) AND STRESS URINARY INCONTINENCE (SUI)

A similar reasoning applies with regard to urinary incontinence, where we only simultaneously correct if clinically relevant. In the event of occult urodynamic SUI, or mild SUI, we discuss a two-stage intervention with the patient if necessary. In our experience, with good pre-operative explanations, this strategy is well understood and approved. We believe this saves patients from unnecessary gests and their possible complications. An increasing number of urogynecologists are adopting this strategy with regard to occult urinary stress incontinence, whereby they treat as a second step after repairing the prolapse only if it becomes symptomatic (56, 57). It is sustained by our recent studies. In our RALLS study, 60% of women with preoperative SUI were cured after the operation and there were only 5.9% of de novo SUI. In our LLS series, 40% were cured with the POP surgery alone (44). In other LLS series, de novo SUI was only 2.5% (46) and 3.7% (39), which is also less than the average 9% described for SCP (22).

ROBOTIC ASSISTANCE

Both techniques (SCP and LLS) have been reproduced by robot-assisted laparoscopy. Robotic assistance offers many advantages, in particular 3D vision which allows for clean bloodless dissections. Several reviews show similar results of RSCP in relation to laparoscopy or the abdominal route (58). For lateral suspension, there is still little literature, but it is also very promising. The robot makes it possible to correct ergonomic problems and has enabled us to reduce the number of scars. It allowed us to place the working trocars very laterally, enabling removal of the prosthetic braces by the same route, rather than by additional supra-iliac incision, such as in the standard laparoscopic technique described by

Dubuisson. The preliminary results do not show any difference with the laparoscopic approach encouraging the use of the robot in this restorative surgery (45, 46, 59).

DISCUSSION

Although we contrast SCP and LLS in this article, we believe these two POP repair techniques are complementary. Based on our expertise, prosthetic lateral suspension adapts particularly well to hysteropexy, and SCP remains a better option for vaginal vault prolapses. It is important that pelvic floor surgeons master both techniques in order to be able to manage any situation for best patient outcome. In this way, they may better adapt and reduce the perioperative risks when faced with an intraoperative difficulty. For example, dissection of the promontory can be challenging in obese patients, or in the case of vascular anatomical variations, and lateral suspension may represent a safer alternative. On the other hand, a high adhesion status in the right iliac fossa after appendicitis may require dangerous adhesiolysis to access the lateral strip, and SCP may in this case provide lower risks.

However, we attempt to demonstrate in this article that prosthetic lateral suspension is safer and easier to perform, with some advantages over SCP which can be summarized as follows.

Firstly, it avoids the risks associated with the dissection of the promontory, especially the risk of haemorrhage and of spondylodiscitis which can threaten patient prognosis. Contrary to SCP series, which report a 4% risk of laparotomy, there was no such occurrence available in all of the LLS series. Moreover, the learning curve for this technique also seems faster to us.

LLS is also particularly suitable for uterine preservation, which is chosen by many women today. Hysteropexy by prosthetic lateral suspension follows the anatomical attachments of the uterus and makes it possible to preserve the vaginal axis (52). This can help maintain a normal suburethral support and potentially prevent the risk of de novo urinary incontinence, which seems less with LLS than with SCP. This remains however to be demonstrated by comparative studies.

As the distribution of genital prolapse mainly affects the anterior and middle compartments, LLS is perfectly suited to this anatomical situation. The absence of a mesh in the posterior compartment may reduce the risk of subsequent mesh erosion, thereby avoiding a number of unnecessary operations and their possible complications. Since the posterior compartment is best treated vaginally, it can be treated by standard vaginal surgery during the same operation if there is a significant rectocele, or later, if it appears secondarily at postoperative follow-up. Avoiding prophylactic posterior colporraphy may reduce the risk of dyspareunia.

In conclusion, for all these robust reasons stated above, we believe LLS should be upgraded and considered as the new gold standard for treating apical POP with a healthy uterus.

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

PD is the only author of this manuscript.

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Nomogram Predicting Lymph Node Metastasis in the Early-Stage Cervical Cancer

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Background: Accurately predicting the risk level of lymph node metastasis is essential for the treatment of patients with early cervical cancer. The purpose of this study is to construct a new nomogram based on 2-deoxy-2-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) and clinical characteristics to assess early-stage cervical cancer patients' risk of lymph node metastasis.

Materials and Methods: From January 2019 to November 2020, the records of 234 patients with stage IA-IIA [International Federation of Gynecology and Obstetrics (FIGO) 2018] cervical cancer who had undergone PET/CT examination within 30 days before surgery were retrospectively reviewed. A nomogram to predict the risk of lymph node metastasis was constructed based on it. The nomogram was developed and validated by internal and external validation. The validation cohorts included 191 cervical cancer patients from December 2020 to October 2021.

Results: Four factors [squamous cell carcinoma associated antigen (SCCA), maximum standardized uptake value of lymph node (nSUVmax), uterine corpus invasion in PET/CT and tumor size in PET/CT] were finally determined as the predictors of the nomogram. At the area under the receiver operating characteristic curve cohort was 0.926 in the primary and was 0.897 in the validation cohort. The calibration curve shows good agreement between the predicted probability and the actual probability. The decision curve analysis showed the clinical utility of the nomogram.

Conclusion: We had established and verified a simple and effective nomogram, which can be used to predict the lymph node metastasis of cervical cancer patients before surgery.

Keywords: cervical cancer, nomogram, lymph node metastasis, PET/CT, decision curve analysis

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INTRODUCTION

Cervical cancer (CC) is one of the most common gynecological malignancies worldwide. It is estimated that an estimated 569,847 new cases and 311,365 related deaths were diagnosed each year. More than 85% of these cases occur in developing countries (1). The treatment of choice depended on cancer stage. The hallmark of a good staging system is the ability to define anatomical

extent of disease and differentiate survival outcomes. Cancer staging is an evolving process that responds to developments in technology that improves diagnosis and treatment. Since 2018, the presence of pelvic or para-aortic lymph node metastases assigns the case to stage IIIC regardless of other findings for CC instead of clinical assessment of staging (2). Because information on the lymph node (LN) status is necessary to determine the treatment strategy, an accurate and effective preoperative diagnostic approach for lymph node (LN) metastases is urgently required.

Imaging techniques, including magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), positron emission tomography/computed tomography (PET/CT), positron emission tomography/magnetic resonance imaging (PET/MRI), and trans-vaginal ultrasound, can detect lymph node involvement with CC, facilitate determination of spread to the retroperitoneum. However, the sensitivity of these methods for detecting nodal metastasis varies from 60 to 88% (3–5). The role of PET/CT to detect lymph nodal metastasis has been studied in various centers and the results are unsatisfactory with a sensitivity of 48.6–82% (6, 7). Several studies have added radiomics for LN metastasis prediction in CC. In early phase, Kim et al. constructed a nomogram based on age, tumor size by MRI, LN metastasis on PET/CT, and their model could accurately identify patients at low risk of lymph node metastasis (LNM). Similarity, Liu et al. developed a non-invasive and convenient nomogram based on two parameters [squamous cell carcinoma associated antigen (SCCA), maximum standardized uptake value of lymph node (nSUVmax)] for preoperative identification of pelvic lymph node metastasis in early-stage CC and reported a high sensitivity and specificity compared to single parameter (6, 8). Both the nSUVmax of PET/CT and SCCA is very important to confirm the diagnose of CC and the positive lymph node. However, their nomogram just focused on the 2-deoxy-2-fluorodeoxyglucose (^{18}F-FDG) uptake of lymph node (LN), ignoring the size of tumor and the spread of tumor. It is known that endometrial cancer is associated with the high risk of lymphatic metastasis. Previous studies also reported that patients with uterine invasion of CC exhibited high rates of pelvic lymph node metastasis, increased risk of distant metastasis, high rates of recurrence, and poor survival. Recently, Turan et al. reported that patients with uterine invasion had a higher rate of para-aortic lymph node metastasis than patients without uterine invasion (35 vs. 22.8%, $p = 0.046$) (9). Thus, we believed that uterine invasion and size defined by PET/CT is very important to evaluate the pelvic lymph node metastasis.

In this study, we aimed to explore a simple and effective predictive model based on four factors (SCCA, nSUVmax, uterine corpus invasion, and tumor size in PET/CT) for LN metastasis of clinically early-stage cervical cancer. We defined a low-risk group of patients who would least benefit from a surgical treatment and pointed out a guideline in the decision for the need for adjuvant radiotherapy.

MATERIALS AND METHODS

Patients

In this retrospective study, we enrolled 425 cervical cancer patients who underwent surgery at the Obstetrics and Gynecology Hospital of Fudan University from January 2019 to October 2021. All patients were diagnosed with early-stage CC [IA1 with lymph-vascular space invasion (LVSI), IA2-IIA2]. A total of 234 patients from January 2019 to November 2020 and 191 patients from December 2020 to October 2021 was assigned into primary and external validation cohorts, respectively. All private information is strictly secret and only used for the purpose of this research. The clinical and pathological staging of cervical cancer is based on FIGO 2018 guidelines. The ethics committee of Obstetrics and Gynecology Hospital of Fudan University approved this study.

The inclusion criteria were as follows: (1) patients had undergone PET/CT in the 30 days before surgery; (2) patients underwent pelvic lymph node dissection; (3) patients had no chemotherapy or radiation before PET/CT examination. The exclusion criteria were as follows: (1) patients were lack of postoperative pathological report; (2) pathological report suggested that patients had cervical carcinoma *in situ*; (3) Patients undergone hysterectomy or pelvic lymph node dissection before PET/CT examination.

Patients performed pelvic lymph node dissection, and the bilateral common iliac lymph nodes as well as obviously enlarged lymph nodes were used for frozen section during the operation. Not all patients performed para-aortic lymph node dissection. Patient characteristics including age, FIGO stage, number of pregnancies, preoperative SCCA level, menopause, pathological LN metastasis, and PET/CT image date were obtained from the medical records.

Positron Emission Tomography/Computed Tomography Examination

All patients received PET/CT with an integrated PET/CT scanner (Biograph-64, Siemens, Munich, Germany) within the 30 days before surgery. The patients fasted for at least 6 h before the PET/CT examination. The blood glucose level of patients was controlled at <10.0 mmol/L before 2-deoxy-2-fluorodeoxyglucose (^{18}F-FDG) injection (2.9–5.6 MBq/kg body weight). Before scanning, patients were required to be quiet for approximately 1 h after urination. Images were included CT and PET scans from the base of the skull to the mid-thigh level. Then, the attenuation correction of CT data was used to reconstruct PET image data sets and the images were displayed on a workstation.

The most common regions of lymph node metastases for cervical cancer patients are pelvic lymph nodes, para-aortic lymph nodes, and inguinal lymph nodes. Two experienced nuclear medicine physicians analyzed and interpreted all PET/CT parameters independently, such as LN in PET/CT, LN diameter, and maximum standardized uptake value (SUVmax). They were

blindly without knowledge of patient's information, medical data, and pathological results. We reported the lymph node status and uterine corpus invasion in PET/CT scan (the invasion of tumor beyond the internal cervical orifice in PET/CT), and measured the maximum standardized uptake value of tumor (tSUVmax), maximum standardized uptake value of lymph node (nSUVmax), tumor size and LN diameter in PET/CT, and also calculated the value of nSUVmax/tSUVmax. The pathological results served as the gold standard for comparison with the PET/CT results. Pathological stage follows FIGO 2018 guidelines.

TABLE 1 | Patient characteristics and univariate analysis of the risk of lymph node metastasis.

Variable	Primary cohort ($n = 234$)			Validation cohort ($n = 191$)		
	Node negative ($n = 173$)	Node positive ($n = 61$)	*P*	Node negative ($n = 131$)	Node positive ($n = 60$)	*P*
Age (year), n (%)			0.346			0.008
<50	83 (48.0)	25 (41.0)		64 (48.9)	17 (28.3)	
≥50	90 (52.0)	36 (59.0)		67 (51.1)	43 (71.7)	
Menopause, n (%)			0.257			0.027
No	94 (54.3)	28 (45.9)		75 (57.3)	24 (40.0)	
Yes	79 (45.7)	33 (54.1)		56 (42.7)	36 (60.0)	
Number of pregnancies, n (%)			0.442			0.635
<3	75 (43.4)	23 (37.7)		52 (39.7)	26 (43.3)	
≥3	98 (56.6)	38 (62.3)		79 (60.3)	34 (56.7)	
Hypertension, n (%)			0.185			0.500
No	151 (87.3)	49 (80.3)		112 (85.5)	49 (81.7)	
Yes	22 (12.7)	12 (19.7)		19 (14.5)	11 (18.3)	
Diabetes, n (%)			>1.000			>1.000
No	167 (96.5)	59 (96.7)		122 (93.1)	56 (93.3)	
Yes	6 (3.5)	2 (3.3)		9 (6.9)	4 (6.7)	
Tumor histology, n (%)			0.099			0.337
Squamous cell cancer	138 (79.8)	54 (88.6)		108 (82.4)	52 (86.7)	
Adenocarcinoma	22 (12.7)	6 (9.8)		13 (10.0)	2 (3.3)	
Adenosequamous cancer	9 (5.2)	0 (0.0)		7 (5.3)	5 (8.3)	
Others	4 (2.3)	1 (1.6)		3 (2.3)	1 (1.7)	
2018 FIGO stage, n (%)			<0.001			<0.001
IA	9 (5.2)	0 (0.0)		9 (6.9)	0 (0.0)	
IB	136 (78.6)	27 (44.3)		77 (58.8)	26 (43.3)	
IIA	28 (16.2)	34 (55.7)		45 (34.3)	34 (56.7)	
SCCA (ng/mL)						
Mean (SD)	1.9 (2.4)	8.8 (13.1)	<0.001	2.8 (3.4)	12.5 (15.3)	<0.001
Tumor size in PET/CT (cm)						
Mean (SD)	2.2 (1.7)	4.1 (1.9)	<0.001	2.7 (1.5)	4.3 (1.7)	<0.001
LN diameter in PET/CT (cm)						
Mean (SD)	0.4 (0.4)	1.0 (0.7)	<0.001	0.3 (0.4)	1.2 (1.1)	<0.001
tSUVmax						
Mean (SD)	8.3 (6.1)	11.2 (6.3)	<0.001	8.6 (6.3)	11.7 (5.1)	<0.001
nSUVmax						
Mean (SD)	0.7 (1.1)	4.5 (4.5)	<0.001	0.6 (1.1)	4.6 (5.4)	<0.001
nSUVmax/tSUVmax						
Mean (SD)	0.1 (0.2)	0.5 (0.5)	<0.001	0.1 (0.2)	0.4 (0.6)	<0.001
Uterine corpus invasion in PET/CT, n (%)			<0.001			<0.001
No	163 (94.2)	34 (55.7)		114 (87.0)	27 (45.0)	
Yes	10 (5.8)	27 (44.3)		17 (13.0)	33 (55.0)	
LN status in PET/CT, n (%)			<0.001			<0.001
No	132 (76.3)	12 (19.7)		105 (80.2)	18 (30.0)	
Yes	41 (23.7)	49 (80.3)		26 (19.8)	42 (70.0)	

LN, lymph node; SCCA, squamous cell carcinoma associated antigen; SUVmax, maximum standardized uptake value; nSUVmax, SUVmax of lymph node; tSUVmax, SUVmax of tumor; PET/CT, positron emission tomography/computed tomography.

Statistical Analysis

IBM SPSS (version 23.0; IBM, Inc., Chicago, IL, United States) and R (version 4.1.2[1]; The R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis. Continuous variables were described as mean with standard deviation (SD), and categorical variables were described as frequencies with percentages. Univariate and multivariable analysis were performed, and used an odds ratio (OR) with a 95% confidence interval (CI) to estimate correlation strength. Predictors ($P < 0.05$) in univariate analysis were entered a multivariable regression analysis. A nomogram capable of predicting the risk of lymph node metastasis in cervical cancer patients was then developed based on the multivariable regression analysis.

The performance of the nomogram was assessed internally and externally by discrimination and calibration. The discriminative ability of the nomogram in predicting lymph node metastasis was evaluated by calculating the area under the receiver operating characteristics curve (AUC-ROC). The calibration of the model was performed by comparing the predicted and actual probability of lymph node metastasis. The internal verification of the nomogram used 1,000 bootstrap resample in the primary cohort, and the model was applied to the validation cohort for external validation. In addition, decision curve (DCA) was used to determine the clinical usefulness of the nomogram by calculating the net benefits at different threshold probabilities in the primary data set (10). We also analyzed the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of PET/CT alone and nomogram in each cohort. $P < 0.05$ was considered statistically significant.

RESULTS

The characteristics of the enrolled patients are shown in **Table 1**. All patients underwent pelvic lymph node dissection during operation. In the primary cohort, LN metastasis was pathologically confirmed after surgery in 61 cases and 173 cases had no LN metastasis. In a survey, 49 (80.3%) patients with positive LN metastasis in PET/CT and pathological results. The mean (SD) of preoperative SCCA was 1.9 (2.4) ng/ml in patients with negative LN metastasis and the positive patients was 8.8 (13.1) ng/ml. The mean (SD) of nSUVmax of positive or negative LN metastasis was 4.5 (4.5) and 0.7 (1.1). In a survey, 27 (44.3%) cases with LN metastasis had uterine corpus invasion in PET/CT scan. According to the pathological reports, there were 60 cases with LN metastasis and 131 cases without LN metastasis among the validation cohort. Among them, 105 (80.2%) PET/CT scan-negative patients had no LN metastasis, while 42 (70.0%) PET/CT scan-positive patients were confirmed LN metastasis.

According to the results of our final analysis in primary cohort (**Table 2**), SCCA (OR: 1.134; 95% CI: 1.005–1.278; $P = 0.041$), nSUVmax (OR: 1.890; 95% CI: 1.075–3.323; $P = 0.027$), uterine corpus invasion in PET/CT (OR: 4.229; 95% CI: 1.269–14.092; $P = 0.019$), and tumor size in PET/CT (OR: 1.420; 95% CI: 1.049–1.921; $P = 0.023$) are independent hazardous factors for lymph node metastasis in patients with cervical cancer. Ultimately, SCCA, nSUVmax, uterine corpus invasion, and tumor size in PET/CT were chosen to construct a nomogram to predict the lymph node metastasis in cervical cancer patients (**Figure 1**).

The area under the receiver operating characteristic curve was 0.926 (95% CI: 0.890–0.962) in the primary cohort and was 0.897 (95% CI: 0.843–0.951) in the validation cohort, indicating that the nomogram has robust discrimination (**Figures 2A,B**). And calibration curves of the nomogram showed that the excellent concordance between the probability predicted by the nomogram and the actual probability in both groups (**Figures 2C,D**). The decision curve showed that if the threshold probability of a patient is between 5 and 90%, using the nomogram to predict lymph node metastasis can add more benefit than either the treat-all or treat-none scheme (**Figure 3**).

The sensitivity, specificity, PPV, NPV, and accuracy of PET/CT for LN metastasis were 75.2, 78.0, 57.6, 88.8, and 77.2, respectively. Compared with PET/CT alone, our nomogram showed risen sensitivity (82.0, 78.3%), specificity (89.0 and 90.8%), PPV (72.5 and 79.7%), NPV (93.3 and 90.2%), and accuracy (87.2 and 86.9%) in both the primary and validation cohorts (**Table 3**).

DISCUSSION

In 2018, the presence of lymphatic involvement is included in FIGO staging system because of the prognostic importance of lymphatic involvement. In addition, except for the clinical examination, imaging and pathologic findings could be used to determine the stage of the disease. Thus, the precise evaluation of lymph node is very key to guide the treatment and adjuvant

TABLE 2 | The variables identified by logistic multivariable regression analysis.

Variable	Multivariable analysis		
	OR	95% CI	*P*
Age (year)			0.520
<50	Reference		
≥50	1.662	0.353–7.827	
Menopause			0.300
No	Reference		
Yes	0.444	0.096–2.064	
SCCA (ng/mL)	1.134	1.005–1.278	0.041
Tumor size in PET/CT (cm)	1.420	1.049–1.921	0.023
LN diameter in PET/CT (cm)	1.183	0.360–3.886	0.781
tSUVmax	0.950	0.850–1.062	0.366
nSUVmax	1.890	1.075–3.323	0.027
nSUVmax/tSUVmax	1.725	0.051–58.313	0.762
Uterine corpus invasion in PET/CT			0.019
No	Reference		
Yes	4.229	1.269–14.092	

OR, odds ratio; CI, confidence interval.

[1]http://www.r-project.org

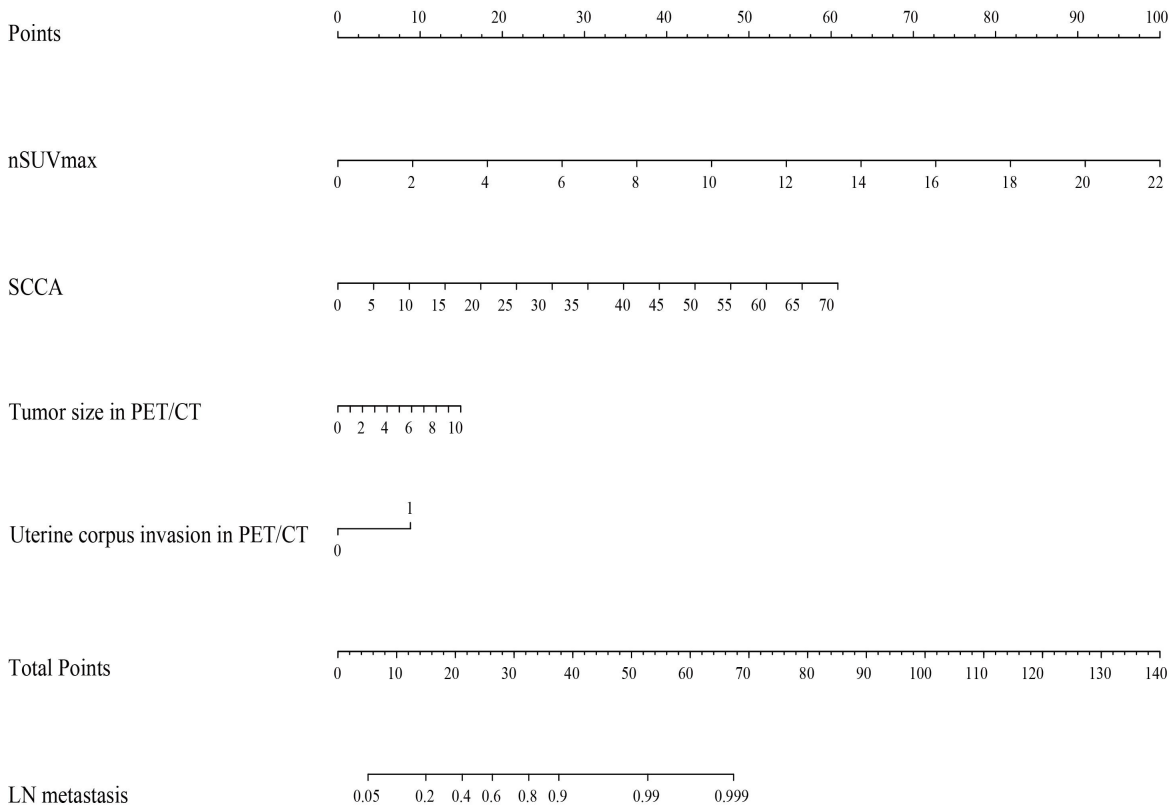

FIGURE 1 | A nomogram predicting the risk of lymph node metastasis in early-stage cervical cancer patients. nSUVmax, maximum standardized uptake value of lymph node; SCCA, squamous cell carcinoma associated antigen; PET/CT, positron emission tomography/computed tomography; LN, lymph node.

radiotherapy postoperatively. In the present study, based on the univariate and multivariate analysis, we identified four factors that were associated with prediction of lymph node metastasis: SCCA, nSUVmax, uterine corpus invasion, and tumor size in PET/CT. Then, we constructed a nomogram to predict the risk of nodal metastasis in early-stage CC. The model presented high specificity and sensitivity.

In recent years, MRI is increasingly applied for the pre-treatment evaluation of local spread of cervical cancer, on the basis of its excellent soft-tissue contrast and high spatial resolution. Radiomics involves the process of the conversion of medical images into high-dimensional, mineable data *via* the automated high-throughput extraction of quantitative imaging features. Hou et al. developed and validated a multiparametric MRI-based radiomics model to evaluate the tumor size, local invasive and LN status in patients with CC (11). Similarly, Xiao et al. constructed a nomogram that incorporates the radiomics signature, MRI-reported LN status, and FIGO stage to predict LN status in patients with early-stage CC (12). Although these studies based on MRI parameters showed favorable discriminative ability for tumor size and local invasive, it presents limitation for evaluating the status of LN metastasis. ^{18}F-FDG PET/CT is a functional method based on the increased glucose metabolism of cancer cells, and can often detect tiny metastatic lymph nodes ranging in size from 5 to 9 mm (13). PET/CT has a unique role in differentiating benign and malignant tumors, evaluating the efficacy of radiotherapy and chemotherapy and the prediction of tumor metastasis, etc. (14, 15). Previous studies had shown that PET/CT was superior to CT and MRI in the evaluation of retroperitoneal lymph nodes, whose sensitivity and specificity was 48.6–82% and 75–98%, respectively (6, 7, 16). However, PET/CT also has some shortcomings. Some benign lymph node diseases can also display high levels of ^{18}F-FDG uptake, making it misdiagnosed as a metastatic lymph node and increasing the false positive rate (17). Therefore, many studies aiming to improve the accurate of PET/CT was performed. For example, Wang et al. developed a nomogram to predict para-aortic lymph node (PALN) involvement. However, all stages of cervical cancer were included. PALN was only assessed by imaging (PET/CT or CT). As previously stated, assessment of node involvement by imaging is far from perfect. A Korean team developed a score based on tumor size and PALN involvement on PET/CT with patient who underwent para-aortic lymphadenectomy in locally advanced cervical cancer (LACC). Likewise, the main limitation of this study is that patients with LACC did not undergo surgical staging. These two studies may have under-estimated the FIGO stage and may have included patients with an initially advanced cervical cancer. Recently, Liu et al. constructed a non-invasive and convenient nomogram based on two parameters (SCCA and nSUVmax) for preoperative evaluation of pelvic

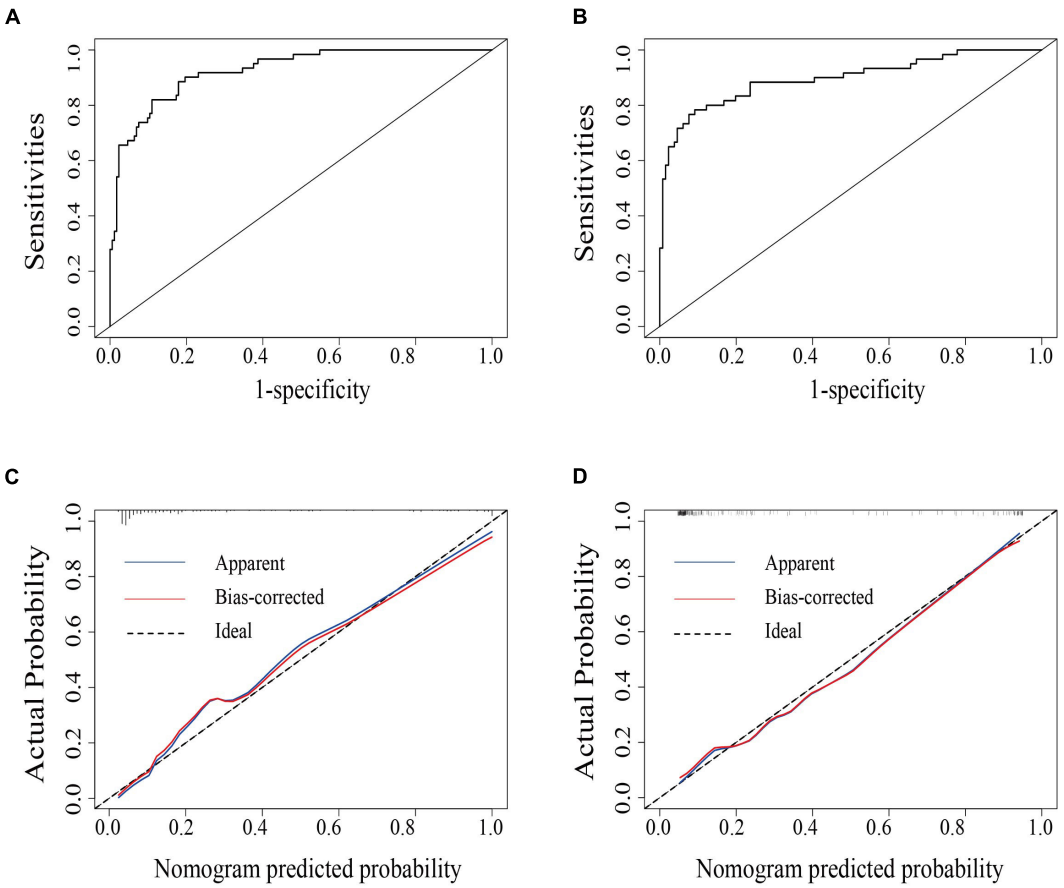

FIGURE 2 | The area under the receiver operating characteristics curve (AUC-ROC) of the model in the primary **(A)** and the validation cohort **(B)**, respectively. Calibration curves of the nomogram for the primary **(C)** and validation cohort **(D)**.

lymph node metastasis in early-stage CC and confirmed it had good diagnostic ability (18–20). However, this study focused on only quantitative parameters of PET/CT (SUVmax), ignoring the effect of tumor size and the uterine corpus invasion.

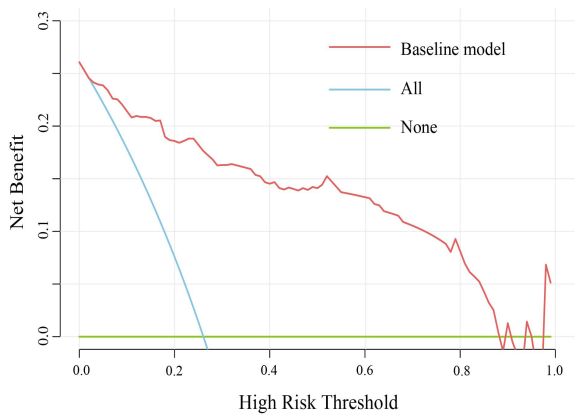

FIGURE 3 | Decision curve analysis for the nomogram.

In early staging systems, patients with a lesion confined to the cervix but extending to the endometrium were regarded as Stage II. However, uterine corpus invasion was disregarded over time. In the 2018 FIGO cervical cancer staging system, uterine corpus invasion has also been disregarded as in previous FIGO staging systems. According to this stage system, involvement of adjacent anatomic structures is associated with a worse prognosis and alters the FIGO stage, except uterine corpus invasion

TABLE 3 | Accuracy values of PET/CT and nomogram in LN metastasis.

Variable	PET/CT	Nomogram	
		Training cohort	Validation cohort
Sensitivity	75.2%	82.0%	78.3%
Specificity	78.0%	89.0%	90.8%
Positive predictive value (PPV)	57.6%	72.5%	79.7%
Negative predictive value (NPV)	88.8%	93.3%	90.2%
Accuracy	77.2%	87.2%	86.9%

PET/CT, positron emission tomography/computed tomography; LN, lymph node.

(9). However, previous studies have shown uterine corpus invasion was an independent risk factor for the prognosis of early cervical cancer patients and verified that it had an association to pelvic lymph node metastasis in CC (21). Hope et al. demonstrated that uterine corpus invasion of cervical cancer was correlated with the presence of lymph node metastasis in PET/CT (22). Uterine corpus invasion in MRI was independently associated with lymph node metastasis (23). It is known that para-aortic/pelvic nodal metastasis is very important in the decision for the need for adjuvant radiotherapy, the need for para-aortic lymphadenectomy or the border of the radiotherapy field. By evaluating the uterine invasion, it is easy to predicate the para-aortic/pelvic nodal metastasis. Another predictive factor of our nomogram was tumor size in PET/CT. Evaluation by PET/CT is part of the standard local-regional spread assessment for CC. Various studies have demonstrated that tumor size is an independent prognostic factor in determining the stage of CC. Togami et al. showed that tumor size greater than 2 cm was independently associated with LNM. Similarly, Han et al. proven tumor size $>$ 3.5 cm was connected with para-aortic lymph node metastasis. This was confirmed by Kim et al., who found that a larger tumor size assessed by MRI was an independent predictor of nodal metastases (8, 24–26). In the present study, our univariate and multivariate analysis also confirmed that uterine corpus invasion and tumor size in PET/CT were associated with high risk of LN metastasis in CC. This may explain the high rate of distant metastasis in endothelial cancer or the presence of uterine invasion of CC in patients treated with radiotherapy (27). Our study confirmed that tumor histology was not associated with LNM, which was consistent with previous reports (8). Recently, a large-scale retrospective study also demonstrated that histological type was not an independent risk factor for LNM in cervical cancer (28). Thus, our nomogram included the corpus invasion and tumor size in PET/CT. When we constructed the nomogram based the four factors, we found our nomogram had higher sensitivity (82.0%, 78.3% vs. 70.5%, 73.1%) and NPV (93.3%, 90.2% vs. 72.3%, 73.1%) and accuracy (87.2%, 86.9% vs. 81.3%, 79.2%) than previous, whether in the primary cohort or the validation cohort (6). Meanwhile, the calibration curve and DCA showed that the nomogram has good clinical applicability.

Our study still had some limitations. First of all, although internal and external verification certificated the model fits well, the retrospective nature may therefore introduce the possibility of some inevitable recall bias. Prospective studies are still required to confirm the predictive value of the model in a clinical practice environment. In addition, in spite of all patients accepting pelvic lymph node dissection, not all underwent para-aortic lymph node dissection, and patients who did not undergo para-aortic lymph node dissection were regarded their para-aortic lymph nodes negative. In fact, lymph node metastasis has always been considered a gradual process in cervical cancer. However, some studies reported that 25–31.2% CC patients had skip lymph node metastases. The latest multiple prospective studies had certified that the rate of skip para-aortic lymph node metastases in cervical cancer was 3.3–6.0% (29–31).

In conclusion, we have established and validated an effective nomogram for predicting preoperative LN metastasis in early-stage cervical cancer. This individualized model provides a more effective and non-invasive preoperative means of assessing patients risk of LN metastasis. The model may identify a low-risk group of patients who would least benefit from a surgical treatment and give a further guideline in the decision for the need for appropriate adjuvant treatment after surgery.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Obstetrics and Gynecology Hospital, Fudan University, Shanghai, China (No. 2020-183). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KH: protocol/project development. CBL: manuscript editing. SY and CLL: manuscript writing, data analysis, and data collection or management. All authors contributed to the article and approved the submitted version.

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