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The Role of Hysterectomy in Modern Gynaecological Surgery

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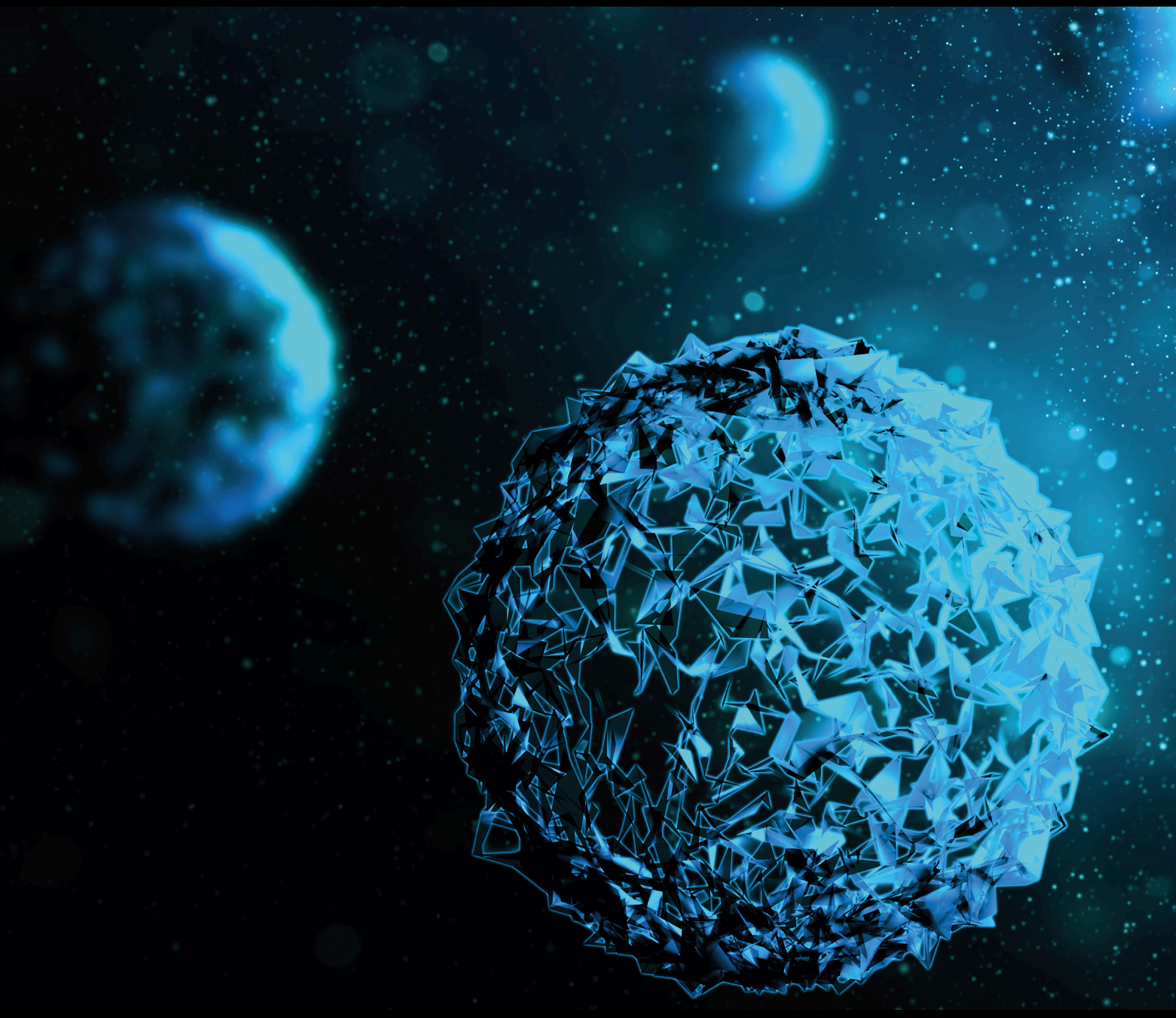

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Editorial Board

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Editorial

The Role of Hysterectomy in Modern Gynaecological Surgery

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Hysterectomy plays a major role in gynecological surgery. The list of indications for hysterectomy is long and includes a variety of benign and malignant diseases. Over the last decades, new techniques allowed the implementation of new surgical approaches. Vaginal and abdominal hysterectomy has been complemented by laparoscopic procedures, such as vaginal hysterectomy assisted by laparoscopy, laparoscopic subtotal and total hysterectomy, and robotic hysterectomy. The implementation of new techniques was related to "new" complications, a series of studies comparing the alternative approaches for hysterectomy and an ongoing craftsmanship among gynecological surgeons about what is possible in laparoscopic surgery [1] [2] [3]. At the same time, a contrary movement dedicated to the preservation of the uterus emerged [4] [5] [6]. Hysterectomy was no longer the only solution in many uterine diseases, as techniques like radiofrequency ablation, uterine artery embolization, high-focused ultrasound, endometrial ablation, and minimally invasive tumor enucleation allowed uterus-sparing procedures in symptomatic patients. In this situation, we raised the question: what is the role of hysterectomy in modern gynecological surgery? G. K. Noé et al. focused on surgical techniques in pelvic floor disorders. The authors emphasized that hysterectomy requires its own indication and should not automatically be part of every pelvic floor intervention [7]. L. A. Torres-de la Roche et al. described a possible complication of uterine artery embolization and discussed the role of hysterectomy as a secondary intervention after treatment failure in uterus-sparing techniques [8]. While Q. Zhang et al. described the impact of B7-H4 expression in precancerous lesions of the uterine cervix and the decision-making process regarding follow-up and conization in patients with CIN2 [9], R. Wojdat et al. presented a retrospective analysis of their experience with vaginal assisted radical laparoscopic hysterectomy in patients with cervical cancer in the post-LACC trial era [10]. The role of hysterectomy in the management of obstetrical complications, especially in peripartum hemorrhage, has been reviewed by D. Tsolakidis et al. [11]. The broad spectrum of this special issue shows the relevance of hysterectomy in gynecological and obstetrical indications. Also, in modern gynecological surgery, hysterectomy plays a crucial role. But complete counseling of patients requires the consideration of all available hysterectomy approaches including vaginal, abdominal, laparoscopic, robotic, or combined techniques and the knowledge of uterus-sparing treatment alternatives. The aim of this special issue is to describe the significance of the uterus in a woman's life span and to highlight the actual trends in hysterectomy.

Conflicts of Interest

The editors declare that they have no conflicts of interest regarding the publication of this special issue.

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H. Krentel
R. L. De Wilde
G. Pados

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Research Article

Extravascular Dispersion of Polyvinyl Alcohol Microsphere Particles in Uterine Artery Embolization

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Uterine artery embolization (UAE) is a common minimally invasive treatment of different uterine pathologies, such as fibroids, adenomyosis, and menorrhagia. The procedure involves the injection of embolic agents into the uterine arteries, whereby various particles can be used, such as polyvinyl alcohol (PVA). Complication of UAE is the dispersion of polyvinyl alcohol (PVA) microsphere particles in the uterine body which can lead to a granular vaginal discharge. We report the management of complications of PVA microspheres dispersed from the uterine body causing postprocedural discomfort due to the vaginal passage of microspheres or because of an induced fibroid-size enlargement. The dispersion of the PVA microspheres is one example of a minor UAE complication, which nevertheless causes significant distress to the patient and eventfully requires further surgical interventions.

1. Introduction

The injection of microspheres of polyvinyl alcohol (PVA) particles can be successfully used as the minimally invasive procedure to obliterate the vasculature of the uterine body (uterine artery embolization; UAE) in the treatment of different uterine pathologies [1]. UAE is used in young women who desire to preserve their uterus and is minimally invasive and has a faster recovery than most surgical treatments [2]. It may be used as an alternative therapy to myomectomy and hysterectomy, but complications are possible [3, 4]. These events can be classified as major or minor [5] and may result in prolonged hospitalization and troublesome outcomes such as pelvic infection, ischemia, ovarian failure, sexual dysfunction, expulsion of degenerated fibroid tissue, nongynecologic embolization, or pulmonary embolism [5]. Despite the fast recovery time after embolization, the procedure is associated with minor complications and a risk of failure, eventually leading to future necessary surgical intervention [6, 7].

The Society of Obstetricians and Gynaecologists of Canada (SOGC) recommends that patients who consider UAE as a treatment option for symptomatic fibroids be counselled about the early results and the lack of data on the long-term benefits regarding future fertility and pregnancy outcomes [8]. Women should also be counselled regarding the risk of major complications and subsequent hysterectomy. Concerning the satisfaction rates of UAE compared to surgical intervention, no differences were reported after two and five years [4, 8].

Considering that dispersion of polyvinyl alcohol microsphere during UAE is an uncommon event, this paper focuses on the management of this complication presented in patients who underwent UAE because of uterine fibroids, adenomyosis, and menorrhagia.

2. Materials and Methods

We retrospectively analyzed the data of patients who presented with complications relating to dispersed PVA

microspheres after UAE was performed for different uterine pathologies. The electronic medical records of the patients were evaluated in terms of their clinical symptoms and diagnostic and surgical treatments. The findings are reported according to the PROCESS statement for reporting cases series [9]. Written informed consent to publish from all patients was obtained, and the approval to conduct the present analysis was obtained from the Ethical Committee of the Dubai London Clinic and Speciality Hospital (DLCEC5012021-1; 15.02.2021).

3. Results

During the last five year of experience in our clinic, we have found four cases of polyvinyl alcohol microsphere particle dispersion during UAE. In the following, we describe the clinical features of these patients and the management provided.

A 51-year-old patient attended due to symptomatic uterine fibroid and adenomyosis. She complained about menorrhagia and metrorrhagia for five years and received UAE in 2016 that was complicated by extrusion of PVA microspheres. During hysterectomy, it was observed that the parametria were infiltrated, resulting in difficult dissection of the pelvic wall and ureter. Microscopic examination revealed the presence of proteinaceous foreign body (PVA) in the uterine substance and the paratubal soft tissue with granulomatous reaction. The postoperative recovery of the patient was uneventful.

The second case was a 35-year-old patient who was referred for infertility and multiple fibroids, having complaints such as menorrhagia and dysmenorrhea. She was initially given a trial of UAE and concomitant medical management with Ulipristal acetate but failed to respond to the treatment. She had repetitive IVF failures and was referred for myomectomy. Thus, laparoscopic myomectomy was performed which revealed extensive dispersion of PVA particles in the myometrium and in the subcapsular surfaces, requiring thorough rinsing and reconstruction of myometrium. Postoperative recovery was uneventful and patient presented to date symptom free. She was advised to report for follow up in two years.

The third case was a 34-year-old patient that visited the clinic for infertility and multiple myomas, failed UAE, and persistent symptoms of hypermenorrhea. She underwent laparoscopic myomectomy and, thereafter, suffered from repeated in vitro fertilization and embryo transfer (IVF-ET) failures and greenish vaginal discharge. Hysteroscopic resection and evacuation of residual myoma and PVA granules was performed followed by adhesion barrier prophylaxis to prevent synechiae. A second-look hysteroscopy was performed to confirm the absence of foreign bodies in the uterus. The patient had a good postoperative recovery and was planned for embryo transfer (ET).

The fourth case was a 53-year-old patient that visited our hospital for heavy menstrual bleeding due to multiple fibroids. She received both UAE and medical management with ulipristal acetate for symptomatic fibroids which failed to improve the symptoms. Hysteroscopic endometrial resection was performed with the primary intention of biopsy, which revealed PVA particles in the endometrium and subendometrial region encapsulating the fibroids closer to the endometrium. She was advised for follow up after 3 months to evaluate her response to therapy.

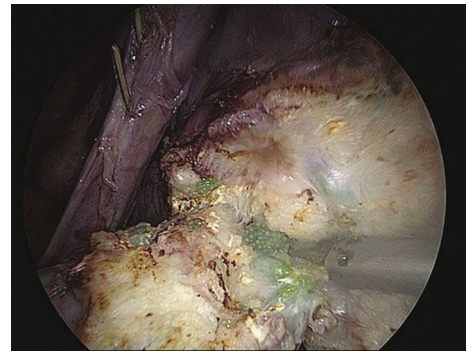


Figure 1: Extrusion of PVA microspheres as observed at laparoscopic supracervical hysterectomy.

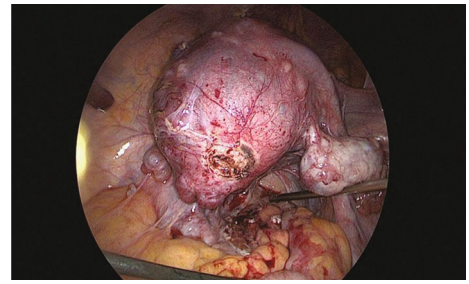


Figure 2: Laparoscopic supracervical hysterectomy in case 1, multiple small myomas visible during operation.

3.1. Management of Extravascular Dispersion of Polyvinyl Alcohol Microsphere Particles. All the aforementioned patients were treated with different treatment modalities following the typical case scenarios in the best interest of the patients. Laparoscopic supracervical hysterectomy was done for the first case with careful preparation of the infiltrated parametrium, and difficult dissection of pelvic wall and ureter, due to extrusion of PVA microspheres (Figure 1). The specimen (Figure 2) was extracted with in-bag morcellation to prevent the spillage of the microspheres into the abdominopelvic cavity. Histopathological analysis revealed benign findings and confirmed PVA particles. No intraoperative or postoperative complications were recorded. Patient was taken into follow up and remained symptom free.

The second case was managed by laparoscopic myomectomy. Cytology was obtained of the peritoneal washings followed by careful enucleation of myomatous tissues and the PVA particles in the uterine myometrium (Figure 3). The myometrium was reconstructed with V LOC^{R} suture. The large multiple myomatous specimen was extracted with in-bag morcellation to prevent the spillage of the microspheres into the abdominopelvic cavity (Figures 4 and 5). Histopathological analysis revealed benign findings and confirmed PVA particles. No intra or postoperative complications were recorded. She had symptom-free follow-up.

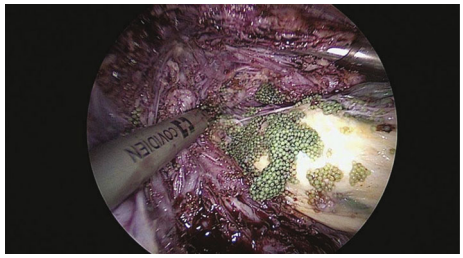


Figure 3: Myomectomy, intraoperative visualization of PVA microspheres.

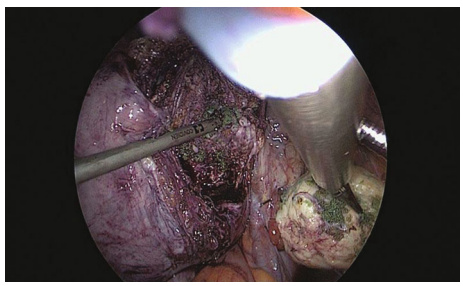


Figure 4: Successful myomectomy.

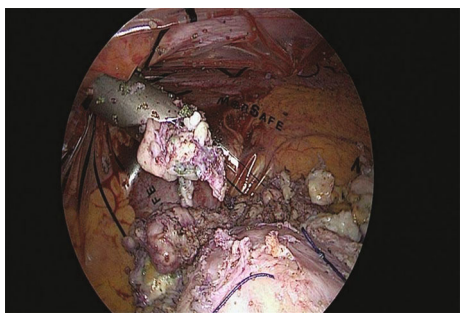


Figure 5: Morcellation of myomas.

The third case was treated with hysteroscopic resection of residual myoma, and PVA granules were evacuated (Figure 6). A second-look hysteroscopy confirmed no foreign body in the cavity. Patient was symptom free and was planned for embryo transfer (ET). She was advised for laparoscopic exploration if needed thereafter for residual myomas.

The fourth case was treated with hysteroscopic resection of the submucous fibroids (Figure 7). Hysteroscopic endometrial resection was performed with primary intention of biopsy (Figure 8), which revealed the PVA particles in the endometrium and subendometrial region, encapsulating the fibroids closer to the endometrium. She was advised for follow-up after 3 months to evaluate response to therapy.

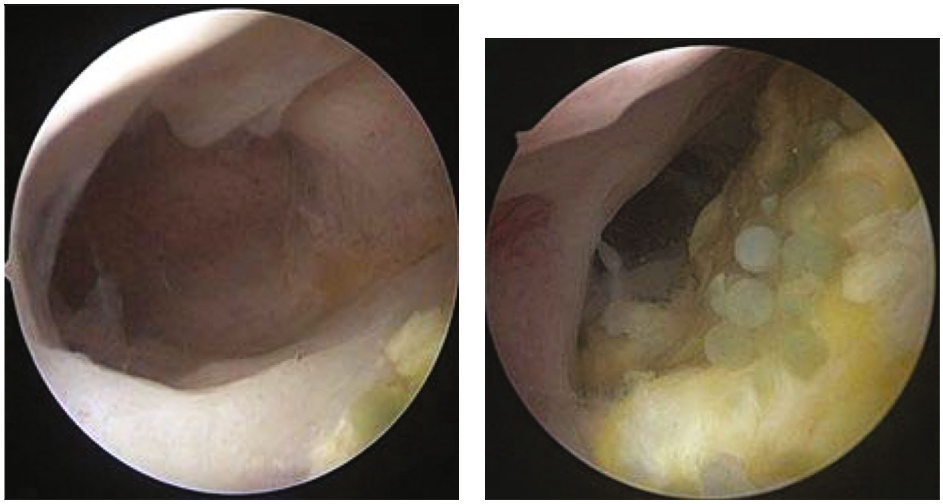
4. Discussion

The use of polyvinyl alcohol (PVA) particles was first reported in 1995 by Ravina et al. in a study of 16 patients treated with UAE for uterine fibroids [10]. On follow-up, 80% of these patients reported resolution of their symptoms, but the others required additional surgery. UAE is associated with shorter hospital stay and better recovery of the patients [5] in comparison to myomectomy or hysterectomy [4]; therefore, UAE can be considered as an alternative to surgery. In our previous publication [5], we found that the patients who benefit most from this therapy are those who are young, suffer from heavy menstrual bleeding resistant to other conservative measures, or have nonpedunculated fibroids, irrespectively of the number and size of fibroids. Pedunculated fibroids are a relative contraindication because of the risk of degeneration and subsequent infection. Regarding the myoma size, aberrant vascularization of large fibroids (>10 cm) should be evaluated before embolization to avoid damage to neighboring abdominal structures. According to a Cochrane Review, involving women wishing to preserve fertility, there is no significant difference between UAE and surgery in patient satisfaction rates at two and five years [4]. Quality-of-life scores were documented better after UAE than high-intensity focused ultrasound ablation (HIFU) [11].

PVA particles have a tendency to clump together to form larger aggregates which can be minimized by their dilution and slow infusion to achieve more distal embolization and sometimes reach the ovarian vessels, potentially affecting the ovarian reserve [12, 13]. Therefore, desired level of occlusion should be determined to select the appropriate particle size to be used. Usually, particles measuring 350–500 or 500–710 μ in diameter are used to achieve complete occlusion of uterine arteries that, in turn, induces ischaemic necrosis of the uterine fibroids. However, there is no conclusive evidence about the impact of the blood flow reduction and ionising radiation received during the procedure on fertility and pregnancy. Although loss of ovarian reserve can occur after hysterectomy, myomectomy, and UAE, it occurs more frequently in women older than 45 years that underwent UAE [14]. Other studies report lower pregnancy rates after UAE than after myomectomy [5] or HIFU [11], as well as, higher miscarriage events than after myomectomy [5]. Nonetheless, many confounding factors affect these results, especially younger patients are underrepresented in most of the studies. With reference to complications, no significant difference between UAE and surgery or HIFU has been observed [4, 11].

In one rare complication inherent to UAE, the possibility of PVA dispersion in parametrial and myometrium arteries, as described, can lead to damage to nearby organs, persistent symptoms and even to complete uterine ischemia or endometrial infection requiring hysterectomy [15]. In cases of intracavitary residual myoma, a hysteroscopic PVA granule evacuation and further fibroid resection is a feasible solution to this complication when the uterus is not severely compromised and for patients seeking to get pregnant. For more complicated cases, where the parametrium is distorted or the pelvic wall and ureter are not easily to dissect, laparoscopic supracervical hysterectomy with in-bag morcellation, to prevent the spillage of the microspheres into the abdominopelvic cavity, could be performed. In accordance to our experience, the acute management of this rare complication should be individualized, taking in consideration the clinical situation and patient's desire.

In addition to proper technique during the UAE procedure, adequate patient selection is crucial to avoid the



(a) (b)

Figure 6: Hysteroscopic aspect of residual myomas and PVA granules. (a) Residual myomas. (b) Polyvinyl alcohol granules.

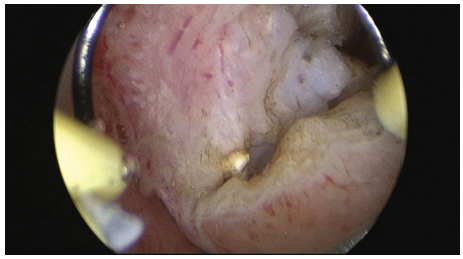


Figure 7: Hysteroscopic resection of the sub-mucous fibroids.

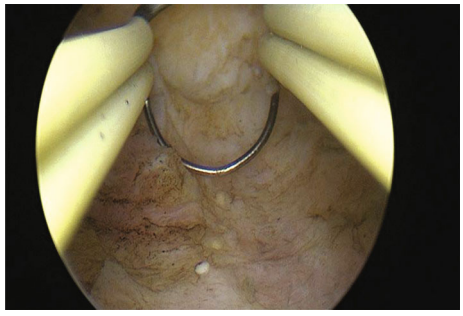


Figure 8: Hysteroscopic resection of endometrium.

aforementioned complication and further interventions [5, 16]. With regard to improving fertility chances after UAE, there are no actual data to support this issue [5], and women should be informed before the procedure [17, 18]. For symptomatic fibroids, UAE may be successfully used as an alternative to hysterectomy or myomectomy, especially in women with desire to preserve their uterus [5]; however, the risk of complications must be discussed with the patients before initiating the therapeutic plan [5].

5. Conclusions

Although UAE is a commonly practiced procedure for the treatment of uterine fibroids specially to preserve the uterus, minor complications have been reported. The dispersion of the PVA microspheres is one of those minor complications which are apparently rare but can cause significant distress to the patient and require further surgical interventions.

The proper selection of cases to receive UAE should be carried out, and a therapeutic plan of the uterus pathology should be established together with the patients, taking into account the current evidence-based data for UAE, therapeutic goals to be achieved, and, last but not least, the possibility of minor and major complications of the procedure. The acute management of complications should be individualized in accordance to the clinical situation and patient's desire.

Data Availability

The clinical data used to support the findings of this study are stored at Department of Laparoscopic Gynecological Minimal-Access Surgery, Dubai London Clinic and Specialty Hospital, United Arab Emirates and are available from corresponding author upon request.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors' Contributions

Torres-de la Roche LA and Cezar C are co-first authors and have equal authorship.

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Research Article

Retrospective Analysis of Cervical Cancer Treatment Outcomes: Ten Years of Experience with the Vaginal Assisted Radical Laparoscopic Hysterectomy VARLH

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Background. LACC trial demonstrated inferiority of laparoscopic approach for the treatment of early-stage cervical cancer. There are still limited data from retrospective trials regarding whether survival outcomes after laparoscopic radical hysterectomy are equivalent to those after open abdominal radical hysterectomy. In this study, we present results of combined vaginal radical laparoscopic hysterectomy in the treatment of early-stage cervical cancer. *Methods*. This retrospective study was carried out at the Department of Gynecology in Mathilden Hospital (Herford, Germany). Between January 2008 and April 2018, all the patients with invasive cervical cancer who underwent combined vaginal assisted radical laparoscopic hysterectomy (VARLH) without the use of any uterine manipulator were enrolled to the study. *Results*. A total number of 124 patients with diagnosis of invasive cervical cancer were enrolled in the study. All of the patients underwent minimally invasive surgery and were divided according to FIGO 2019: stage IA (25.9%), IB1 (25.0%), IB2-IIB (28.4%), and III/IV (20.7%). Overall, the mean age of the patients was 51.84 years. After a study collection, a median follow-up was 45.6 (range 23.7-76.5) months. The 3- and 5-year disease-free survival rates for early-stage cervical cancer were both 98%, and the 3- and 5-year overall survival rates were 100% and 97%, respectively. We have not observed any recurrence in our study group of patients with early-stage cervical cancer. *Conclusions*. Combined VARLH can be considered a safe and effective procedure for the treatment of early-stage cervical cancer. Surgical strategy with oncological principles determines the quality and long-term success of the operation in early cervical cancer regardless of laparoscopic approach.

1. Introduction

In a tragic way, the Laparoscopic Approach to Cervical Cancer (LACC) trial changed the development of laparoscopic surgery for early-stage cervical cancer [1]. Unfortunately, in 2018, it has also altered clinical practice significantly [2–4].

Total radical laparoscopic hysterectomy (TRLH) for early-stage cervical cancer was carried out with increasing frequency for almost three decades [5, 6]. Comparing to open surgery, laparoscopic approach was shown to have shorter operative times and hospital stays and fewer postoperative complications rates [5–7]. Therefore, several studies were conducted to explore this topic and bring back laparoscopic surgery to its rightful place [8–10].

Almost-forgotten vaginal hysterectomy has been replaced by robotic or laparoscopic techniques [10, 11]. Technical feasibility and growing experience with laparoscopic lymphadenectomy have facilitated a revival of radical vaginal hysterectomy. Thus, the Schauta-modified vaginal assisted hysterectomy has become more useful in the light of current research [12]. The procedure was associated with a decreased postoperative mortality when compared with the abdominal route that was invented by

Wertheim [13–15]. However, the lack of experience in performing this technique and evidence of its oncological efficacy needs further analysis to be considered a first-choice procedure.

The change of clinical practice in early-stage cervical cancer drove us to report on our experience and assess the efficacy of combined vaginal assisted radical laparoscopic hysterectomy (VARLH) for early-stage cervical cancer.

2. Material and Methods

REACCT is a retrospective observational study analysing the outcomes of combined vaginal assisted radical laparoscopic hysterectomy (VARLH) in the treatment for early-stage cervical cancer. The diagnosis was made at Department of Gynecology in Mathilden Hospital Herford-Cancer Centre of Excellence (certified Centre of Cervical Dysplasia).

Our study involved all 124 of the patients with the diagnosis of cervical cancer (with initial stage I-IV according to the International Federation of Gynaecology and Obstetrics (FIGO 2019)) who underwent VARLH between January 2008 and April 2018.

After this period, we switched to open surgery for cervical cancer as a favourable technique (according to LACC Trial). We offered all patients comprehensive preoperative patient-centered counselling providing them with information as reported in the recent literature (LACC).

Patient follow-up was updated in the third and fourth quarter of 2020 using phone calls and during clinical visits.

The study was approved by the Ethics Committee on Clinical Studies of Medical University of Münster (UKM).

2.1. Eligibility Criteria for Surgery. Patients with early stage of cancer, stage IA1-IB1, were qualified for surgery (VALRH). Patients with stage IIA-IV (FIGO) were treated with additional personalized treatment (primary or palliative chemoradiotherapy after laparoscopic staging). All of the patients were treated by combined VARLH (lymphadenectomy with ICG sentinel mapping) with respect to disease-free survival (DFS) and overall survival (OS).

2.2. Surgical Technique. VARLH was performed by a senior skilled surgeon (RW). The preoperative routine placement of ureteral double-J catheters as a prophylactic of ureteral injury was performed to all the patients.

Women had their pigtail catheter removed directly in the operating room at the end of the procedure, or when the gynecologist judged that for any reason prolonged catheterization was necessary.

The SLN biopsy technique was as follows: In the beginning, the vaginal part of the surgical procedure the patient was placed in a lithotomy position and ICG (indocyanine green) was injected into the cervix with the 2-quadrant option at 3 and 9 o'clock, after closing the vaginal cuff.

All surgical procedures preserved surgical and oncological safety with "tumor no-touch technique" (gentle surgery, without using vaginal manipulator and without injury to the uterine surface). The vaginal wall was grasped exclusively with blunt clamps. Circular, bloodless incision was made with the use of electrocautery (Figure 1).

Prophylactic antibiotics were routinely administered intravenously immediately prior surgery with a single shot dose of cefuroxime 1.5 g i.v., if there were no contraindications.

All patients received a risk-adjusted amount of low molecular weight heparin, e.g., enoxaparin 0.4 ml s.c.

Selected surgical steps of VARLH were as follows:

(1) Step 1 (Figure 1): circular cut of the vaginal cuff above the cervix (without the use of manipulator)

(2) Step 2 (Figure 2): covering the cervical tumor with vaginal cuff and application of continuously overturned nonabsorbable braided polyester suture Ethibond 1-0 (after mobilizing the vagina in Step 1)

(3) Step 3 (Figure 3): the avoidance of uncontrolled gas evacuation with the use of 22 Ch urine catheter (filled with 50-80 ml NaCl).

2.3. Statistical Analysis. Statistical analysis was performed with SPSS version 25.0 for Windows (IBM). Categorical variables are presented as frequency and percentage, while continuous variables are presented as mean and standard deviation (SD) or median (interquartile range), as appropriate. The Kaplan-Meier survival analysis was carried out to estimate mean and overall survival (OS) and disease-free survival (DFS), with the 95% confidence interval (CI), as well as to analyse factors associated with survival (logrank tests). Results are presented as mean (95% CI) survival with the logrank test. An analysis of variance (ANOVA) was used to analyse normally distributed numerical variables, while the chi-square tests were used to analyse categorical variables. The level of statistical significance was set to 0.05 to reject null hypothesis.

3. Results

All the patients were diagnosed with a histologically confirmed cervical cancer in the Cancer Centre of Excellence at Mathilden Hospital Herford. 124 patients fulfilled the inclusion criteria of invasive cervical cancer. The mean (SD) age was 51.84 years (SD: 15.41, median: 47.5). We lost 8 patients in the follow-up; thus, retrospective analysis included 116 patients. There was no conversion to laparotomy necessary in any patient. We did not observe any complications during the surgery, increased intraoperative blood loss, big vessels, or genitourinary tract injury. Lymphocele occurred in 2 patients in long-term postoperative period.

Tumor characteristics describes Table 1 (according to FIGO 2019 for cervical cancer) stage IA (25.9%), IB1 (25.0%), IB2-IIB (28.4%), and III/IV (20.7%). The majority of the participants were grade G2 (47.4%) or G3 (38.8%) (Table 2). Median (IQR) follow-up time was 45.6 (23.7-76.5) months.

Table 3 depicts the distribution of patients in IB1 and IB2 groups.

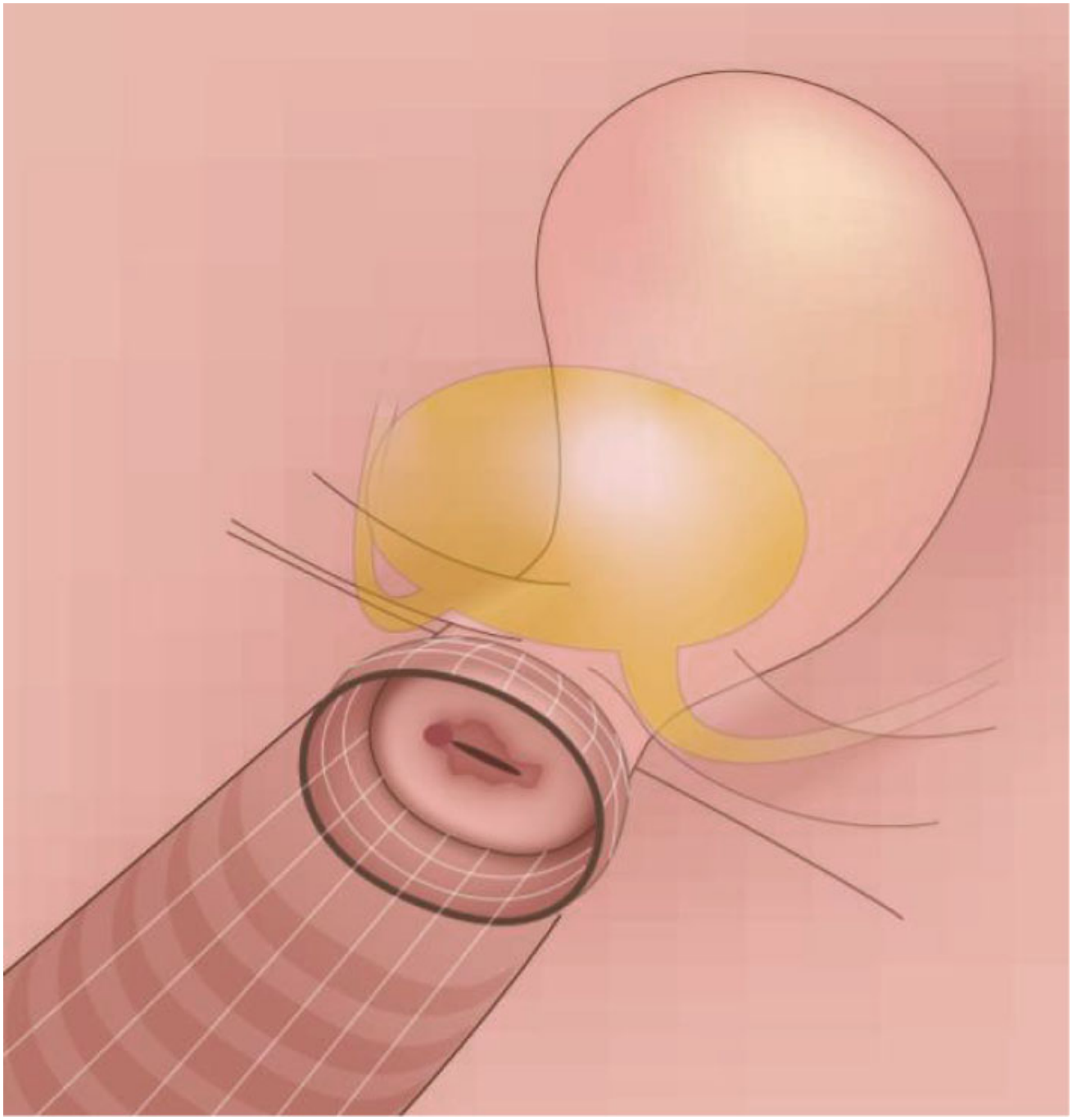

Figure 1: Schematic drawing of the vagina and uterus with prepared vaginal cuff. Anatomical landmarks (parametria, ureters, and urinary bladder) are depicted in this figure.

In one case, postoperative radiochemotherapy was necessary in the group of IB1 patients. In the IB2 FIGO group, 5 from 6 cases were indicated to postoperative radiochemotherapy.

The *DFS* for *patients* with stage IA-IB1 (45) disease was 98% after 5 years. The DFS for 25 in this group after 5 years was 98%. 18 of these patient's follow-up data of at least 5 years' duration are available. They were not included in the analysis, because we obtained data after primary registration was finished. According to our knowledge, all of the patients are in good physical condition are disease-free.

Figures 4 and 5 show the Kaplan-Meier curves by grading for overall survival (OS) and disease-free survival (DFS) by stages 1A-1B1 and 1B2-IV. Patients of stages 1A-1B1 were significantly younger than patients of 1B2-IV (45.47 vs. 58.44 years, $F = 24.774$, $p < 0.000$).

The mean (95% CI) overall survival was 150.62 months (95% CI: 144.63-156.62) for stages 1A-1B1. The mean

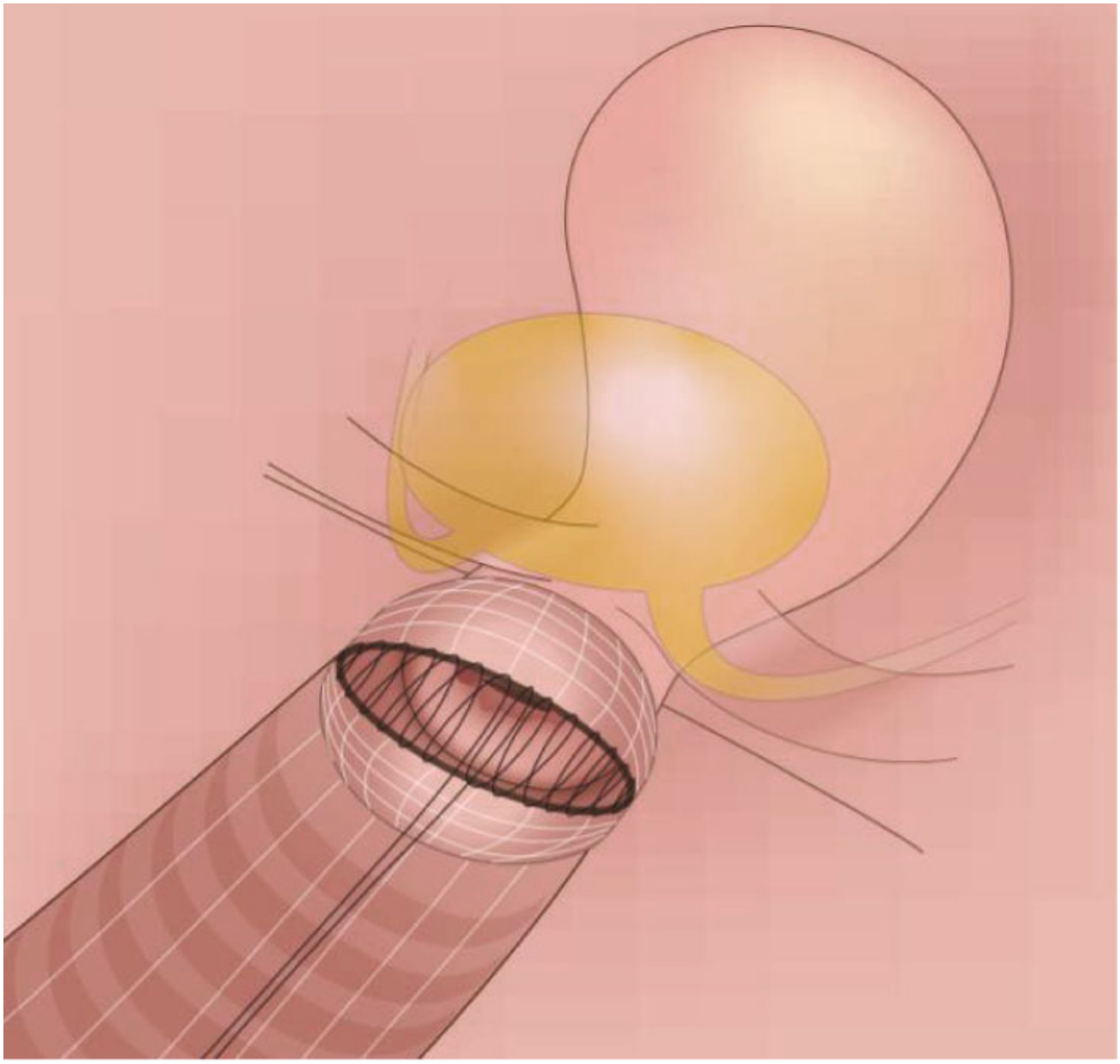

Figure 2: Schematic drawing of the sutures applied on the vaginal cuff. Closure direction, from the outside to the middle.

overall survival was 104.63 months (95% CI: 83.87-125.40) for stages 1B2-IV. The mean OS decreased significantly with TNM stage (logrank test, $chi^2 = 18.285$, $p = <0.001$).

The mean DFS was 151.23 (95% CI: 146.36-156.09) months for stages 1A-1B1. Thee mean DFS was 105.56 months (95% CI: 83.74-127.39) for stages 1B2-IV. The mean DFS decreased significantly with TNM stage in case of recurrence (logrank test, $chi^2 = 16.463$, $p < 0.001$).

OS and DFS rates are compared (Tables 4 and 5) with the respective results of the LACC TRIAL (reference), open surgery (reference), and Koehler (reference).

The age and stage distribution of the patients in our population corresponds to normal distribution of morbidity [16].

4. Discussion

In 2018, at the Society of Gynecologic Oncology Annual Meeting on Women's Cancer, Ramirez et al. presented the results of the LACC Trial and thus casted a shadow on the importance of laparoscopic surgery in the treatment of early-stage cervical cancer [1].

Minimally invasive surgery many times proved its advantages and has overtaken open surgery as the choice of procedure with regard to the complication rate and period of convalescence time [5–7], especially for the treatment of cervical cancer, where it seemed to maintain the untouched position [5–8]. Established as a safety and effective procedure with relatively high overall survival rate, laparoscopic

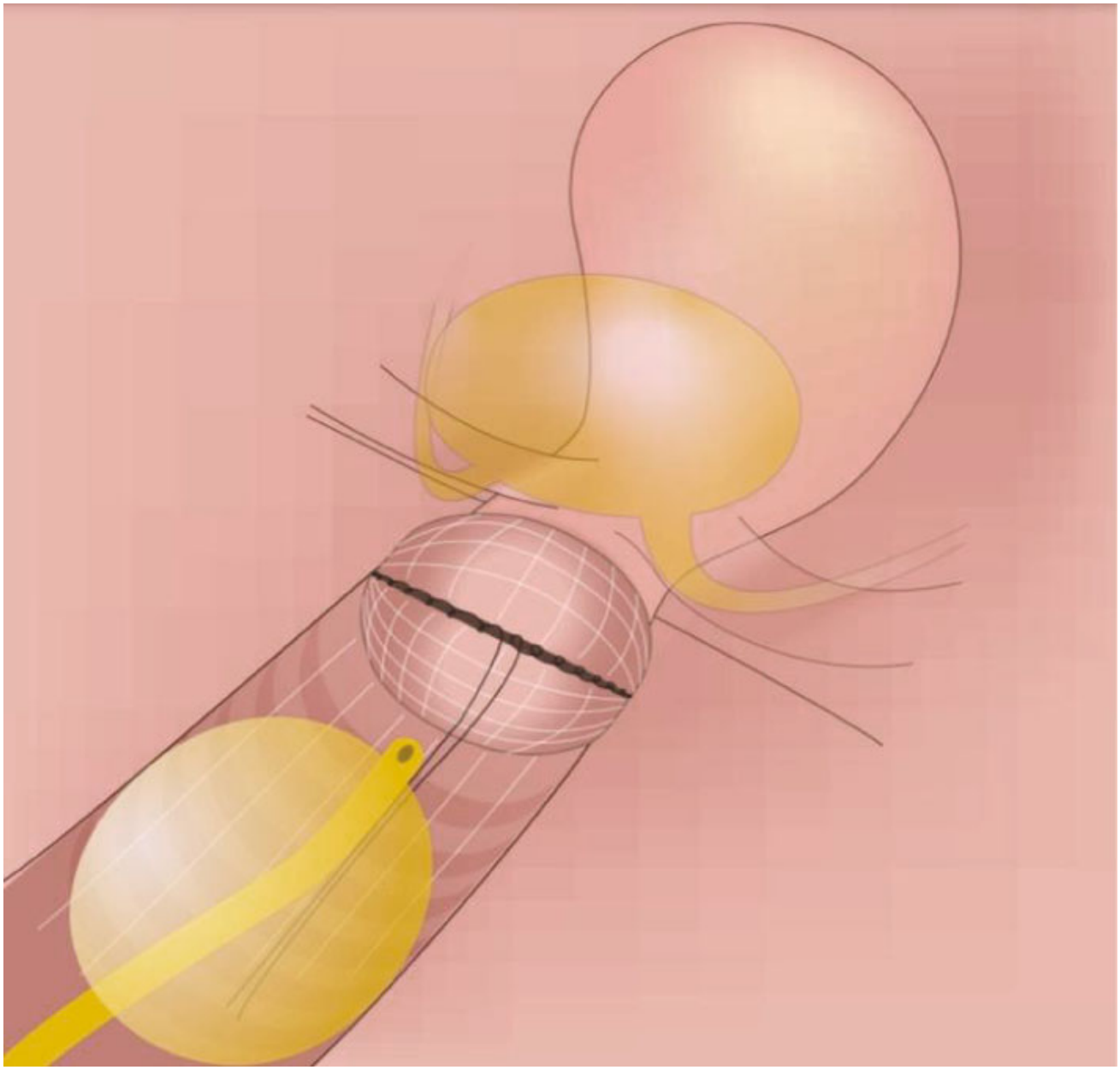

Figure 3: The vaginal cuff completely covers the cervix. Sutures are left in the vagina in order to remove the uterus afterwards with the pull-out technique. The vaginal canal is blocked with a urine catheter.

surgery has gained many advocates [8–10]. When faced with studies that contradict accepted practice, members of medical community assumed a defensive stance. After these unexpected results, they started an extensive analysis [2–4, 8]. Therefore, the question arises: what determines success in the treatment of early-stage cervical cancer? Is it really the matter of surgical access, or maybe should we take a closer look how the surgery per se impact the efficacy of treatment?

Some particular technical aspects of the MIS approach impact oncological safety and possible actions can be taken to improve the quality of surgical care. There is still an ongoing discussion regarding the use of uterus manipulator in gynecological oncology and its influence on the spread of tumor cells [9, 17]. In some studies, in patients diagnosed with endometrial cancer, uterine manipulator was associated with a worse oncological outcome [18, 19]. Also, other investigators avoid the use of a uterine manipulator during minimal invasive radical hysterectomy in the case of intraoperative tumor injuries [20, 21]. However, Nica et al. reported that the use of an intrauterine manipulator in patients with early cervical cancer was not an independent factor associated with rate of recurrence [22].

Interestingly, in a nationwide German survey, more than 50% responders answered that possible reasons and explanations for the inferior outcome of the MIS group in the LACC

Table 1: Distribution of FIGO-stages (percent (%)).

Stage (FIGO 2019)		Frequency	Percent	Valid percent
Valid	IA	30	25.9	25.9
	IB1	29	25.0	25.0
	IB2-IIB	33	28.4	28.4
	III/IV	24	20.7	20.7
	Total	116	100.0	100.0

Table 2: Distribution of histological grade (percent (%)).

Grading		Frequency	Percent	Valid percent
Valid	G1	16	13.8	13.8
	G2	55	47.4	47.4
	G3	45	38.8	38.8
	Total	116	100.0	100.0

Table 3: Distribution of therapy in stage 1B1 and 1B2 (unimodal: patients who underwent surgical therapy only, multimodal: patients who underwent (additionally) radiochemotherapy).

Stage FIGO 2019 Valid	Frequency of cases	Percentage from all patients	Ratio of therapy: single cases of unimodal/multimodal therapy
IB1	29	25.0	28/1
IB2	6	5.2	1/5

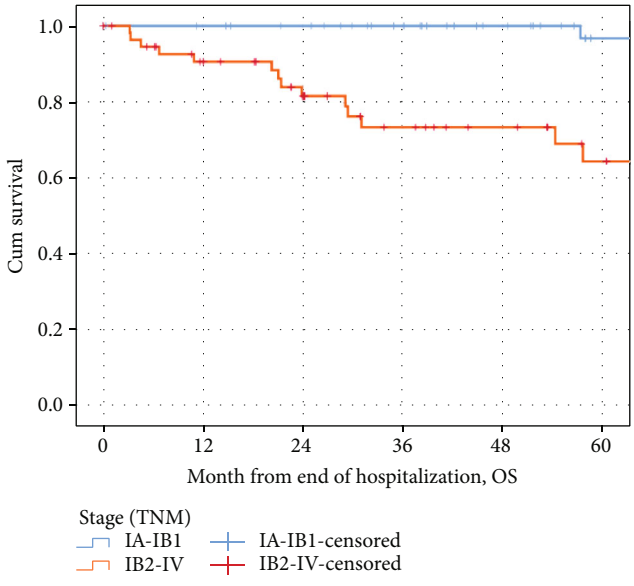

Figure 4: The Kaplan-Meier curves by grading for overall survival (OS) by stages 1A-1B1 and 1B2-IV.

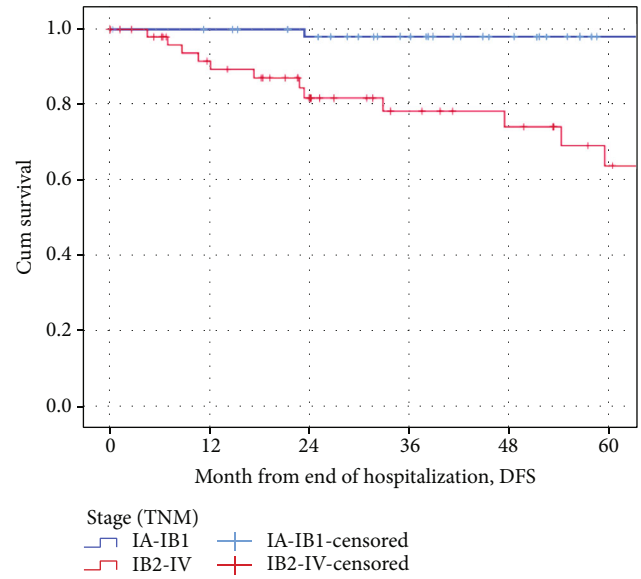

Figure 5: The Kaplan-Meier curves by grading for disease-free survival (DFS) by stages 1A-1B1 and 1B2-IV.

trial was the use of manipulator and wrong surgical technique [23]. Unfortunately, the results of NOGGO survey pointed laparotomy as a preferred surgical technique in the treatment of cervical cancer, and vaginal hysterectomy took the last place [23]. No better results were achieved by Wenzel et al.'s research group [24]. Only 33% of laparoscopic hysterectomies were performed before LACC trial came out [23]. How then surgical treatment really looked like before the pre-LACC era?

Similar controversies rose when FDA warned about the cancer-spreading risks of power morcellator devices used in gynecological surgery, which also resulted in a decrease of minimally invasive surgery [25]. All extirpating procedures used for hysterectomy, whether performed with laparotomy or laparoscopy, involve the risk of disseminating malignant cells in the abdominal cavity. However, gentle surgery, without unnecessary manipulations and without injury to the uterine surface, could significantly reduce this risk [26].

The modified Schauta procedure has been shown a high cure for stages IB to IIA cervical cancer in previous studies [27, 28]. This procedure consists of a radical hysterectomy performed vaginally without the need for a lateral perineotomy [29]. Our modification does not involve the "click maneuver" (a method that allows a vaginal exposure of the ureter). When vaginal part of the procedure was finished, visualization and preparation of both ureters were done from laparoscopic approach. Routine preoperative bilateral ureteral catheterization was helpful for intraoperative ureter identification.

Combined laparoscopic-vaginal approach offers surgical safety and allows to avoid contamination with cancer cells by covering the cervical tumor with vaginal cuff. Furthermore, with an application of continuous suture, we avoid potential dissemination of tumor cells by gas evacuation.

Table 4: Comparison of OS in different studies.

OS	Follow-up	3-year OS No. at risk %	5-year OS No. at risk %
LSC/robot arm in LACC trial	2.5 years	93.8%, 150 (47%)	n/a, 5 (2%)
Laparotomy arm in LACC trial	2.5 years	99%, 136 (44%)	n/a, 7 (2%)
Multicenter results Chr. Köhler et al.	>8 years (99 months)	98.5%, 306 (78%)	97.6%, 265 (68%)
MH Herford 2010-2020 R. Wojdat et al.	3.8 years (45.6 months)	IA-IB1: 100%, 45 (75%) IIB-III/IV: 74%, 22 (39%)	IA-IB1: 97%, 25 (44%) IIB-III/IV: 55%, 11 (20%)

LACC: Laparoscopic Approach to Cervical Cancer; OS; overall survival.

Table 5: Comparison of DFS in different studies.

DFS	Follow-up	3-year OS No. at risk %	5-year OS No. at risk %
LSC/robot arm in LACC trial	2.5 years	87.1%, 142 (47%)	n/a, 5 (2%)
Laparotomy arm in LACC trial	2.5 years	97.1%, 134 (43%)	n/a, 7 (2%)
Multicenter results Chr. Köhler et al.	>8 years (99 months)	96.8%, 306 (78%)	95.7%, 264 (68%)
MH Herford 2010-2020 R. Wojdat et al.	3.8 years (45.6 months)	IA-IB1: 98%, 45 (75%) IIB-III/IV: 79%, 22 (39%)	IA-IB1: 98%, 25 (44%) IIB-III/IV: 53%, 11 (20%)

DFS: disease-free survival; LACC: Laparoscopic Approach to Cervical Cancer.

Other techniques, like vaginal closure with the surgical stapler, were described in the literature to prevent tumor spillage [30, 31].

Our experience in laparoscopic surgery has grown over the years, and we observe a rapid advancement of medical technology. This led us to apply indocyanine green (ICG) to identify sentinel lymph nodes in oncological gynecology. SLN mapping is routinely performed in our department since 2010. Before ICG, we used the combination of blue dye and radioisotope techniques with Technetium-99. However, we did not change the surgical method, which is constant since many years. Sentinel lymph node mapping with ICG in cervical cancer followed by systemic pelvic lymphadenectomy was helpful with intraoperative decision-making process. The information about lymph node status given by the ultrastaging allowed us to carefully select a group of patients appropriate for multimodal treatment and decrease the risk of complications of unnecessary surgery [32–34].

The results of LACC trial showed lower disease-free survival (DFS) and overall survival (OS) in the minimally invasive surgery (MIS) arm [1]. The 4.5-year DFS rate was 86% for the MIS arm compared with 96.5% for the OPEN arm [1]. In our study the 3- and 5-year disease-free survival rates for early-stage cervical cancer were both 98% and the 3- and 5-year overall survival rates were 100% and 97%, respectively.

In a multicenter analysis, Köhler et al. achieved over 95.7% disease-free and 97.6% overall survival in long-term follow-up, similar to the laparotomy arm of the LACC trial and our results [35]. Data in Tables 4 and 5 depicts that the disease-free survival rate (DFS) and the overall survival (OS) rate between the studies did not differ significantly. It was 99% (3-year OS) for laparotomy arm in LACC trial, 98.5% for multicenter trial, and 100% OS for Mathilden Hospital [1, 35]. In our study, the 3 years of 100% OS was observed for IA-IB1 stage of cancer. In LSC arm of the LACC trial, this number was 93%. We also reported no recurrence at final follow-up. According to these results, we are of the opinion that combined VARLH provides a safe procedure with good clinical outcomes.

Figure 6 shows the distribution of the age-dependent patients to the corresponding stages of the disease. Earlier stages can be found more frequently in younger patients, while more advanced stages are more likely to be found in older patients.

Perhaps, when evaluating our results according to old FIGO staging system, we would define incorrectly more patients in early-stage cervical cancer group. At the time, our results would be worse, which only proves that the inferior border of 2 cm according to FIGO 2019 is justifiable.

From our perspective, the implementation of the new FIGO 2019 classification enables us to make a better decision about a stage adapted therapy. In other words, it helps us better to avoid unnecessary multimodal therapy [36, 37]. Our findings are in good agreement with previous results [35]. Although the number of groups differs, the results show a clear tendency.

We expect that the new classification will be a helpful tool for better risk stratification of cervical cancer patients and that it will facilitate more personalized treatment recommendations.

Presented study is an evaluation of a single institution's experience of laparoscopic radical hysterectomy. The limits of our study are the number of patients with early-stage cervical cancer. Nevertheless, we want to point out that 124 patients with the diagnosis of invasive cervical cancer were diagnosed and treated in one center. This is quite a large sample size as compared to other studies where two or even three centers involved about 200 or less patients [23, 38]. Collecting more data regarding the efficacy of laparoscopic

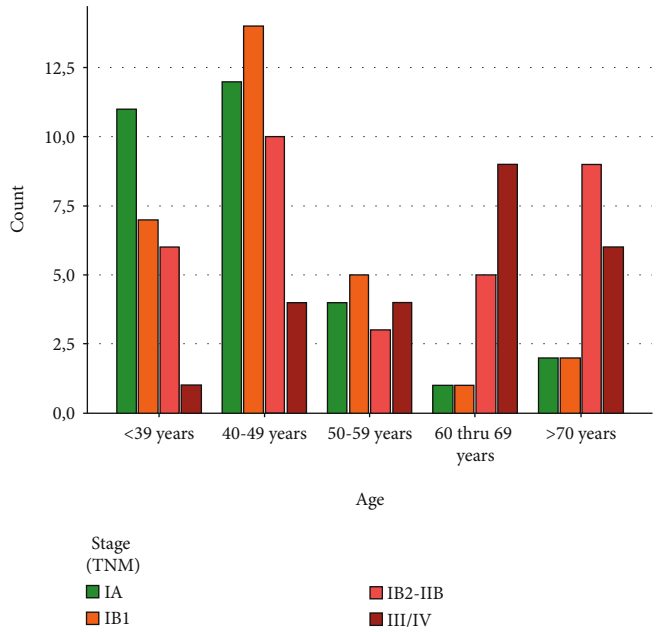

Figure 6: Age-dependent distribution of patients according to the stages of the disease.

treatment for early-stage cervical cancer will no longer be possible due to changed clinical practice. For this reason, we need prospective randomised trials including preservation of oncological safety to analyse the topic more precisely and compare the results.

Treatment method should be selected individually, but oncological carefulness has to address the vast majority [39, 40]. Promising results of our study prove that laparoscopic surgery should not be excluded in the treatment for early-stage cervical cancer. We have to look closer for the best therapy we can offer to our patients. However, by questioning the minimally invasive surgery in the treatment of early-stage cervical cancer, we may take them the possibility, which in the end may turn out to be the best.

5. Conclusion

Presented combined VARLH technique should be considered a safe oncological intervention in the treatment of early-stage cervical cancer.

Surgical strategy with oncological care is a key to success in the treatment for cervical cancer.

Data Availability

All data generated or analysed during this study are included in this published article.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

R.W. carried out the surgical procedures and patient's investigation. M. Bromba performed the statistical calculations. R.W. supervised the project. E.M. prepared the manuscript. Both R.W. and E.M. contributed to the conception of the work, drafted the paper, approved the version to be published, and are accountable for all aspects of the work. The authors read and approved the final manuscript. R. Wojdat and E. Malanowska contributed equally to this work.

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Research Article

B7-H4 Expression in Precancerous Lesions of the Uterine Cervix

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Over 10% of patients diagnosed with cervical intraepithelial neoplasia (CIN) have no lesions detected in their cervical conization specimens. The purpose of this study was to determine the factors related to the absence of such lesions. We particularly sought to investigate whether the expression of B7-H4 in precancerous lesions and cancer of the uterine cervix plays a role in the presence or absence of residual lesions in conization specimens and whether this protein is associated with T cells (i.e., $Foxp3^+$ regulatory T cells, $CD4^+$, and $CD8^+$) and interferon-γ production. Of the 807 patients with CIN treated by conization, 104 (12.9%) had no lesions in their conization specimens. Seventy-five of these patients were deemed the study group and were matched with 75 patients who did have CIN detected in their conization specimens (the control group). Immunohistochemistry and immunofluorescence staining were used to detect B7-H4, Foxp3, CD4, CD8, and interferon-γ in the 75 pairs of specimens obtained via biopsy; 20 samples were found to have chronic cervicitis, and another 20 had squamous cell carcinoma of the cervix. Menopause, the absence of human papillomavirus, low-grade histological findings, and a diagnosis of CIN1 and CIN2 on biopsy correlated with a low probability of lesions on conization specimens. B7-H4 expression was detected in 11.1% of CIN2, 46.6% of CIN3, and 70% of cervical cancer samples, but not in tissues representing chronic cervicitis or CIN1. B7-H4 expression was associated with the presence of lesions on conization specimens, increased regulatory T cells, decreased $CD8^+$ T cells, and lower interferon-γ production. These data suggest that close follow-up and thorough reevaluation should be considered for patients diagnosed with CIN2 who are negative for B7-H4 expression on biopsy before proceeding with cervical conization.

1. Introduction

Cervical cancer develops through a multistep process that includes the development of low-grade squamous intraepithelial lesion (LSIL)/cervical intraepithelial neoplasia (CIN1) followed by high-grade squamous intraepithelial lesion (HSIL)/CIN2–3. High-risk human papillomavirus (HPV) infection contributes significantly to the pathogenesis of precancerous lesions and cancer of the cervix. Cervical excision is the standard treatment method for patients with CIN2–3 as well as for patients with CIN1 who have inadequate colposcopy and/or recurrent high-grade cytologic findings. Cold knife conization (CKC) and the loop electrosurgical excision procedure (LEEP) are commonly used cervical conization methods, which are safe and effective in clinical practice and can reduce the risk of cervical cancer by 95% [1, 2]. However, several observational studies have highlighted the potential adverse effects of conization on fertility and pregnancy outcomes (such as preterm delivery, premature membrane rupture, low birth weight, caesarean section, and perinatal death) when the lesions are located in the columnar epithelium, or the excised cone has to be deep, up to the internal os of the cervix [3, 4]. Notably, however, 13.8–16.5% patients with histologically confirmed

CIN2–3 on a previous biopsy have no residual CIN in their final excision specimens. Therefore, it is necessary to identify factors that can predict the absence of CIN in conization specimens to avoid unnecessary treatment and unexpected complications [5].

HPV infection is self-limiting and can be eradicated by the immune response in the normal cervical microenvironment. The reduction in immune surveillance and clearance rates is an important contributor to cervical pathogenesis and development [6, 7]. To that end, B7 family members and their receptors are crucial for the regulation of antigen-specific immune responses [8]. B7 homolog 4 (B7-H4, B7x, or B7S1) is an immunoregulatory member of the B7 family that was identified recently [9–11]; this protein has been found in several tumor types, including ovarian, breast, kidney, liver, lung, spleen, thymus, and placental cancers [12]. Previous studies showed that the expression of B7-H4 in cervical cancer is associated with immunosuppression in the tumor microenvironment as well as tumor progression and poor prognosis [13, 14]. Furthermore, B7-H4 has been implicated in the inhibition of T cell-mediated immunity and downregulation of T cell response via the inhibition of T cell proliferation, cytokine production, and cell cycle progression [11, 15, 16]; these events suppress the antitumor immune function. Moreover, our previous study found that the level of serum B7-H4 was higher in patients with CIN than in healthy volunteers [14]. However, B7-H4 expression in CIN and its potential association with the presence or absence of excised conization specimens remain unknown, as does its relationship with tumor-infiltrating T lymphocytes.

The purpose of this study was to identify predictors of CIN lesion absence in cervical conization samples from patients diagnosed with CIN via biopsy, to investigate the expression of B7-H4 in CIN and cervical cancer, and to determine the association between this protein and the pathological features and T cells of the immune microenvironment.

2. Materials and Methods

2.1. Patients. A total of 807 patients who underwent either a CKC or LEEP procedure after cervical biopsy between July 2005 and December 2013 at Qilu Hospital of Shandong University (Ji'nan, China) were identified. Data were extracted from the colposcopy computer database and the hospital's patient database, which included the patients' age, menopausal status, cone lesion depth, punch biopsy histological grade, histological grade and margin status of the excised sample, and glandular involvement. This study was approved by the Institutional Review Board (KYLL-2017-560); informed consent was not required owing to its retrospective nature.

2.2. Tissue Samples. To evaluate whether B7-H4 expression was associated with the absence of lesions in conization specimens, we compared B7-H4 expression in lesion-absent and lesion-present groups. Seventy-five biopsy specimens from the group with absent lesions in their excised cervical samples were available for immunohistochemistry (IHC). Hence, 75 propensity score-matched patients were selected from the 703 who had lesions in their conization specimens. There were no significant differences between the matched groups in terms of age, menopause, thin-prep cytology test (TCT), punch biopsy, HPV status, margin involvement, glandular involvement, colposcopy, and excision methods. Hematoxylin-eosin-stained slides and paraffin-embedded tissues from the 75 pairs of biopsy specimens were obtained from the Department of Pathology, Qilu Hospital of Shandong University. The initial histopathological diagnoses were rereviewed by two gynecological pathologists. Additionally, 20 biopsy samples, each representing chronic cervicitis and squamous cell carcinoma (SCC) of the cervix, were used for IHC and immunofluorescence staining.

2.3. IHC. IHC was performed using our laboratory protocol as described previously [17–19]. Briefly, 4 μm TMA serial sections were deparaffinized and subjected to heat-induced epitope retrieval with 10 mM sodium citrate (pH 6.0) at 95°C for 20 min. The endogenous peroxidase activity was quenched using a 0.3% hydrogen peroxide solution. Sections were incubated with primary antibody against B7-H4 (dilution 1 : 200, clone D1M8I, Cell Signaling Technology, Danvers, USA). Human placental tissues treated with primary antibodies were used as positive controls, while the same tissues with isotype-matched antibodies comprised negative controls.

2.4. Immunofluorescence. Immunofluorescence-based staining was performed to detect $CD4^+$ T cells as well as $CD8^+$ T cells, $CD4^+Foxp3^+$ regulatory T cells (Tregs), and interferon- (IFN-) γ^+CD8^+ T cells in cervical tissues. The slides were prepared using the same procedure as that for IHC. After blocking with 5% goat serum, slides were incubated with the following primary antibodies overnight at 4°C: rabbit anti-human Foxp3 (dilution 1 : 300, NB100-39002SS, Novus Biologicals, Littleton, CO, USA), mouse anti-human CD4 (dilution 1 : 200, NBP2-27216, Novus Biologicals), mouse anti-human CD8 alpha (dilution 1 : 200, NBP2-32836, Novus Biologicals), and rabbit anti-human IFN-γ (dilution 1 : 100, 8455P, Cell Signaling Technology). The secondary antibodies were goat anti-mouse IgG-phycoerythrin (dilution 1 : 1000, ab97024; ab150079) and goat anti-rabbit IgG-allophycocyanin conjugate (Abcam, Cambridge, MA, USA). After antibody removal and washing, the appropriate secondary antibody was applied, and the slides were incubated for 2 h at room temperature in the dark. Coverslips were applied to the slides using Prolong® Gold antifade reagent.

2.5. Image Analysis. IHC analysis was performed by two independent investigators. Brown or yellow B7-H4 staining of the membrane or cytoplasm was considered positive. Images of the various stained tissue sections were digitally photographed using a color camera (BX53; Olympus, Japan) attached to a light microscope. For B7-H4-positive samples, ×100 magnified images were captured, and the numbers of positive cells and their staining intensities were then analyzed using the Image-Pro Plus software, version 6.0 (Media Cybernetics, Silver Spring, MD, USA). For

immunofluorescence staining analyses, six photographs were obtained using high-power fields (×200 magnification) per section via confocal microscopy (E2V Andor Revolution, England). The numbers of each type of T lymphocytes were autocounted using the statistical software package.

2.6. Statistical Analysis. Statistical analysis was performed using the SPSS version 22.0 for Windows (IBM Corp., Armonk, NY, USA). Discrete variables are expressed as the medians (ranges) and categorical variables as numbers (percentages). Analysis of categorical data was performed using the chi-square test or Fisher's exact test. Multivariate logistic regression models were used to identify variables that were independent prognostic factors; the hazard ratios were calculated as indicators of risk. Quantitative data are expressed as mean percentages ± standard deviations, and their significance was determined using Student's t-test or Wilcoxon rank sum test. All P values were two-tailed, and $P \leq 0.05$ was considered statistically significant.

3. Results

3.1. Patient Characteristics. A total of 807 patients underwent cervical conization after first having undergone punch biopsies; their ages ranged from 21 to 62 years with a mean of 38.8 ± 8.0 years. The patients' detailed characteristics are shown in Table 1.

3.2. Factors Associated with the Absence of Lesions on Excised Conization Tissues. Factors associated with the absence of lesions on excised specimens are shown in Table 1. Of the 807 conization samples, 104 (12.9%) lacked lesions. Menopause, absence of HPV DNA, inadequate colposcopy sample collection, absence of glandular involvement in biopsy samples, and a conization depth ≤ 18 mm were significantly associated with the absence of lesions in excised specimens. Patients diagnosed with CIN1 and CIN2 on cervical punch biopsy, those with "negative for intraepithelial lesion or malignancy" status, those with atypical squamous cells/LSIL on TCT, and those who underwent LEEP were less likely to have lesions on their excision specimens. Neither the patients' age nor the number of biopsies during the initial colposcopy or interval between biopsy and excision was associated with the absence of lesions on excised conization tissues. Multivariate logistic regression analysis revealed that menopause and CIN2 on biopsy were independent predictors of a lack of lesions in excised conization specimens (Table 2).

3.3. Expression of B7-H4 in Precancerous Lesions and SCC of the Uterine Cervix. B7-H4 was detected in cervical cancer cells and in CIN2–3 epithelial cells (exhibiting a cytoplasmic/membranous staining pattern), but not in CIN1 or chronic cervicitis (Figure 1). B7-H4 expression was observed in 11.1% of the patients with CIN2, 46.7% of those with CIN3, and 70% of those with cervical cancers (Table 3). No differences in the intensity and positivity proportion of B7-H4 were observed between B7-H4-positive CIN2–3 samples and tumor samples.

B7-H4 was detected in 17.3% (13/75) of the biopsy samples from patients with absent lesions in excised conization samples and in 38.7% (29/75) of the biopsy samples from those with such lesions present; the difference was statistically significant ($P = 0.004$).

3.4. Correlation between B7-H4 Expression and Tumor-Infiltrating T Lymphocytes. The tumor-infiltrating T lymphocytes were mainly distributed in the surrounding matrix of cervical SCC nests and were occasionally detected in some tumoral and CIN nests.

The numbers of tumor-infiltrating $CD8^+$ T cells, INF-γ^+, and INF-γ^+CD8^+ T cells in B7-H4-negative samples were significantly higher than those in B7-H4-positive counterparts. However, the number of Tregs ($CD4^+Foxp3^+$) in B7-H4-positive samples was significantly higher than that in B7-H4-negative counterparts (Table 4). The numbers of $CD4^+$ T cells were not significantly different between the B7-H4-negative and B7-H4-positive groups. These data indicate that B7-H4 is associated with inhibitory signals in the tumor microenvironment. Representative images of double immunofluorescence staining for $CD4^+Foxp3^+$ and IFN-γ^+CD8^+ T cells are shown in Figure 2.

4. Discussion

In this study, 12.9% of our patients who were diagnosed with CIN via punch biopsy (104/807) ultimately lacked lesions on their excised conization specimens. This was consistent with a rate of 16% in a previous study [20]. We also found that menopause, absence of HPV DNA, a conization depth ≤ 18 mm, low-grade findings on TCT, and CIN1 and CIN2 on biopsy correlated with the absence of lesions in the excised tissues. One explanation for the absence of CIN in conization specimens following a biopsy that diagnoses CIN is the total removal of the dysplastic lesions during the biopsy [21]. Another is that lesions embedded deep in the endocervical canal are usually not visible and may therefore be missed during cervical conization. Moreover, cervical conization may not remove the affected area in patients with small and/or peripheral transformation zones. Another possibility is the destruction of the dysplastic region by post-biopsy inflammation, spontaneous regression of the lesion, or immune system-mediated elimination after the biopsy. A previous study found that approximately 20% of CIN2–3 lesions regressed spontaneously after a confirmatory biopsy [22]. In our present study, 20.5% of the patients with CIN2 and 8.3% of those with CIN3 did not exhibit any lesions in their cervical excision specimens. The high percentage of absent lesions after a confirmed CIN2 diagnosis by biopsy suggests that women diagnosed with CIN2 may only require close follow-up and reevaluation.

B7-H4 protein is not detected in most healthy tissues but is widely expressed in various cancers. In some types of malignancies, it is associated with adverse clinical features and unfavorable prognoses [23]. Chen et al. investigated B7-H4 protein in precancerous lesions of the esophagus and found it highly expressed in 9.1% of normal tissues, 40.7% of low-grade intraepithelial neoplasia, and 81.0% of

Table 1: Patient characteristics as well as factors associated with the absence of lesions in excised conization tissues in patients who had undergone uterine cervical biopsies ($N = 807$).

Characteristics	Group	N	Lesion in excision specimens, N (%)		P value
			Present	Absent	
Age (years)	≤35	277	245 (88.4)	32 (11.6)	0.413
	>35	530	458 (86.4)	72 (13.6)	
Menopause	Yes	65	45 (69.2)	20 (30.8)	<0.001
	No	742	658 (88.7)	84 (11.3)	
Referral cytology	NILM	43	36 (83.7)	7 (16.3)	0.038
	ASCUS/LSIL	377	323 (85.7)	54 (14.3)	
	ASC-H/HSIL	210	196 (93.3)	14 (6.6)	
	Cancer	7	6 (85.7)	1 (14.3)	
Referral HPV DNA ($N = 631$)	Positive	577	501 (86.8)	76 (13.2)	0.01
	Negative	54	40 (74.0)	14 (26.0)	
Punch biopsy	CIN1	43	34 (79.0)	9 (20.9)	<0.01
	CIN2	259	206 (79.5)	53 (20.5)	
	CIN3	504	462 (91.7)	42 (8.3)	
Number of biopsies	<4	134	119 (88.8)	15 (11.2)	0.760
	4	612	532 (86.9)	80 (13.1)	
	>4	61	52 (85.2)	9 (14.8)	
Colposcopy examination ($N = 411$)	Adequacy	327	292 (89.3)	35 (10.7)	0.039
	Inadequacy	84	68 (81.0)	16 (19.0)	
Glandular involvement ($N = 797$)	Free	418	348 (83.3)	70 (16.7)	<0.01
	Involved	379	347 (91.6)	32 (8.4)	
Depth of conization	≤18 mm	333	279 (83.8)	54 (16.2)	0.022
	>18 mm	468	418 (89.3)	50 (10.7)	
Interval between biopsy and excision (months)	<1	428	370 (86.4)	58 (13.6)	0.918
	1–2	153	134 (87.6)	19 (12.4)	
	2–3	29	24 (82.8)	5 (17.2)	
	>3	30	26 (86.7)	4 (13.3)	
Conization methods	CKC	563	502 (89.2)	61 (10.8)	0.008
	LEEP	243	200 (82.3)	43 (17.7)	

CKC: cold knife conization; LEEP: loop electrosurgical excision procedure; CIN: cervical intraepithelial neoplasia; HPV: human papilloma virus; TCT: thin-prep test; ASCUS: atypical squamous cells; LSIL: low-grade squamous intraepithelial lesion; ASC-H: atypical squamous cells (cannot exclude high-grade squamous intraepithelial lesions); HSIL: high-grade squamous intraepithelial lesion; NILM: negative for intraepithelial lesion or malignancy.

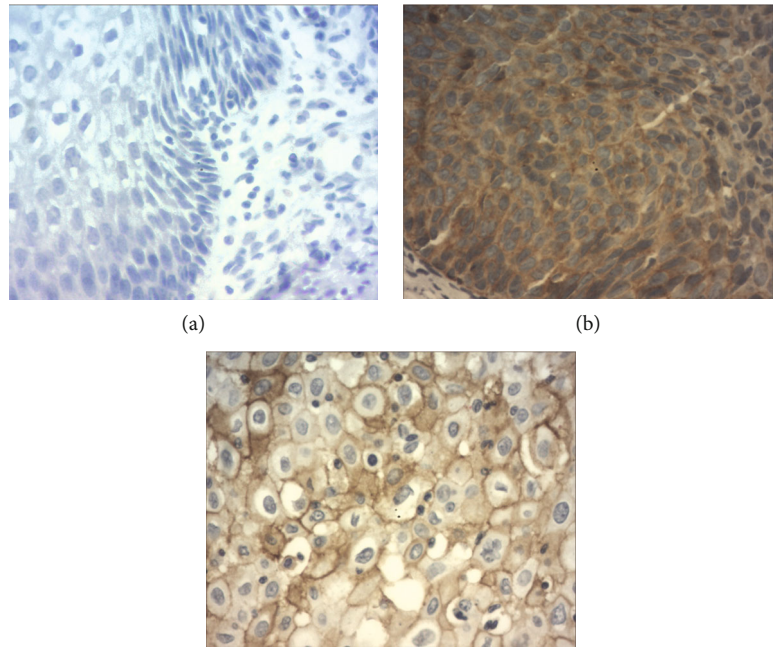
Table 2: Multivariate logistic regression analysis of factors predictive of the absence of lesions in excised conization specimens among patients who had undergone punch biopsies.

Parameters	Hazard ratios (95% confidence interval)	P value
Menopause		
Yes *vs.* no	0.244 (0.107–0.554)	0.001
Punch biopsy		
CIN1 *vs.* CIN3	1.724 (0.576–5.165)	0.330
CIN2 *vs.* CIN3	2.508 (1.329–4.732)	0.005

CIN: cervical intraepithelial neoplasia.

high-grade intraepithelial neoplasia. Similarly, B7-H4 was detected in HSIL and SCC in our study but not in LSIL or tissues from chronic cervicitis. These findings indicate that B7-H4 expression increases during the process of uterine cervix carcinogenesis. Furthermore, we found that negative B7-H4 expression correlates with the absence of CIN in cervical conization specimens postbiopsy. This suggests that patients with negative B7-H4 on biopsy are less likely to have lesions detected in conization specimens; therefore, unnecessary treatments such as cervical conization can be avoided and be replaced with close follow-up and thorough subsequent reevaluation.

B7-H4 expression and its association with $CD8^+$ T cells, $CD4^+Foxp3^+$ Tregs, and IFN-γ production have been



(a) (b) (c)

Figure 1: Expression of B7-H4 in cervical tissues. (a) Negative B7-H4 staining in chronic cervicitis, (b) positive B7-H4 staining in cervical intraepithelial neoplasia-3, and (c) positive B7-H4 staining in squamous cell carcinoma of the cervix. Magnification: ×200.

Table 3: B7-H4 expression in precancerous lesions and in cancers of the uterine cervix.

Cervical tissues	N	B7-H4, N (%)	
		Positive	Negative
Cervicitis	20	0 (0.0)	20 (100)
CIN1	12	0 (0.0)	12 (100)
CIN2	63	7 (11.1)	56 (89.9)
CIN3	75	35 (46.7)	40 (53.3)
SCC	20	14 (70.0)	6 (30.0)

CIN: cervical intraepithelial neoplasia; SCC: squamous cell carcinoma. P-value <0.001.

investigated in many tumors [8, 16, 24, 25]. B7-H4 expression was inversely correlated with $CD8^+$ T cell infiltration in breast tumor cells and was associated with reduced activation, expansion, and cytotoxicity of $CD8^+$ T cells [24, 25]. In a study of 67 patients with cervical cancer, Wang et al. found that the number of infiltrating $CD8^+$ T cells in B7-H4-negative tumors was significantly higher than that in B7-H4-positive counterparts, as was their IFN-γ production [8]. Consistent with previous studies, we found that $CD8^+$ T cells and INF-γ^+CD8^+ T cells were lower in B7-H4-positive precancerous cervical lesions. Moreover, the number of $CD4^+Foxp3^+$ Tregs was higher in our B7-H4-positive specimens than that in our B7-H4-negative ones, which reflects a previously reported positive association between Tregs and B7-H4 in ovarian cancers [16, 26]. It is worth noting that Tregs are able to trigger macrophages to secrete interleukin-6 (IL-6) and IL-10, which in turn stimulate expression of B7-H4 [26]. In our present study, IFN-γ secretion was decreased in B7-H4-positive samples; previous studies have shown that blocking B7-H4 enhanced the secretion of IFN-γ from $CD4^+$ and $CD8^+$ T cells [25, 27]. Podojil et al. demonstrated that the B7-H4 antibody inhibits T cell function via interleukin-10/Treg-dependent mechanisms [28]. Rahbar et al. demonstrated that IFN-γ upregulated B7-H4 expression on mouse embryo fibroblasts and that the upregulation of B7-H4 in tumors was T cell-dependent [29]. INF-γ participates in antitumor immunity by promoting the activation of macrophages and natural killer cells while enhancing the destructive potential of $CD8^+$ T cells. Taken together, these data show that B7-H4 positivity is associated with a decrease in $CD8^+$ T cell function and with a more immunosuppressive microenvironment in precancerous lesions and SCCs of the uterine cervix. As such, inhibiting B7-H4 using therapeutic antibodies or increasing IFN-γ may be potential treatment for HSIL of the cervix.

We acknowledge some limitations in our study. First, it was a retrospective investigation that produced inherent, unavoidable biases. Second, B7-H4 was detected in a relatively small size of samples. Lastly, our study was limited by its single-center nature and a lack of an independent validation cohort. Further studies from independent cohorts are needed to validate our findings.

In conclusion, we found that at least one-tenth of the patients did not have lesions in their cervical conization specimens after having undergone a diagnostic biopsy, especially those who were postmenopausal, exhibited an absence of HPV DNA, had low-grade findings on TCT, and/or were diagnosed with CIN1 and CIN2 on biopsy. Moreover, the immune checkpoint B7-H4 was detected in HSILs and SCCs but not in LSILs or cervicitis, and its

Table 4: Correlation between B7-H4 expression and the number of infiltrating T lymphocytes and cytokines in patients with cervical disease.

T lymphocytes/cytokine	$X \pm S$	B7-H4		P value
		Positive	Negative	
$CD4^+$ T cells	9.67 ± 6.22	10.00 ± 8.89	9.33 ± 4.16	0.912
Tregs	11.00 ± 7.04	17.33 ± 1.53	4.66 ± 1.15	<0.001
$CD8^+$ T cells	9.50 ± 9.07	2.67 ± 3.06	16.33 ± 7.51	0.043
INF-γ	7.83 ± 5.98	3.33 ± 4.93	12.33 ± 2.08	0.040
INF-γ^+CD8^+ T cells	6.00 ± 6.48	0.50 ± 0.70	11.50 ± 2.12	0.020

$X \pm S$: mean ± standard deviation; INF: interferon.

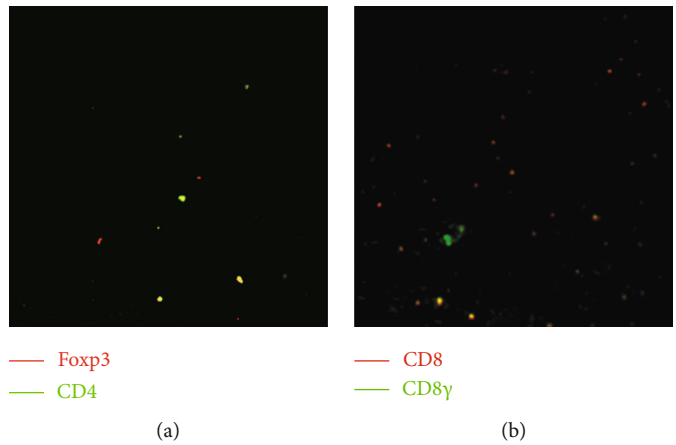


Figure 2: Double immunofluorescence-based staining of (a) $CD4^+Foxp3^+$ and (b) interferon (IFN)-γ^+CD8^+ T cells. Magnification: ×200.

expression was associated with the presence of lesions in conization specimens, increased Tregs, fewer $CD8^+$ T cells, and decreased IFN-γ production. These data suggest that close follow-up and thorough reevaluation can be considered for patients diagnosed with CIN2 who have negative B7-H4 expression on biopsy in lieu of cervical conization.

Data Availability

The relevant data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Review Article

Pregnancy-Related Hysterectomy for Peripartum Hemorrhage: A Literature Narrative Review of the Diagnosis, Management, and Techniques

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Postpartum hemorrhage is a life-threatening situation, in which hysterectomy can be performed to prevent maternal death. However, it is associated with high rates of maternal morbidity and mortality and permanent infertility. The incidence of pregnancy-related hysterectomy varies across countries, but its main indications are the following: uterine atony and placenta spectrum (PAS) disorders. PAS disorder prevalence is rising during the last years, mainly due to the increased number of cesarean sections. As a result, obstetricians should be aware of the difficulties of this emergent condition and improve its accurate antenatal diagnosis rates, as well as its modern management strategies. Of course, special skills are required during a pregnancy-related hysterectomy, so these patients should be referred to centers of excellence in antenatal care, where a multidisciplinary team approach is followed. This study is a narrative review of the literature of the last 5 years (PubMed, Cochrane) regarding postpartum hemorrhage to offer obstetricians up-to-date knowledge on this pregnancy-related life-threatening issue. However, there is a lack of available high-quality data, because most published papers are retrospective case series or observational cohorts.

1. Introduction

Postpartum hysterectomy is an intervention performed in life-threatening situations to prevent maternal death [1]. Obstetricians face a dilemma: to perform postpartum hysterectomy or to attempt other conservative uterine sparing techniques that may result in severe morbidity or death. Unfortunately, postpartum hysterectomy results in the loss of future fertility and is associated with high prevalence of maternal morbidity and mortality [2]. Historically, it was first performed successfully by Porro in 1871 [3] and become in the 1950s an elective but controversial procedure, due to excessive blood loss and high incidence of urinary tract injuries [4, 5]. Today, it is mainly used as the final step in several postpartum hemorrhage protocols, because blood transfusions and other interventions (e.g., uterotonics) have reduced its need [6].

There is no globally accepted definition that places a limit in the period of time that the hysterectomy is performed, so the definitions vary among published studies. Some authors define peripartum hysterectomy as the hysterectomy performed at the time of delivery, or at any time from the delivery to discharge at the same hospitalization [7], while others as the removal of the uterus during pregnancy or immediate postpartum [8]. When performed at the time of the cesarean delivery, it is defined as cesarean hysterectomy. Another used term is postpartum hysterectomy, when it is performed after the delivery of the fetus within 24 h or 48 h or during the same hospitalization or within 6 weeks [6]. All these different definitions, in combination with the low incidence of hysterectomy associated with pregnancy, make it difficult to compare results between studies [9]. Therefore, the International Network of Obstetric Survey Systems (INOSS) proposed a definition of "pregnancy-related hysterectomy": surgical removal of the uterus during pregnancy, from 22 weeks of gestation or up to 42 days postpartum [10]. The term includes hysterectomies after cesarean or vaginal delivery. This definition is wide enough to include all possible indications of hysterectomy.

Worldwide, the incidence of pregnancy-related hysterectomies varies widely [7] and is increasing over time (71.6 to 82.6 per 100.000 deliveries) [11]. The main indication for pregnancy-related hysterectomy is severe uterine bleeding that cannot be controlled by conservative measures [12]. The main causes that lead to severe uterine hemorrhage and cesarean hysterectomy are uterine atony, placenta spectrum disorders, uterine rupture, and sepsis [10]. Possible risk factors for pregnancy-related hysterectomy are abnormal placentation, advanced maternal age, high parity, and cesarean delivery in current or previous pregnancies [9, 12]. Many studies have reported a strong association between cesarean sections, placenta pathologies, and pregnancy-related hysterectomy [13–19]. The relative risk for hysterectomy is known to be increased for every additional previous cesarean section (odds ratios: 0.7 to 15.2 from 1st prior to 6th or more cesarean sections) [20].

Furthermore, it is important to state that the adverse events related to pregnancy-related hysterectomy are substantially higher than those from nonobstetric hysterectomy [2, 21]. It is associated with increased peri- and postoperative complications, especially in low-volume centers, where multidisciplinary team management of these cases is not available [21]. The most common complication is bladder injury (9%), followed by ureteral injury, massive hemorrhage, wound dehiscence, and venous thrombosis [2, 22]. Globally, the risk of death in pregnancy-related hysterectomy is 1% compared to 0.04% for nonobstetric hysterectomy [2].

2. Postpartum Hemorrhage

Hemorrhage is a significant cause of maternal mortality and is currently responsible for 27% of all maternal deaths worldwide. It is the 4th leading cause of maternal mortality in the United States and the leading cause worldwide. Postpartum hemorrhage (PPH) is defined as a blood loss of >500 ml after vaginal delivery or >1000 ml after cesarean section within 24 h after birth. However, it is well known that estimation of blood loss during delivery is hard and can be inaccurate. So, the American College of Obstetricians and Gynecologists (ACOG) proposed that PPH is defined as a cumulative blood loss greater than 1000 ml or any degree of blood loss that causes signs or symptoms of hypovolemia, such as tachycardia, tachypnea, oliguria, hypotension, dizziness, pallor, or any altered mental status, occurring within 24 h from delivery. Other authors define severe PPH as a blood loss that requires ≥4 blood units.

The timing for the optimal therapeutic dichotomy between conservative management and pregnancy-related hysterectomy has not been yet defined in cases of PPH, and the highly inaccurate visual calculation of blood loss makes it even harder. So, the need to establish some parameters to evaluate or even predict PPH is necessary. The use of shock parameters (blood pressure, heart rate, and urinary output) has been strongly recommended [23].

During the last years, the shock index, grade of shock, and number of packed red blood cells (PRBCs) have been proposed as possible parameters that can predict the volume of blood loss [24–26]. The shock index can be calculated as the ratio of the heart ratio/systolic pressure. The grade of shock is defined by several parameters: systolic and diastolic pressure, heart ratio, urinary output, and respiration. On the other hand, hemoglobin values and coagulation parameters were not reliable to differentiate the severity of blood loss and were also time consuming. Taking the above into consideration, a massive blood transfusion protocol should be adapted and the choice between conservative aggressive (hysterectomy) treatments should be based on hemodynamic parameters and not on laboratory tests [24]. Moreover, a retrospective study from Lee et al. proposed a predictive scoring model for PPH in PAS disorders [27]. The model included maternal old age (<35: 0, ≥35: 1), antepartum bleeding (no: 0, yes: 2), fetal noncephalic presentation (no: 0, yes: 2), placenta previa type (incomplete: 0, complete: 1), placenta location (posterior: 0, anterior: 1), uteroplacental vascularity (no: 0, yes: 2), and multiple lacunae (no: 0, yes: 1). A score of 5/10 has a sensitivity of 81% and a specificity of 77% for prediction of a severe PPH. The negative predictive value was 95.9%, while the positive predictive value was 38.1%.

Currently, the most common cause of PPH and therefore pregnancy-related hysterectomy is uterine atony, but the rate of PAS disorders as a cause for PPH continues to increase [28]. A recent systematic review and meta-analysis [12] which included women worldwide confirmed the data from other studies [29] and showed that PAS disorders could become the leading cause, because of the rising use of uterotonics and the increasing number of cesarean sections. These findings were also presented in two large multinational cohort studies that were published recently: one that included data from the WOMAN trial [7] and the other from INOSS [10]. Both studies included a large number of pregnancy-related hysterectomies (1020 and 1320, respectively) and showed that the main indication of the hysterectomy was uterine atony (35.3%), followed closely by PAS disorders (34.8%) and uterine rupture as the third cause.

Another important issue is the timing of the hysterectomy which differs from the cause of bleeding. When PAS disorders were the cause, the median time was 0.6 h, compared to ≥13 h for uterine atony. Furthermore, PAS disorders were associated with three times higher risk of hysterectomy compared to uterine atony. In addition, cesarean section was found to increase the risk of hysterectomy (fourfold higher odds) as compared to vaginal delivery. These results could be explained by the fact that prenatal diagnosis of PAS disorders lead to a cesarean section and may inevitably require a hysterectomy. Another undeniable fact is that during a cesarean section, the patient is already in the operating room and the uterus is readily accessible, while during vaginal delivery, the obstetricians might try more other conservative methods to control the PPH. Moreover, the number of previous cesarean sections showed an increased risk for pregnancy-related hysterectomy, and every additional operation added a higher chance of maternal morbidity. Older maternal age was also a significant factor for higher risk of hysterectomy, especially in pregnant women over 40 years old, after adjusting for all confounding factors.

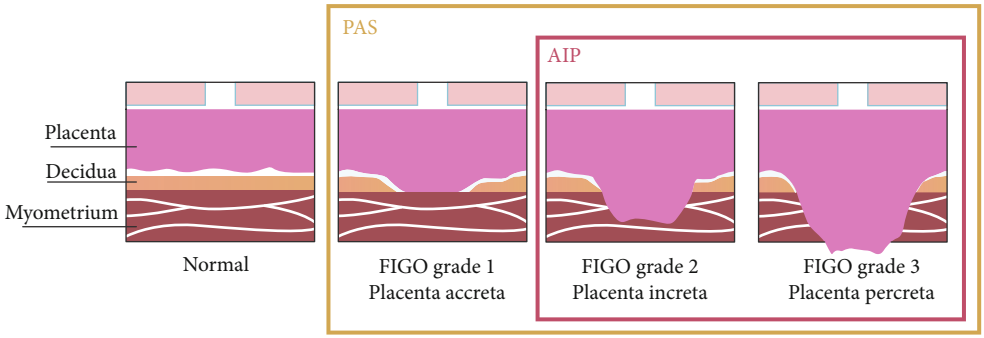

Figure 1: PAS, AIP, and FIGO abnormal placentation definition (from Morlando and Collins [30] with permission).

3. PAS Disorders

3.1. Definitions. PAS is a heterogenous group of disorders, and its definitions vary among literature [30]. The use of the term PAS disorders is a wide term that encompasses the whole spectrum of pathology (Figure 1) and recently has been endorsed by several scientific societies, such as FIGO [31], RCOG [32], ACOG, and SMFM [33]. Based on the depth of the myometrial invasion from the trophoblast, three types of PAS can be categorized [34]: placenta accreta (grade 1) (also referred to as creta, vera, and adherenta), where the chorionic villi attach directly to the surface of the myometrium in the absence of the decidual layer [35]; placenta increta (grade 2), where the chorionic villi penetrate deeply into the myometrium reaching the external layer [36]; and placenta percreta (grade 3), where the chorionic villi invade, reach, and penetrate through the uterine serosa [34, 37]. A clinical-histological grading system has been proposed by FIGO to describe and categorize the different aspects of PAS disorders (Table 1) [38]. The severity of the disorder, hence the possibility of pregnancy-related hysterectomy, increases from placenta accreta to percreta. It is important to be able to recognize other entities-cases that can be easily mistaken as PAS disorders. Firstly, the "uterine window," which is a dehiscence of the uterine myometrium after a prior cesarean section and the placenta, is visible under the serosa at the time of the operation (Figure 2) [34]. Secondly, there is retention of the placenta during vaginal delivery, when the placenta is separated normally from the uterine wall, in contrast to the PAS disorders, but it is entrapped into the uterus due to the strong or tetanic contraction of the cervix [30].

Another term that is usually used when describing the PAS disorders is placenta previa. This term concerns the positioning of the placenta [39]. Placenta previa develops in the lower segment of the uterus, instead of the upper one, and it is classified according to the relationship/distance of the lower placenta edge from the internal os of the uterine cervix. Definition of minor placenta previa is when the lower edge lies inside the lower uterine segment down to the internal os, and that of major placenta previa is when the placenta covers the uterine cervix. Both are further subdivided into two categories: minor placenta previa to low-lying placenta when the lower placenta edge does not reach the internal os and marginal placenta previa when it does. Major placenta previa is described as partial or complete depending on the amount of the placenta covering the cervix.

3.2. Pathophysiology. Many theories have been proposed about how PAS disorders can occur. The one that prevails is that iatrogenic defect of the endometrium-myometrium interface leads to a failure of normal decidualization at the site of the uterine scar and therefore enables abnormally deep trophoblastic infiltration [37]. The extent of the infiltration of the villous tissue inside the myometrium is likely to be connected with the extent of the deciduo-myometrial damage. Another mechanism that has been suggested is that during IVF cycles, a characteristic hormonal milieu at the time of the implantation and placentation may promote deep trophoblast invasion that resulted in PAS [40]. This could be explained either from elevated serum estrogen levels at the time of the implantation, enabling excessive trophoblastic invasion deep inside the myometrium, or from lower serum estradiol levels together with the presence of the thinner decidualized endometrium [41]. Last but not least, one additional theory is based on the finding of unusual uteroplacental vasculature, meaning physiological changes in larger arteries deep in the myometrium, when abnormal invasive placentation is present, compared to normal pregnancies [42].

3.3. Risk Factors. Epidemiological studies have shown a strong association between the incidence of PAS disorders, cesarean section rates, and prior cesarean section numbers [36]. Globally, over the last 40 years, the rate of cesarean deliveries has risen from 10% to 40%, and at the same time, there has been a 10-fold increase in the incidence of PAS disorders [31]. Moreover, increased cesarean sections have increased the incidence of placenta previa [43]. The incidence of PAS disorders also increases with every prior cesarean delivery: from 4.5% for one up to 44.9% for four or more cesarean sections, compared to vaginal deliveries [44]. Similarly, the risk of PAS disorders in women with a placenta previa and prior cesarean section was 3%, 11%, 40%, 61%, and 67% for the first, second, third, fourth, and fifth or more cesarean sections, respectively [20]. Current data suggest that over 90% of women diagnosed with any PAS disorder also have a placenta previa [45]. The combination of these two pathologies leads to high maternal

Table 1: Clinical and histological grading system for PAS disorders (FIGO guidelines).

Grade	Definition	
	Clinical criteria	Histologic criteria
1. Abnormally adherent placenta (accreta)	At vaginal delivery: no separation with synthetic oxytocin and gentle controlled cord traction; attempts at manual removal of the placenta result in heavy bleeding from the placenta implantation site requiring mechanical or surgical procedures If laparotomy is required (including for cesarean delivery): the same as above; macroscopically, the uterus shows no obvious distension over the placental bed (placental "bulge"), no placental tissue is seen invading through the surface of the uterus, and there is no or minimal neovascularity	Microscopic examination of the placental bed samples from the hysterectomy specimen shows extended areas of absent decidua between villous tissue and myometrium with placental villi attached directly to the superficial myometrium. The diagnosis cannot be made on just delivered placental tissue or on random biopsies of the placental bed
2. Abnormally invasive placenta (increta)	At laparotomy: abnormal macroscopic findings over the placental bed: bluish/purple coloring and distension (placental "bulge"); significant amounts of hypervascularity (dense tangled bed of vessels or multiple vessels running parallel craniocaudally in the uterine serosa); no placental tissue seen to be invading through the uterine serosa; gentle cord traction results in the uterus being pulled inwards without separation of the placenta (so-called the dimple sign)	Hysterectomy specimen or partial myometrial resection of the increta area shows placental villi within the muscular fibers and sometimes in the lumen of the deep uterine vasculature (radial or arcuate arteries)
3. Abnormally invasive placenta (percreta)		
3a. Limited to the uterine serosa	At laparotomy: abnormal macroscopic findings on the uterine serosal surface (as above) and placental tissue seen to be invading through the surface of the uterus; no invasion into any other organ, including the posterior wall of the bladder (a clear surgical plane can be identified between the bladder and uterus)	Hysterectomy specimen showing villous tissue within or breaching the uterine serosa
3b. With urinary bladder invasion	At laparotomy: placental villi are seen to be invading the bladder but no other organs: clear surgical plane cannot be identified between the bladder and uterus	Hysterectomy specimen showing villous tissue breaching the uterine serosa and invading the bladder wall tissue or urothelium
3c. With invasion of other pelvic tissue or organs	At laparotomy: placental villi are seen to be invading the broad ligament, vaginal wall, pelvic sidewall, or any other pelvic organ (with or without invasion of the bladder)	Hysterectomy specimen showing villous tissue breaching the uterine serosa and invading pelvic tissues/organs (with or without invasion of the bladder)

From Jauniaux et al. [38] with permission.

morbidity and mortality due the severe postpartum hemorrhage [46, 47]. The maternal mortality has been reported in some studies as high as 7%, when placenta previa with percreta is present [48].

Other risk factors except placenta previa, cesarean section, and prior cesarean section numbers are any procedure that causes surgical damage to the uterine wall integrity [36, 37]. Specifically, operative hysteroscopy, suction curettage, surgical termination, and endometrial ablation have been reported to cause later PAS disorders to nulliparous women (no other risk factor) [37, 49]. Cases of PAS can occur even after myomectomy, but with a relative lower risk [50]. Finally, studies from the later years have shown that IVF, especially with cryopreserved embryos, increases 4- to 13-fold the risk of PAS disorders [51].

3.4. Diagnosis. Accurate antenatal diagnosis of PAS disorders is essential for the maternal morbidity and mortality. A false-negative antenatal diagnosis may lead to a routine low transverse uterine incision and a massive placental blood loss, even before the fetus is delivered. On the other hand, a false-positive diagnosis will result in an unnecessary midline skin incision and a fundus uterine incision, which increases the risk of intra- and postoperative complications [45]. It is of high importance that these cases should be diagnosed on time and referred to a center of excellence, where a multidisciplinary team (MDT) approach is available. These centers of excellence are less likely to require an emergency surgery, large-volume transfusion protocols, and reoperation within 7 days from delivery for any complication, compared to centers with no standardized management protocol [52–54]. A recent systematic review and meta-analysis confirmed that maternal outcomes have improved over time with increasing experience within a center of excellence with the MDT approach performing 2-3 cases per month [55]. Some criteria have been proposed for these centers of excellence (Table 2)

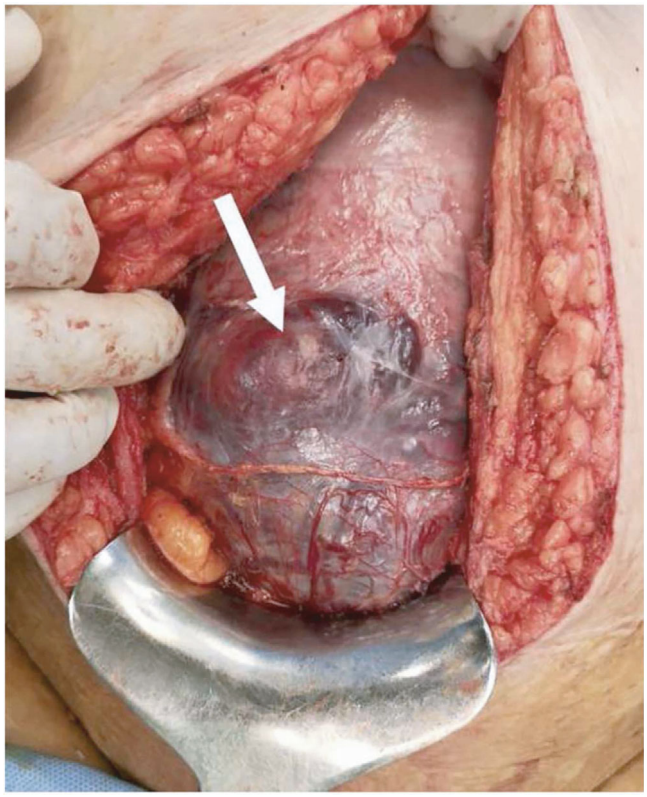

Figure 2: Uterine myometrial dehiscence at 35 weeks, due to prior cesarean sections (from Jauniaux et al. [51] with permission).

Table 2: Criteria for centers of excellence for PAS disorders.

1. Multidisciplinary team
a. Experienced maternal-fetal medicine physician or obstetrician
b. Imaging experts (ultrasound and MRI)
c. Pelvic surgeon (i.e., gynecologic oncology or urogynecology)
d. Anesthesiologist (i.e., obstetric or cardiac anesthesia)
e. Urologist
f. Trauma or general surgeon
g. Interventional radiologist
h. Neonatologist
2. ICU and facilities
a. Interventional radiology
b. Surgical or medical ICU (24-hour availability of intensive care specialists)
c. Neonatal ICU (gestational age appropriate for neonate)
3. Blood services
a. Massive transfusion capabilities
b. Cell saver and perfusionists
c. Experience and access to alternative blood products
d. Guidance of transfusion medicine specialists or blood bank pathologists

From Silver et al. [53] with permission.

[53]. Prenatally unsuspected PAS disorders are usually associated with higher risk of severe PPH, due to the repeatedly attempts of the surgeons to remove the placenta from the uterine wall [56]. When the placenta is left in situ, because it was antenatally diagnosed, there is less blood loss and less need for transfusion [57]. These findings were confirmed from a recent systematic review and meta-analysis, which showed that antenatal diagnosis of PAS reduces perioperative complications and especially surgical bleeding [58]. The antenatal diagnostic accuracy of PAS is between 90 and 95% in several studies [45, 59, 60], especially in experienced centers. However, recent population studies show that PAS disorders remain undiagnosed until delivery in half [57, 59] to two-thirds [61] of the cases in the overall population.

3.5. Ultrasound. Ultrasound imaging during pregnancy is considered highly accurate in the detection of PAS disorders, when it is performed by a skilled operator [32]. A recent systemic review and meta-analysis found a pooled sensitivity of 88% and 97% in retrospective and prospective studies, respectively [45]. Numerous techniques have been added to the grayscale ultrasound, such as color Doppler and 3D power Doppler, to improve the sensitivity of the exam [45, 62]. Over the years, many studies investigated the predictive value of several signs for PAS, and their performance has shown considerable variability [63]. This could be attributed to the limitations of these studies and the different terminology reported: the same sign described using different names or the same term for different findings [30]. Another additional problem is the fact that the diagnostic technique relies strongly on the opinion of the operator, according to his experience and training [64]. Other factors that can alter the ultrasound signs are the scanning conditions (e.g., too full or too empty bladder), ultrasound equipment, and gestational age [30]. One important problem, which still remains, is the lack of sign or combination of signs that can effectively predict the depth of myometrial invasion from the trophoblast [34, 45, 65]. Recently, the European Working Group on Abnormal Invasive Placenta (EW-AIP) has proposed some standardized descriptions of ultrasound signs associated with PAS disorders (Table 3) [64].

3.6. Magnetic Resonance Imaging (MRI). Although ultrasound is the first-line imaging tool for the screening and diagnosis of PAS disorders, the role of MRI has been well established for the diagnosis of PAS, with high sensitivity and specificity [66]. Both MRI and ultrasound have comparable predictive parameters, and no superiority has been demonstrated [66, 67]. It is unclear if MRI can improve the diagnosis for PAS compared to what can be achieved from an experienced ultrasound operator [32, 33]. MRI may be less operator-dependent, but the high cost and the limited access to equipment and an expert radiologist make it impractical as a screening tool [68]. Moreover, a recent study found that MRI resulted in a change in diagnosis that could alter clinical management of PAS in more than one-third of cases, but, when changed, the diagnosis was often incorrect [69]. So, it is recommended that the first screening is performed by ultrasound, and if a suspicion of PAS is raised, then an MRI should be proposed as a second-line imaging tool [30]. It helps to assess the depth of myometrial invasion and

Table 3: Ultrasound sign definitions for PAS disorders.

US finding	EW-AIP definition
2D grayscale	
Loss of "clear zone"	Loss, or irregularity, of the hypoechoic plane in the myometrium underneath the placental bed ("clear zone")
Abnormal placental lacunae	Presence of numerous lacunae including some that are large and irregular (Finberg grade 3), often containing turbulent flow visible on grayscale imaging
Bladder wall interruption	Loss or interruption of the bright bladder wall (hyperechoic band or "line" between the uterine serosa and bladder lumen)
Myometrial thinning	Thinning of the myometrium overlying the placenta to <1 mm or undetectable
Placental bulge	Deviation of the uterine serosa away from the expected plane, caused by abnormal placental tissue into neighboring organ, typically bladder; uterine serosa appears intact, but outline shape is distorted
Focal exophytic mass	Placental tissue seen breaking through the uterine serosa and extending beyond it; most often seen inside the filled urinary bladder
2D color Doppler	
Uterovesical hypervascularity	Striking amount of color Doppler signal seen between the myometrium and posterior wall of the bladder; this sign probably indicates numerous closely packed tortuous vessels in that region (demonstrating multidirectional flow and aliasing artifact)
Subplacental hypervascularity	Striking amount of color Doppler signal seen in the placental bed; this sign probably indicates numerous closely packed tortuous vessels in that region (demonstrating multidirectional flow and aliasing artifact)
Bridging vessels	Vessels appearing to extend from the placenta, across the myometrium and beyond the serosa into the bladder or other organs; often running perpendicular to the myometrium
Placental lacuna feeder vessels	Vessels with high-velocity blood flow leading from the myometrium into placental lacunae, causing turbulence upon entry
3D ultrasound+power Doppler	
Intraplacental hypervascularity	Complex, irregular arrangement of numerous placental vessels, exhibiting tortuous courses and varying calibers
Placental bulge	Same as in 2D
Focal exophytic mass	Same as in 2D
Bridging vessels	Same as in 2D

From Collins et al. [64] with permission.

Table 4: MRI sign definitions for PAS disorders.

MRI findings	IS-AIP definition	Sequence type
Heterogeneous placenta	Heterogeneous signal within the placenta	T2W and T1W
Placental bulge	Deviation of the uterine serosa from the expected plane caused by abnormal bulge of placental tissue into neighboring organs (typically the bladder). Uterine serosa appears intact, but outline shape is distorted	T2W and T1W
Dark intraplacental bands	One or more areas of hypointensity with a linear appearance, in contact with the maternal surface of the placenta	T2W
Placental ischemic infarction	Areas of increased signal intensity (T2W) and decreased signal intensity (T1W)	T2W and T1W
Loss of the retroplacental dark zone	Loss of the thin dark zone lying beneath the placental bed	T2W
Myometrial thinning	Thinning of the myometrium overlying the placenta to less than 1 mm or invisible	T2W
Bladder wall interruption	Irregularity or disruption of the normal hypointense urinary bladder wall	T2W
Focal exophytic mass	Placental tissue seen protruding through the uterine wall and extending beyond it. Most often seen inside a filled urinary bladder	T2W and T1W
Placental bed abnormal vascularization	Large vessels within the placental bed with disruption of the uteroplacental interface	T2W

From Morel et al. [70] with permission.

parametrial involvement [32]. Another advantage is that MRI can overcome certain technical limitations of the ultrasound in the diagnosis of PAS: unfavorable placenta location (posterior) or high maternal BMI, and the entire pelvis can be easily studied and reevaluated by different physicians [30]. The International Society for Abnormally Invasive Placenta (IS-AIP) has recently proposed standardized definitions of the MRI descriptors (Table 4) [70].

3.7. Clinical Criteria. The ultimate confirmation of PAS should be performed peripartum, before any surgical treatment. There is no established clinical diagnostic method; therefore, surgeons should be aware of all possible predictive clinical signs [53, 71–75]: difficult manual or piecemeal removal of the placenta, absence of placenta separation 20-30 min after delivery (despite active management with bimanual uterine massage, umbilical cord traction, and use of oxytocin), retained placenta fragments requiring curettage (vaginal delivery), and severe bleeding from the placenta bed after its removal (cesarean section). However, some basic steps have been proposed during laparotomy for the

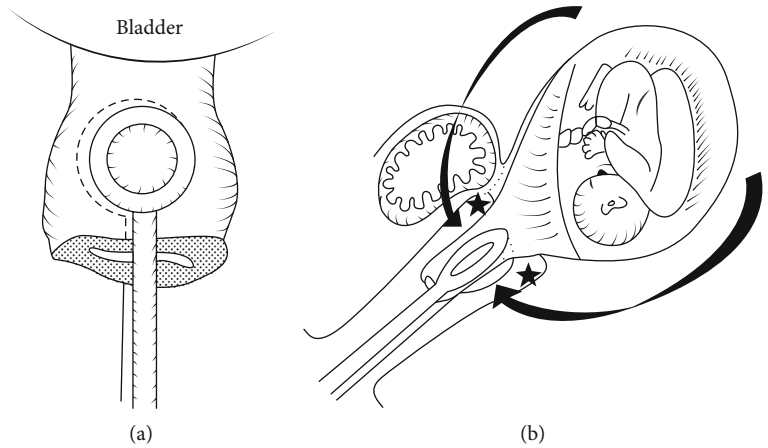

Figure 3: Holding the cervix: (a) anterior-posterior view; (b) lateral view (from Matsubara et al. [109] with permission).

diagnosis of PAS [76]. (a) The external surface of the uterus and the pelvis was inspected for abnormal appearance of the serosa over the placental bed (bluish/purple appearance) with evident distension (placental bulge) or obvious invasion through the uterine surface. (b) If there is no evidence of the most severe PAS disorders, a uterine incision, leaving the placenta intact, should be performed and gentle cord traction should be attempted. If the uterine wall is pulled towards the direction of the traction with no placenta separation ("dimple" sign) and there is apparent contraction of the uterus separating from the placenta bed, then PAS can be diagnosed. (c) If the previous two steps do not reveal PAS, then a gentle digital exploration can be attempted to assess the presence of a cleavage plane between the uterus and the placenta.

3.8. Histopathological Criteria. The histopathological diagnosis of PAS can be very difficult, because of the surgeons' attempts to remove the placenta from the uterus and the fact that when conservative management is attempted, the whole placenta is left in situ [51]. The main histopathological criterion used for the diagnosis is the absence of decidual/Nitabuch layer between the tip of anchoring villi and superficial myometrium [77]. Nevertheless, this criterion can be elusive and simplistic, because these areas can be found at placentas in advanced gestational age pregnancies, without the presence of PAS disorders [34]. When PAS disorders are found during the histopathological examination, it is of high importance to confirm and report the depth of villous invasion of the uterine myometrium, in order to differentiate the types of PAS [51]. But often enough, there is a lack of clear description of the histological criteria used to define the different types/grades of PAS [65, 78].

3.9. Biomarkers. Several possible biomarkers have been proposed and tested for years in different studies for the diagnosis of PAS, depending on the gestational age [79]. When PAS disorders are present, β-hCG was lower and PAPP-A higher, compared to normal pregnancies, at 11-12 weeks of gestation, while at 14-22 weeks of gestation, serum levels of β-hCG and AFP were higher [30]. Currently, there is no effective established biomarker for a serological screening of PAS [62].

4. Management Strategies: Hysterectomy

The majority of the surgeons that are experts on pregnancy-related hysterectomy prefer to leave the placenta in situ and perform a primary cesarean hysterectomy at delivery [80–83]. However, some authors in the literature opt for conserving treatment for PAS disorders and leave the placenta in the uterus with the expectation of spontaneous placenta absorption or delivery [84]. This conservative management may decrease the maternal morbidity of the pregnancy-related hysterectomy, but there are several complications that accompany this treatment plan: massive hemorrhage, infection, sepsis, disseminated intravascular coagulation, and ultimately hysterectomy [85, 86]. Questions have been raised about the high prevalence of PAS in recent population studies and the even higher successful rates of conservative treatment, which could be a misleading conclusion, due to the wrongful inclusion of no PAS placenta retention or/and uterine dehiscence in their data [51]. A recent systematic review [87] on conservative treatment for PAS disorders revealed high maternal morbidity during conservative treatment for placenta percreta, which is one of the main reasons that pregnancy-related hysterectomy is not preferred as a first-choice treatment. Another systemic review and meta-analysis stated that conservative management failed to prevent a secondary hysterectomy in the majority of the cases of previa PAS [45]. Overall, there are no RCTs or well-designed prospective observational studies comparing hysterectomy and conservative treatment for the same type of PAS disorder. Any attempt for conservative treatment should be made in large and experienced centers, where surgery could be performed in a 24 h manner from experienced surgeons [88].

The steps for pregnancy-related hysterectomy are the same as those for nonobstetric hysterectomy [6]:

(1) Separation of the round ligament

(2) Separation of the broad ligament

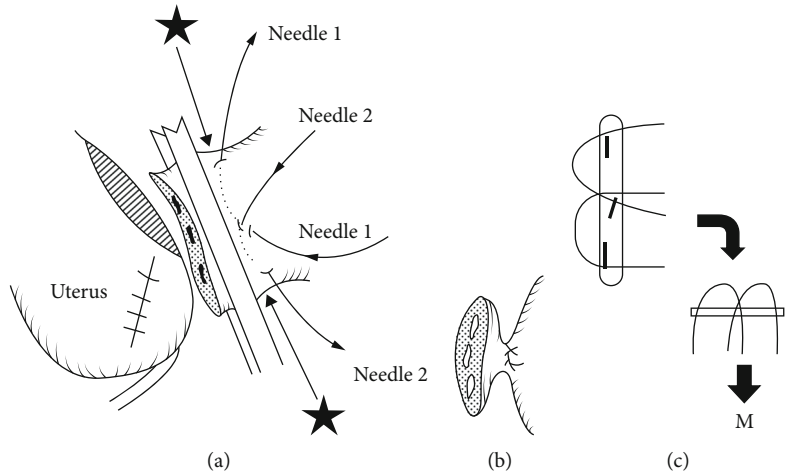

Figure 4: M cross double ligation for the ovarian ligament (from Matsubara et al. [109] with permission).

(3) Dissection of the bladder and perivesicular space

(4) Palpation, clamping, and separation of the cardinal ligament and uterine arteries

(5) Separation of the uterosacral ligament

(6) Closure of the vaginal cuff

However, the changes that occur to the female reproductive system during pregnancy may further complicate the procedure [6]. The main difficulty is the increased uterine blood flow, especially during late gestation. There is a 10- to 30-fold increase in the uterine blood flow from the beginning to the end of pregnancy [89, 90]. Tissue fragility and edema are also increased, which makes handling tissue more difficult. The enlarged uterus makes its manipulation and overall visualization of the pelvis much harder, and the normal anatomical relationships and structures are often displaced. The closest important structures that should be recognized and preserved are the ureters which are tortuous and distended and with significant hydroureter. Completion of pregnancy-related hysterectomy can be either total or subtotal, without the removal of the cervix. The goal should be total hysterectomy, because of the potential risk of malignancy developing in the cervical stump and the need for regular cervical cytology, and most of the times, the cervix is the cause of postoperative bleeding (placenta previa PAS) [91]. But when its removal may compromise the hemostasis, it should be left in place. The ovaries should be reserved, but the fallopian tubes should be removed to reduce ovarian cancer risk.

The position of the patient is either supine or dorsal lithotomy, and the incision is based on the expected difficulty and complications, either vertical or extended transverse. Preoperative prophylactic antibiotics should be administrated, to reduce surgical site infection, which was confirmed for a Cochrane review where the use of antibiotics reduced the risk of wound infection, endometritis, and serious maternal infection [92]. Large-bore venous access and pneumatic compression devices are recommended, and central venous access should be considered [56]. In a randomized trial involving women with severe PPH, it showed that the use of tranexamic acid reduced the risk of death due to blood loss [93]. One study compared the surgical outcome with or without LigaSure during pregnancy-related hysterectomy and found that its use resulted in less operative time, less blood loss, and reduced incidence of severe PPH [94]. Moreover, these women are at increased risk for postpartum venous thromboembolism, due to their long and complex surgery and their immobilization [56].

4.1. Hysterectomy for PAS Disorders. The increasing incidence of PAS disorders and the high maternal morbidity during hysterectomy for abnormal placentation make the management strategy of this pathology very difficult. There are no RCTs or high-quality studies for the management of PAS disorders, and the only available data are from retrospective cohort studies and case series. As a result, different strategies have been proposed from several authors.

The cornerstone for the management of PAS disorders is to avoid any attempt to remove the placenta from the uterine wall [30]. Making no attempt decreases hemorrhage and blood transfusion [57]. Recommendations [30] to avoid intercourse and cervical examination are of unproven efficacy, but these measures might have some meaning in cases of placenta previa. Bed rest is recommended in women with bleeding, but it is also unknown if it affects the outcome of the pregnancy. Early elective cesarean section may reduce the risk of bleeding [95], but it increases the risk of neonatal prematurity. So, it is of high importance to define the best time for delivery in women with PAS disorders. Planned delivery ranges from 34 to 38 weeks [30]. Delivery until after 36 w+0 d could be offered to women with no history of prior preterm birth, no vaginal bleeding, no preterm premature rapture of membranes (PPROM), and no uterine contractions. On the other hand, delivery around 34 w+0 d could be offered to women with any of the above-mentioned problems. 34-35-week pregnancy-related hysterectomy with the placenta left in situ is recommended by ACOG [33].

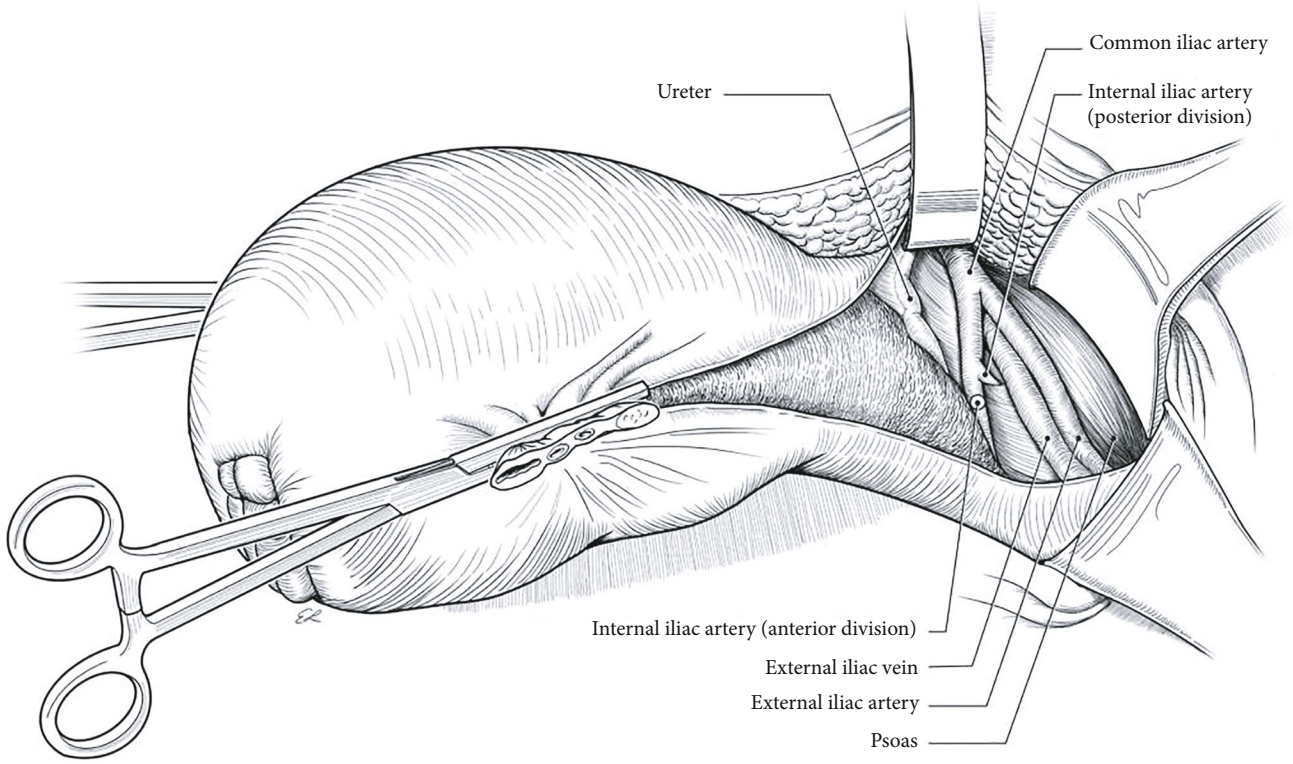

Figure 5: Retroperitoneal devascularization (from Kingdom et al. [110] with permission).

Antenatal steroid prophylaxis should be administrated to the mother (12 mg of betamethasone intramuscularly from 2 to 7 days before delivery and repeated 24 h later) in order to enhance fetal pulmonary lung maturity [96].

Pregnancy-related hysterectomy is the gold standard for the treatment of PAS disorders. However, this radical approach is associated with high rates (40-50%) of severe maternal morbidity, especially hemorrhage and trauma to the surrounding organs, and a 7% rate of maternal mortality [97, 98]. These figures are improved significantly when women with PAS are referred to centers of excellence, where the MDT approach is available and rates of 0.05% of mortality are achievable [78]. General and regional anesthetic techniques can be safely offered to these women [32], but always there might be a need to convert from regional to general during the procedure [91]. Most surgeons prefer a vertical skin incision to allow adequate access to the uterus (especially when the placenta is anterior and towards the level of the umbilicus) and the pelvic wall, while some opt for a large transverse incision, like a modified Maylard incision, for faster healing and better cosmetic result [30, 51], but there is insufficient data of its use in the management of PAS disorders [91]. The uterine incision should always avoid the placenta, so in many cases, a fundal incision is chosen. Intraoperative ultrasound could help to identify the upper edge of the placenta and safely guide the hysterotomy for the delivery of the fetus [99]. Pregnancy-related hysterectomy for PAS disorders is rather technically challenging, compared to hysterectomy for uterine atony, due to high risk of adjacent organ damage [100]. Urinary tract injuries are described in 29% of the procedures, with a reported rate of 76% for bladder lacerations, 17% for ureteral injuries, and 5% for genitourinary fistulas [101]. Injuries to other abdominal organs are less common [102]. The main risk factors for these injuries are depth and extension of placenta invasion, intraoperative blood loss, and the number of prior cesarean sections [103].

Another proposed scenario is the delayed hysterectomy, instead of primary radical surgery [30]. After the delivery of the fetus, the uterus is closed with the placenta left in situ, and the maternal abdomen is also closed. Then, a planned hysterectomy is performed 3-12 weeks postpartum [32]. This approach has the rationale that the uterine perfusion and vascularity are reduced, even with the placenta in situ, so the delayed hysterectomy is less risky. This scenario is an option during an emergency pregnancy-related hysterectomy, when the surgeon has limited experience at this complex surgical procedure [30].

Although uterine stent placement can be beneficial in preventing ureteral injury and intraoperative complications, there is no strong evidence in order to routinely recommend them to all PAS cases [76, 101]. So, their placement should be individualized based on the depth and lateral extent of the invasive placentation. Prophylactic endovascular balloon catheters have been proposed as a method to reduce intraoperative blood loss during pregnancy-related hysterectomy, in order to improve maternal morbidity and also allow the surgeon to operate in a "cleaner"—improved visibly—field. However, their use is controversial, mainly because of their high possible complication rates, such as vessel rapture, thromboembolism, risks for damage of pelvic structures,

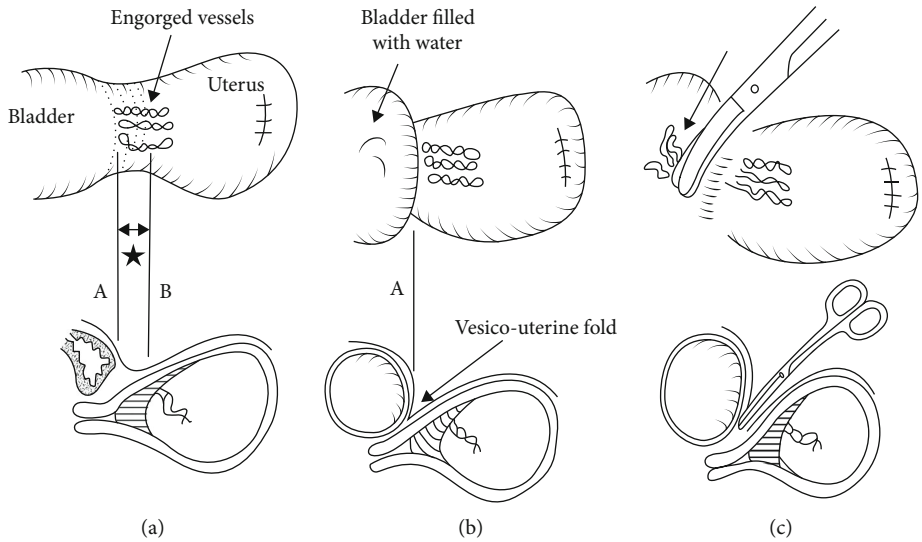

Figure 6: Bladder wall dissection, with filling the bladder (from Matsubara et al. [109] with permission).

and disturbance of blood supply to the lower limbs [30, 104, 105]. Furthermore, PAS is associated with extensive aberrant neovascularization, and the occlusion of some pelvic vessels may lead to increased blood loss from the collateral vessels [30]. In addition, two RCTs comparing the placement of balloon catheters in the iliac arteries with no intervention at all found no difference in the number of PRBCs transfused to the patients [106, 107], and a recent RTC comparing bilateral internal iliac artery ligation versus controls found no difference regarding intraoperative blood loss [108].

The main goal during pregnancy-related hysterectomy for PAS is to minimize surgical blood loss. During the procedure, especially for previa percreta, some key steps can be recognized [109, 110]. Each of these steps takes time, and the total skin-to-skin duration can take 2-3 hours for experienced surgical teams:

(1) Intra-arterial occlusion balloon catheter placement

This is not always necessary. A balloon is placed in both common iliac arteries [111]. The balloon is inflated at the ligation of the upper uterine artery branch or when the bladder separation is started. However, the balloon occlusion should be within 40 min.

(2) Ureter stent placement

This is not always necessary. When needed, they should be placed in the operating theater, just before surgery. There is a risk of emergency surgery, due to uterine contractions, when the stents are placed the day before the surgery.

(3) "Holding the cervix" technique

The uterine cervix is closed with round forceps, simultaneously over the anterior and posterior cervical lip (Figure 3) [112, 113]. This has two advantages: firstly, there should be better evaluation of bleeding over time, because without the occlusion of the cervix, the blood flowed to the vagina and the operating field looked falsely dry. Secondly, the metal consistency of the forceps clearly indicates the site to be transected, because pregnancy makes the tissue of the uterus soft and hard to identify the vaginal transection site.

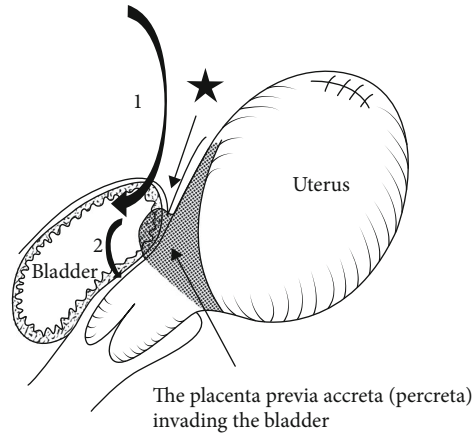

Figure 7: Intentional bladder opening (from Matsubara et al. [109] with permission).

(4) Midline access and hysterotomy

Midline skin incision extended from 2 cm above the pubic bone to 3-4 cm below the umbilicus. Hysterotomy usually towards the fundus vertically, avoiding the placenta, for the delivery of the fetus minimizes blood loss before the delivery.

(5) Avoiding uterotonic agents

Uterotonic agents should not be used, because they might cause partial placenta separation, leading to severe PPH at the beginning of the hysterectomy.

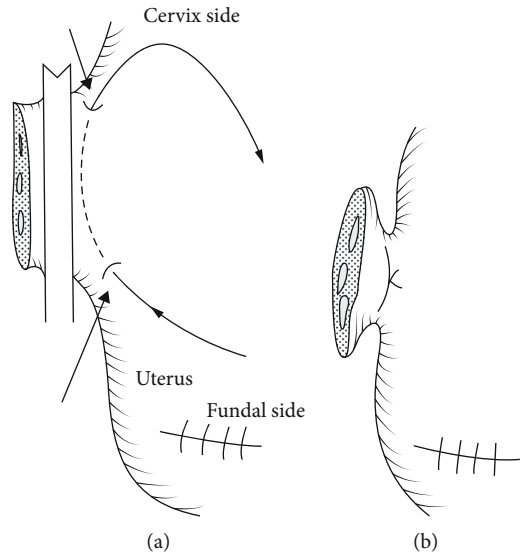

Figure 8: Double distal edge pickup (from Matsubara et al. [109] with permission).

(6) Superior devascularization (M cross double ligation)

Release and ligation of the round ligaments and utero-ovarian bilateral pedicle (Figure 4) are performed. At this stage, the risk of bleeding is from excessive upward traction of the uterus from the lateral straight clamps.

(7) Retroperitoneal Dissection

Skeletonization of the uterus down to the cardinal ligaments and opening of the paravesical spaces occur. It also includes a cephalad pelvic sidewall dissection, medially of the psoas muscle to locate the common iliac artery and the external iliac vein and artery. Then, there is exposure of the internal iliac artery and medially the ureters, where ureterolysis is performed (establishing a safe distance between the ureter and the cardinal ligament) (Figure 5). An alternation of this step is the ligation of the internal iliac arteries, 3-5 cm distal from their separation. The exposed arteries could be either sutured or left with a suture loop, for later rapid ligation if severe hemorrhage occurs. Aortograms showed that the low immediate effectiveness of this ligation was substantially diminished by the presence of other pelvic anastomoses [114]. As a result, any clinical benefit in blood loss from this intervention is only short-term and less than 20 minutes in duration.

(8) Bladder Dissection

This step is prolonged compared to the nonobstetric hysterectomy, up to 30-40 minutes. At this step, severe hemorrhage may occur. In most women, due to prior cesarean sections, the bladder top is located more cephalad than normal, therefore tempting the surgeon to start the dissection higher (line B at Figure 6) to avoid bladder injury, traumatizing the engorged vessels, causing severe hemorrhage. Cautious lateral to medial dissection is performed, including dividing the engorged blood vessels and adipose layer down with the bladder. Filling the bladder with 100-300 ml of methylene blue could help identify the superior bladder wall margin (line A at Figure 6). This helps to identify the engorged vessels and carefully avoid them (Figure 6). In case of bladder invasion from the placenta, this step is modified, and intentionally cystotomy is performed with resection of the affected portion of the posterior wall of the bladder en bloc with the uterus, followed by bladder repair (Figure 7) [115]. In case of parametrial placenta invasion, extensive retroperitoneal dissection might be required, in order to achieve hemostasis, or a subtotal hysterectomy could be performed [116].

(9) Colpotomy

This step also has a high risk of severe hemorrhage. Adequate exposure for the vault entry is created, the main uterine artery pedicles are ligated, and the vaginal angles are secured. The uterine side should remain clamped or ligated using "double distal edge pickup", to avoid blocking the view from the forceps (Figure 8). Then, colpotomy is performed, and the uterus is removed. The incised edges are clamped incrementally as the vault is opened, in order to minimize blood loss from the margins, followed by suturing of the vault.

Last but not least, it is of high importance that centers which treat patients with PAS disorders follow standardized protocols with a multidisciplinary strategy (Figure 9). This protocol should include pre-, intra-, and postoperative information about the treatment plan of patients with PAS disorders [52]. Briefly, patients should be admitted at 33-34 weeks of gestation, and a planned hysterectomy should be performed at 34-35 weeks of gestation. All referred patients should undergo an ultrasound examination to confirm the diagnosis, and in cases of lateral or posterior placentation, MRI might be considered. Combined spinal-epidural anesthesia should be offered, and if needed, ureteral stents can be placed. Before induction of general anesthesia, large-bore venous lines, an arterial line, and a central venous line should

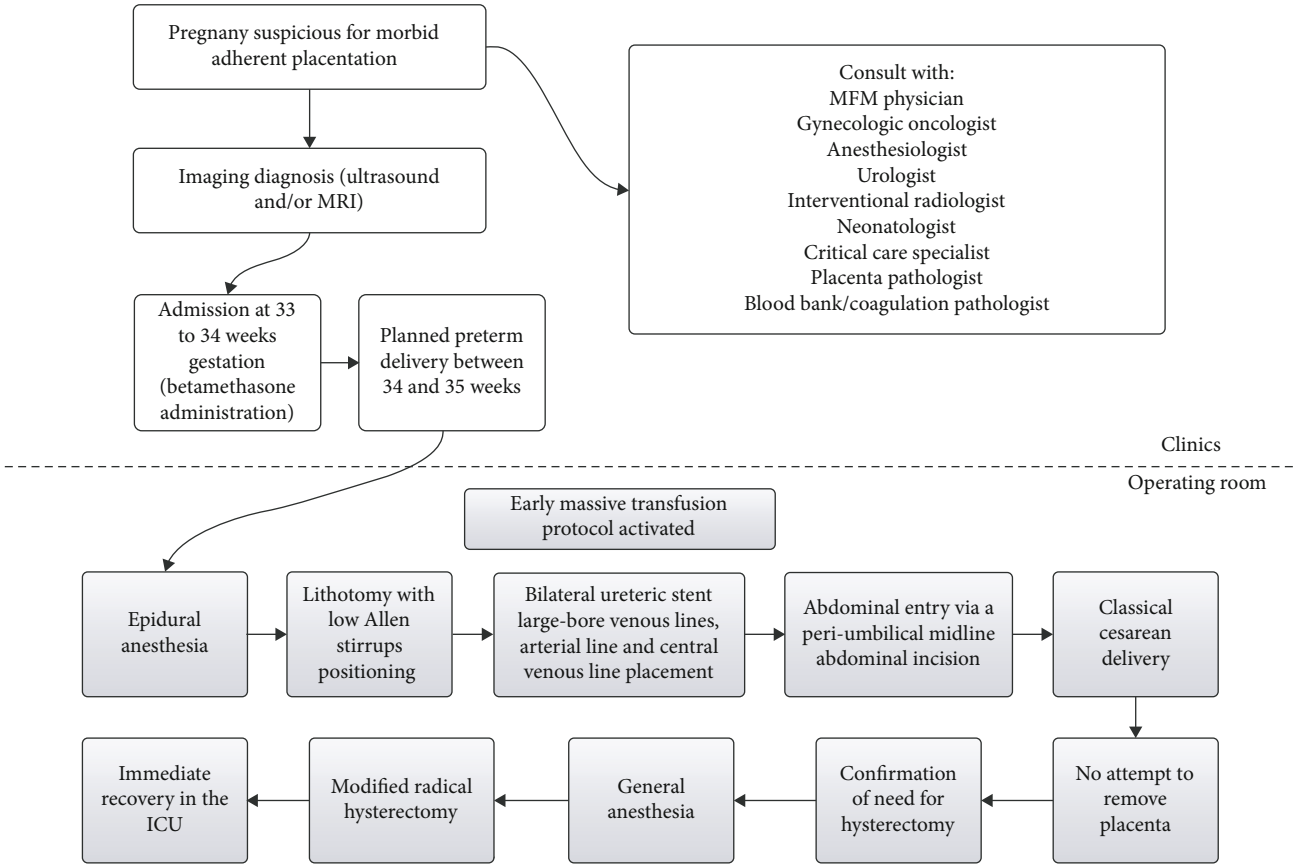

Figure 9: Multidisciplinary protocol for PAS disorders (from Shamshirsaz et al. [52] with permission).

be placed. All patients receive underbody and overbody forced air warming plus warmed intravenous infusions. Patients are in lithotomy position with low Allen stirrups to allow visualization of the vaginal bleeding. An abdominal entry is created through a periumbilical midline incision and exteriorization of the pregnant uterus, to allow a fundal or posterior hysterotomy, avoiding the placenta. The placenta is left in situ, without any attempt of removal. 500 ml albumin 5% was administered, before the start of the hysterectomy, because acute volume expansion with colloid reduces intraoperative crystalloid requirement and facilitates hemodilution before hemorrhage [117]. A modified radical hysterectomy technique, which includes ureterolysis, should be performed, with extensive use of a bipolar cautery device (LigaSure). This technique ensures wide enough margins from the friable uterine wall and its fragile vessels. The retroperitoneum should be accessed lateral to the round ligament, exposing the iliac vessels and the ureters. The ovaries can be preserved, but the fallopian tubes should be removed. Ureterolysis should be performed to protect the ureters and allow step-by-step devascularization of the lower segment of the uterus. The engorged vessels between the bladder and the uterine lower segment can be identified and cauterized much easier after the exposure of the lateral anatomy. In cases of deep placenta invasion of the bladder, cystotomy and bladder repair should be preferred instead of persistent attempts of bladder dissection, minimizing blood loss. During hemorrhage, early blood product replacement, using a massive transfusion protocol (PRBCs and frozen plasma in a 1 : 1 ratio), should be encouraged, and electrolyte, ionized calcium, and potassium levels should be measured. In cases of acute-severe hemorrhage, complete laboratory tests can be drawn every 20 minutes. Postoperatively, all patients should receive immediate recovery in the ICU after the operation.

5. Conclusions

Hysterectomy is an uncommon procedure for obstetric patients; however, it is the final step of every PPH management protocol. Pregnancy-related hysterectomy might have the same surgical steps as a nonobstetric hysterectomy, but special knowledge is needed in order to prevent severe hemorrhage. It is a life-saving procedure, but with substantial maternal morbidity and mortality. It is of high importance for healthcare professionals to understand that a multidisciplinary management strategy is needed in order to successfully perform this type of hysterectomy, but all obstetricians should know the basic steps and possible complications during a pregnancy-related hysterectomy, in order to successfully perform one in an emergency case. The commonest indications of pregnancy-related hysterectomy are uterine atony, followed closely by PAS disorders. PAS is showing a rapid increase in the last decades, and given the increased rates of cesarean sections, its incidence is likely to increase even more over time. Therefore, physicians

should be aware of this pathology and its difficulties in diagnosis and management.

Furthermore, it should be mentioned that the surgical steps—tips and generally the management algorithms—proposed in this narrative review of the literature are based on low-quality studies (mainly retrospective case series), but from high-quality centers with a multidisciplinary approach. The aim of this study was to offer up-to-date knowledge about the latest data on the management of pregnancy-related hysterectomy, but obstetricians should remember that surgical steps might differ from center to center and a risk of bias is possible. Future studies should focus on the collection of high-quality data from well-designed prospective studies on diagnosis (antenatal imaging) and a multidisciplinary team approach for the management strategy.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Review Article

Current Role of Hysterectomy in Pelvic Floor Surgery: Time for Reappraisal? A Review of Current Literature and Expert Discussion

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Since hysterectomy could be performed with low risk, it has been part of the standard of surgical prolapse therapy for decades. This has not been scrutinized for a long time. In this review, we describe the development of this issue in recent years. The current literature suggests that hysterectomy requires its own indication. The article describes the various options for a uterine-preserving surgical technique and the available data.

1. Introduction

Most of the literature on which the article is based was researched via PubMed (2020). In addition, we have used historical book literature for the introduction. Surgical techniques for the correction of vaginal prolapse have been in use since the 19th century [1]. These were aimed at the narrowing of the vaginal canal, and hysterectomy did not play an integral part in addressing prolapse. At the beginning of the 20th century, the Manchester-Fothergill operation was introduced [1]. This procedure is based on the amputation of the cervix and relocation of the suspending ligaments to the lower corpus uteri. This technique is still in use today, but unfortunately, there is limited data on complications, long-term effects, or success rates.

Other techniques, such as those described by Schauta, Wertheim, and Watkins, utilized the uterus as a support by steeply anteverting it and then sewing it to the anterior vaginal wall [1]. Like the Manchester operation, uterine interposition has long had supporters in Scandinavia. As these techniques predate rigorous modern scientific assessment, empiric data is lacking. The first sacropexy was described as early as 1920 in Germany. Either the uterus or the vault was sutured to the promontory via laparotomy.

The indications for a hysterectomy as part of a prolapse operation have repeatedly changed, as described in a German study over the period from 1960 to 1985. Only 24.3% of the prolapsed interventions were combined with a hysterectomy between 1960 and 1963, while between 1978 and 1985 97.7% of the interventions were combined with a hysterectomy [2]. The indications for the inclusion of a hysterectomy were mainly cancer prevention and birth control. The hysterectomy offered no improvement in the long-term success of the prolapse procedure. On the contrary, DeLancey stressed the importance of the paracervical structures as early as 1992 for the prevention of cystocele and rectocele [3]. Disadvantages of uterine conservation have not yet been reported. A new study from the Netherlands has investigated the sacrospinous fixation with uterine preservation versus the combination with a hysterectomy. Superiority for uterine preservation was determined [4] (follow-up after 5 years: 87% versus 76%). These results are not surprising since, for example, problems with the mesh fixation in combination with hysterectomy are known in sacropexy [5]. The study

would be more meaningful if the technique had also been compared with patients who had had a previous hysterectomy.

A meta-analysis from 2018 describes generally shorter operation times, lower blood loss, and lower mesh exposure rates when the uterus is preserved. The analysis is based on 54 abstracts that compared vaginal and abdominal procedures with and without hysterectomy. Although the essential results (less operating time and blood loss) were to be expected, the analysis supports the advantage of attaching mesh or suture material to the cervix [6].

There are certainly clear indications for a hysterectomy that are medically justified. A German study group has defined the following indications and recommended them as German S3 guidelines: symptomatic fibroids or painful adenomyosis, recent or previous cervical pathology, abnormal or postmenopausal bleeding, tamoxifen therapy, familiar BRCA 1 and 2 risk, status post hereditary nonpolyposis colorectal cancer with 40-50% lifetime risk of endometrial cancer, and no regular gynecological follow-up assured [7]. These indications are however not mandatory in all cases, since hysterectomies are still possible after a prolapse operation.

A 2010 study with a cohort of 501 patients reported that the risk of missing an endometrial malignancy is approximately 0.8% [8]. Unfortunately, the cohort is too small to allow for generalization. In our own data, we found 2 endometrial cancers in 600 procedures with hysterectomy (0.03%) and none in the hysteropexy group to date. Larger studies are needed to determine the true incidence; however, 0.5% seems likely.

One important consideration should be the patient's desire. A study from 2013 investigated reasons for hysterectomy as reported by patients; 213 women were interviewed at multiple centers. Only 20% of the women desired a hysterectomy while 36% were clearly opposed to it. In the second group, a fifth would have accepted a poorer outcome, while 44% were unable to commit themselves [9]. In addition to the possibly better outcome, we currently see the desire to retain fertility and the desire to preserve the physical integrity of the body as reasons for maintaining the uterus.

Vaginal as well as laparoscopic techniques are available in many centers today. While sacropexy is considered an established practice, the study data for vaginal techniques (especially vaginal meshes) are limited. In 2013, the data of 507 women who underwent laparoscopic hysteropexy over a period of 10 years were retrospectively examined [10].

Outstanding features of the study were a low complication rate of 1.8% and no mesh exposure. The hysteropexy could not be completed in 17 patients (3.4%). A total of 93.8% of the patients stated that their prolapse was "very much" or "much" better. Only 2.8% required repeated apical surgery.

Based on the literature, one can state that the preservation of the apical structures has a positive effect on operative data and long-term results. We have already listed clear indications. The question is that are there any other indications for a hysterectomy? With an abdominal approach, a large uterus can cause technical difficulties. This relates to access to the operative field and difficulties in bringing in additional meshes. There are no data in this regard, only expert recommendations. A recommendation based on weight or size would be difficult to define, since all local conditions in the pelvis have to be taken into account. With a vaginal approach, there are fewer limitations due to the size of the uterus.

2. Available Techniques

2.1. Vaginal Techniques. For several decades, the sacrospinous ligament was used for apical fixation. Sacrospinous fixation was introduced in the 1950s [11]. It was used all over the world and was a great advancement in vaginal apical fixation. It could be combined very well with a colporrhaphy, but anatomically, it had the disadvantage that it was a unilateral suspension so that the vaginal axis shifted. A 2013 Cochrane analysis looked at randomized trials that compared vaginal (especially sacrospinous fixation) and sacrocolpopexy (SC). The review showed the superiority of SC, but also highlighted the significantly longer operating times and the longer learning curve for SC [12].

After emerging criticism of mesh surgery and severe restrictions or even bans on these technologies, the sacrospinous fixation was revived. It is still performed according to the traditional method or with the help of suturing devices to fix the sutures [13]. Numerous companies offer small meshes instead of sutures to improve the result. The meshes are fixed with sutures or anchors. Similar to the traditional procedure, the anchors or sutures are placed in the ligament close to the pudendal nerve. The execution of the techniques under direct vision is very difficult and is therefore usually done blindly under the guidance of the index finger. Therefore, good surgical skills and extensive training are necessary. Incorrect placement can result in very uncomfortable long-term consequences for the patient. So far, only relatively limited data from single-center studies are available [14, 15]. These studies report excellent results for the combination of bilateral mesh-assisted sacrospinous fixation with traditional colporrhaphy.

A review published in 2021 reports, among other things, 300 mesh-supported hysteropexies carried out in a German single center. The author states that the technique can be completed in just 22 minutes and provides excellent results. Despite the high number, unfortunately, no study has been published in this regard yet [16]. Most publications relate to short-term data with no results for long-term mesh-related complications that can arise from fibrosis or mechanical stress or irritation. The same applies to traditional methods such as the Manchester-Fothergill technique or high-uterosacral fixation. The literature search yielded a handful of small studies and case reports. Neither randomized nor prospective studies are available in published form.

The culdoplasty procedure, often referred to as the McCall technique, is used to prevent prolapse after a hysterectomy. As part of the general mesh discussion, these techniques are also recommended as native tissue apical repair techniques at conferences. This can of course also be thought of as a uterus-preserving technique. There is also no usable data in this regard. Schiavi et al. compared two suturing techniques for culdoplasty and found the preventive value of both techniques. Suspension sutures were performed in all

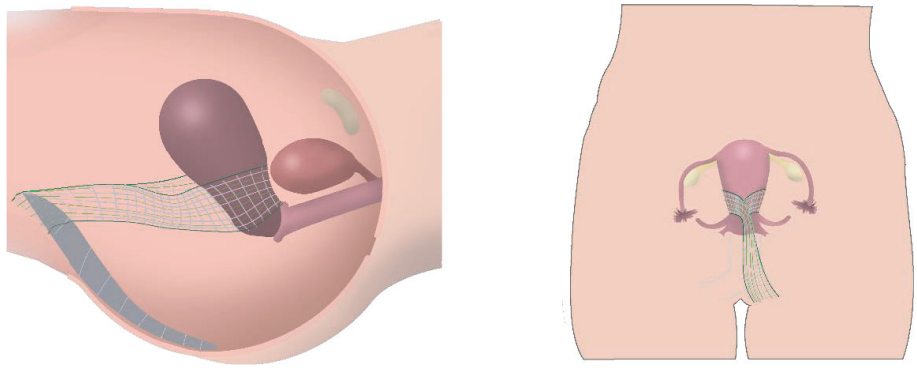

Figure 1: Hysterosacropexy in Oxford technique.

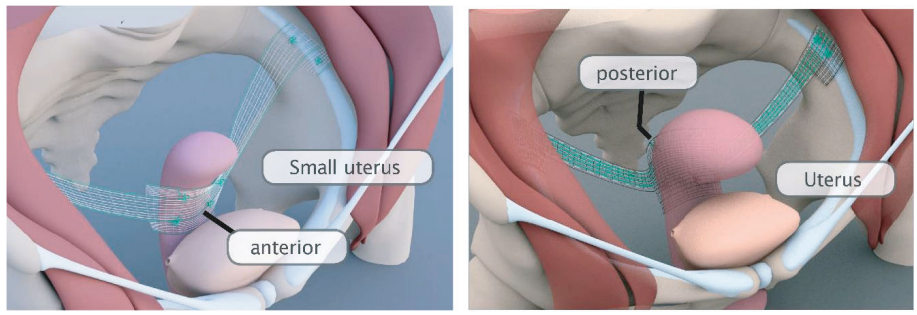

Figure 2: Anterior fixation and posterior fixation in hysteropectopexy with PRP 3 × 15 or PRP 3 × 18, respectively.

patients in both study groups. There was no control group in the study, and it did not provide an analysis of the general risks of a pelvic floor defect. Despite these fundamental study flaws, the authors come to the conclusion that the method is effective [17]. Therefore, there is a lack of real evidence for the efficacy of these procedures as prophylaxis and they cannot be recommended as a replacement for apical fixation. A study that proves the efficacy of what is known as prolapse hysterectomy should not go unmentioned. Similar to the Manchester technique, the technique is based on the high-level integration of the uterine ligaments [18]. Even if the data are convincing, the complete lack of real long-term data, randomized studies, or multicenter applications also applies here.

2.2. Laparoscopic Procedures. In laparoscopy, sacropexy dominates due to its widespread use. Very often it is combined with subtotal hysterectomies or with a total hysterectomy. For the latter, there is a higher exposure rate to consider [5]. Unfortunately, there are no case numbers on the frequencies of the procedures used. Currently, it can still be assumed that one of the forms of hysterectomy is used in the majority of cases [19]. Different procedures are described in the literature for hysteropexy. On the one hand, a mesh is only attached between the sacrum and the posterior wall of the cervix, while others carry out bilateral fixations and sew a mesh onto or through the posterior wall of the cervix [20]. An often-cited surgical approach is a method known, among others, as the Oxford technique (Figure 1). A caudally 2-armed mesh is passed through a window in the broad ligament and tied anteriorly to the cervix [21]. The cranial portion is then attached to the promontory, and the mesh is then peritonealized.

In 2016, Jefferis et al. published a 10-year follow-up with highly satisfying data. The majority of the patients had been treated in the 6 years before the evaluation (after completing the learning curve). Only 2.8% of the women had to undergo another operation and stated a high level of satisfaction. The intraoperative complication rates were also very low. The surgical method therefore seems to be very safe and successful. One weakness of the study is that the patients were not physically reexamined and the data related to returnees and records. In addition, there is a lack of randomized prospective studies or even multicenter analyses when used outside of a specialized center.

Another surgical technique that is often used is the lateral suspension. So far, there is little published study data for the procedure and no description of the hysteropexy.

In 2010, the laparoscopic pectopexy was first published with a small pilot study [22]. After initial prospective randomized study, the safety of the technology in widespread use was proven by a multicenter study with 11 clinics and 13 surgeons [23]. The follow-up to this study was also able to demonstrate the high effectiveness of the technology [24]. Hysteropexy can also be performed with this technique. Small uteri can easily be fixed anteriorly to the standard mesh. For larger uteri, an extended mesh was developed (Figure 2) (DynaMesh PRP 3 × 18) which enables the uterus to be picked up dorsally. The dorsal fixation is done to prevent retroflexion. The PRP 3 × 15 can be attached directly

Table 1: Hysteropexy studies 2010-2021.

Author	Technique	DOI	rT	Multicenter	Single center	Prospective	Follow-up time	Outcome	*n*
Veit-Rubin	Lateral suspension	10.1007/s00192-015-2859-6	No	No	Yes	No	1 year	82.7% success	250
Yassa	Lateral suspension	10.1055/a-0941-3485	No	No	Yes	No	2 years	94.12	17
Detollenaere	Sacrospinous hysterectomy versus preservation	10.1136/bmj.h3717	Yes	Yes	No	Yes	1 year	Similar outcome in both groups	208
Lo	Sacrospinous hysterectomy versus preservation	10.1111/jog.12678	No	No	Yes	No	7 years	Similar outcome	146/26
Nager	Sacrospinous hysterectomy versus preservation	10.1016/j.ajog.2021.03.012	Yes	No	Yes	Yes	5 years	Hysteropexy with mesh is superior to hysterectomy with uterosacral suture suspension	
Gutman	Vaginal versus laparoscopic hysteropexy		No	No	Yes	No	1 year	Similar anatomical outcome vaginal mesh exposure 3 times higher	150
Price	Sacropexy	10.1111/j.1471-0528.2009.02396.x	No	No	Yes	No	3 months	High satisfaction	51
Jefferice	Sacropexy	10.1007/s00192-016-3257-4	No	No	Yes	No	3 months	92%	498
Li	Sacropexy	10.4103/tcmj.tcmj_131_19	No	No	Yes	No	1 year	Similar outcome	26
Pan	Sacropexy TLH versus hysteropexy	10.1007/s00192-015-2775-9	No	No	Yes	No	1 year	Similar outcome	99
Van IJsselmuiden	Sacropexy versus sacrospinous	10.1111/1471-0528.16242	Yes	No	Yes	Yes	1 year	Anatomical similar LSH defecation disorders and OAB more frequent, less dyspareunia	126
Letouzy	Ant mesh repair	10.1007/s00192-015-2748-z	No	No	Yes	No	1 year	92% 8% exposure	114

No data for uterus weight or other distinguishing features for indication available.

to the uterus with a PVDF (polyvinylidene fluoride) thread without the need for peritonealization. This is possible because both the mesh and the thread are made of PVDF and thus do not provoke any adhesions. The lateral arms are passed through a small window in the broad ligament and then typically fixed laterally (Table 1 gives an overview on the current studies dealing with hysteropexy).

3. Conclusion

Today, it is undisputed that the hysterectomy itself does not make a significant contribution to the correction of pelvic floor defects. In fact, there are rather clear indications that the procedure is disadvantageous. Longer operating times and higher mesh exposure rates in total hysterectomy are documented. Few true indications are clear, and some are relative as described above. The influence of uterus size on abdominal procedures is unclear. The size ratio between the pelvic space and the uterus should allow a smooth operation. Ultimately, this must be decided by the surgeon and, if possible, planned ahead. Both vaginal and abdominal procedures for hysteropexy are available. Abdominal, predominantly laparoscopic surgical techniques have been scientifically proven. Some of the newer vaginal procedures are very promising, but require well-structured, scientific research, especially with regard to the mesh problem of recent years.

Surgical technique today should be resilient with regard to the skills of the surgeon. Since urogynecological interventions are carried out worldwide and not exclusively by specialists, techniques should be investigated in their broad application. This requires multicenter studies. Too many techniques are said to be simple, and even less well-trained surgeons may be tempted to perform them. This has also been one of the problems with vaginal mesh surgery. The removal of the uterus should always be subject to strict indications, and the reflex hysterectomy should be relegated to the past. As previously noted, there is a long tradition of hysterectomy as part of prolapse surgery, so research must further specify the indications.

Data Availability

All data are related to the cited references in the manuscript.

Conflicts of Interest

All 4 authors have no conflict of interest regarding the content of the article.

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