**BACKGROUND:** Placenta percreta is described as the most severe grade of placenta accreta spectrum and accounts for a quarter of all cases of placenta accreta spectrum reported in the literature.

**OBJECTIVE:** We investigated the hypothesis that placenta percreta, which has been described clinically as placental tissue invading through the full thickness of the uterus, is a heterogeneous category with most cases owing to primary or secondary uterine abnormality rather than an abnormally invasive form of placenta.

**STUDY DESIGN:** We have evaluated the agreement between the intraoperative findings using the International Federation of Gynecology and Obstetrics classification with the postoperative histopathology diagnosis in a prospective cohort of 101 consecutive singleton pregnancies presenting with a low-lying placenta or placenta previa, a history of at least 1 prior cesarean delivery and ultrasound signs suggestive of placenta accreta spectrum. Furthermore, a systematic literature review of case reports of placenta percreta, which included histopathologic findings and gross images, was performed.

**RESULTS:** Samples for histologic examination were available in 80 of 101 cases of the cohort, which were managed by hysterectomy or partial myometrial resection. Microscopic examination showed evidence of placenta accreta spectrum in 65 cases (creta, 9; increta, 56). Of 101 cases included in the cohort, 44 (43.5%) and 54 (53.5%) were graded as percreta by observer A and observer B, respectively. There was a moderate agreement between observers. Of note, 11 of 36 cases that showed no evidence of abnormal placental attachment at delivery and/or microscopic examination were classified as percreta by both observers. The systematic literature review identified 41 case reports of placenta percreta with microscopic images and presenting symptomatology, suggesting that most cases were the consequence of a uterine rupture. The microscopic descriptions were heterogeneous, and all descriptions demonstrated histology of placenta creta rather than percreta.

**CONCLUSION:** Our study supported the concept that placenta accreta is not an invasive disorder of placentation but the consequence of postoperative surgical remodeling or a preexisting uterine pathology and found no histologic evidence supporting the existence of a condition where the villous tissue penetrates the entire uterine wall, including the serosa and beyond.

**Key words:** placenta accreta, placenta percreta, placenta previa accreta, uterine adhesion, uterine rupture, villous invasion

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**Introduction**

Placenta percreta is described as a full-thickness myometrial invasion by placental tissue in the setting of placenta accreta spectrum (PAS) sometimes reaching and disrupting the adjacent pelvic organs and vasculature. The term “placenta percreta” was first used in 1950 by McCarthy and Nichols. By 1956, only 8 cases had been reported in the medical literature, all associated with a uterine rupture. Modern histopathologic cohort studies have reported on the different grades of villous invasion in accreta placentation (ie, placenta creta, placenta increta, and placenta percreta) and suggested that they can coexist in the same specimen. Similarly, authors of textbooks on the pathology of the human placenta have described, in detail, individual cases of placenta percreta. However, reported histologic criteria for percreta are heterogeneous, with most authors describing injury or remodeling of the underlying uterine wall or extension of the trophoblastic cells into tissues other than the uterine smooth muscle, in addition to the classic histologic criteria showing gaps in the decidual layer with direct attachment of villous tissue to the myometrium, as originally described by Irving and Hertig in 1937. Overall, the reporting of placenta percreta in the literature is based on the gross findings of hysterectomy specimens presenting with villous tissue having penetrated through the entire uterine wall, and textbook descriptions are illustrated by diagrams showing placental villi protruding into the peritoneal cavity after crossing the myometrium and uterine serosa. These diagrams have been used by many authors of diagnostic and management studies to describe the different grades of PAS. Luke et al. reported that most hysterectomy specimens arrive at the laboratory distorted by attempts to remove the placenta during delivery, limiting considerably the macroscopic examination and sampling and adding to the confusion in reporting different grades of PAS in both epidemiologic and clinical studies. Furthermore, in cases of PAS where the placenta abuts the uterine serosa, the villous tissue is almost always contained within the scar shelf before delivery, and it is the surgical manipulation and complex dissection that expose the underlying placental tissue often leading to false clinical diagnosis of placenta percreta.
Why was this study conducted?
This study aimed to evaluate the current clinical and histopathologic criteria used to diagnose and confirm placenta percreta at delivery.

Key findings
Our cohort study and systematic review of case reports described as placenta percreta in the literature found no histopathologic evidence of transmural villous tissue invasion into the uterine serosa and/or pelvis.

What does this add to what is known?
This study has provided meaningful clinical and histopathologic data indicating that placenta accreta spectrum is not an invasive disorder of placentation but the consequence in most cases of postoperative surgical remodeling.

Most authors of PAS cohort series do not provide complete information on gross and microscopic findings, such as a cross-sectional gross image of the area of uterine penetration. Not surprisingly, the incidence of placenta percreta reported in those studies ranges between 6.6% and 51.9% (average 22.1%) in general population studies and between 2.4% and 35.3% (average 13.4%) in diagnostic studies of placenta previa accreta. To standardize the definition of PAS categories, the International Federation of Gynecology and Obstetrics (FIGO) has recently proposed a new classification for the diagnosis and grading of PAS, which includes clinical criteria at delivery confirmed by histopathologic findings of villous adherence or invasiveness. The main objective of this study was to prospectively evaluate the agreement between diagnosis of FIGO grade 3 (percreta) based on antepartum hemorrhage (APH) and/or premature labor.

Macroscopic features during surgery and gross examination of the hysterec- tomy specimens were recorded using an image capture digital photographic protocol as previously described. Depending on the size of the adherent area, 2 to 6 samples of the full thickness of the uterine wall with a third of the placcental thickness were obtained from the areas of abnormal attachment, processed for histologic examination, and stained with hematoxylin and eosin.

In the present study, 2 specialist research fellows in obstetrics and gynecology (R.A.E. and R.M.E.), with 3-year experience in the MDT, reviewed the intraoperative gross findings of the whole cohort independently and graded them using the FIGO classification. They were blinded to the surgical outcome, histopathology data, and examination results of each other. All records were examined within the research center, and all images were anonymized for data analysis. Institutional Scientific and Research Ethical Committee approval (RSEC 021001) was obtained before the start of this study, and all patients consented to the use of the photographic images obtained before and during delivery.

Systematic literature review eligibility criteria, information sources, and search strategy
A systematic review was undertaken of articles describing case reports of placenta percreta. PubMed, Google Scholar, and MEDLINE were searched for articles published between the first prenatal ultrasound description of PAS in August 1982 by Tabsh et al and April 2021 (Supplemental Table). The search protocol was designed a priori and data reported as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 guidelines (www.prisma-statement.org). The overall search strategy was inclusive of Medical Subject Headings for the following terms “placenta accreta,” “placenta increta,” “placenta percreta,” “abnormally invasive placenta,” “villous invasion,” and “morbidly adherent placenta.” We combined these with terms related to “uterine rupture,” “peripartum hysterectomy,” and “cesarean hysterectomy.” Titles, abstracts, and full texts were independently assessed by the authors (E.J. and R.A.E.) for content, data extraction, and analysis. Additional relevant studies were identified from reference lists of reviews and editorials. Duplicates were removed by hand. The search was limited to articles published in English.

Study selection
Two independent investigators (E.J. and R.M.E.) selected studies in 2 stages. The abstracts of all potentially relevant papers were individually examined for suitability. Papers were only ruled out at this stage if they did not meet the inclusion criteria. The remaining papers were obtained in full text and were independently assessed for content, data extraction, and analysis. Disagreements between the 2 original reviewers were resolved by discussion with the third investigator (A.M.H.). We excluded studies published before July 1982, cohort studies, and case reports
containing no microscopic image of the histologic diagnosis.

**Data extraction**
Study characteristics were subsequently extracted independently by 2 reviewers (M.M.T. and A.M.H.) using a predefined data extraction form that included all studies: year of publication, country of origin, gravidity, parity, maternal age, surgical history macroscopic images, microscopic images, and corresponding legends. The primary outcomes were the evaluation of different criteria used for intraoperative diagnosis of PAS and the histologic confirmation of the diagnosis. The secondary outcomes included the clinical background data, including the medical and surgical history and main clinical symptoms.

The gross images were reviewed for the morphologic appearance, and histologic images were analyzed for the presence of villous invasion, depth of villous invasion, depth of extravillous trophoblastic (EVT) migration, and structure of the uterine wall underneath the basal plate of the placenta (E.J. and J.L.H.) using the new classification and reporting guidelines for the pathology diagnosis of PAS.²

**Statistical analysis**
Stata/IC (version 15.0; StataCorp LLC, College Station, TX) was used to analyze the data. A standard Kurtosis analysis indicated that the demographic values were normally distributed, and therefore, data were presented as mean and standard deviation. Intraoperative findings were graded using the FIGO classification. Because of the ordered categorical nature of the outcome, the interobserver agreement was assessed using the weight value of the kappa method, which measures the agreement over and above that which would be expected because of chance. The kappa analyses were first performed using the 5 individual categories of the FIGO classification. The analysis was repeated combining the grade 3 categories (3a, 3b, and 3c) into 1 category. Kappa statistics and percentage agreement were reported according to Landis and Koch.²³ Kappa values of 0.61 to 0.80 were interpreted as substantial, whereas values between 0.81 and 1.00 were interpreted as excellent agreement.

**Results**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean maternal age (y)</td>
<td>31.3 (4.4)</td>
</tr>
<tr>
<td>Mean gravidity</td>
<td>4.7 (1.8)</td>
</tr>
<tr>
<td>Mean parity</td>
<td>3.1 (1.3)</td>
</tr>
<tr>
<td>Mean number of previous CD</td>
<td>2.8 (1.7)</td>
</tr>
<tr>
<td>Mean gestational age at delivery (wk)</td>
<td>36.1 (1.3)</td>
</tr>
</tbody>
</table>

**Surgical outcome**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD hysterectomy</td>
<td>73 (72.3)</td>
</tr>
<tr>
<td>Conservative management</td>
<td>28 (27.7)</td>
</tr>
</tbody>
</table>

**Results of histologic examination (n=80)**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAS: creta</td>
<td>9 (11.3)</td>
</tr>
<tr>
<td>PAS: increta</td>
<td>56 (70.0)</td>
</tr>
<tr>
<td>No evidence of PAS</td>
<td>15 (18.7)</td>
</tr>
</tbody>
</table>

The data are presented for 101 cases.

CD, cesarean delivery; PAS, placenta accreta spectrum; SD, standard deviation.

categories were examined separately or whether they were combined, indicating a “moderate” agreement between the 2 observers.

Of note, 11 cases that were classified as percreta 3a (n = 9), 3b (n = 1), 3c (n = 1) by both observers intraoperatively (Figures 1 and 2) were found to be placenta previa nonaccreta with no evidence of abnormal placental attachment at delivery.

**Systematic review–report characteristics**

The initial search provided 819 records with cross-referencing providing an additional 14 studies, making a total of 833 potentially relevant articles (Figure 3). After the exclusion of duplicates, 805 articles remained. On screening the titles and abstracts, 637 articles were excluded as the reported outcomes were not relevant (cohort studies, letters, and expert reviews), leaving 168 articles that were obtained for full-text review. An additional 127 articles were excluded after full review as they included diagnosis and management before 13 weeks of gestation and/or contained no histologic images, leaving 41 articles for the final analysis.

**Synthesis of results**

Table 3 displays the maternal characteristics, presenting symptoms, and surgical outcome data of the 41 case reports included in the review.24–61 In 24 cases, the patients had a history of at least 1 CD. Moreover, 5 patients were primiparous, including patients with a previous radiotherapy (2 for childhood cancer, 1 for sarcoma,32 and 1 for leukemia38), and 1 patient has had a previous myomectomy.64 In 1 case, the patient had a previous history of myomectomy followed by uterine rupture in her first pregnancy. The most common presenting symptom was sudden severe pelvic, suprapubic, or abdominal pain, which was reported in 17 cases (41.5%). Of note, 1 patient with a history of 2 previous CDs and ultrasound features of placenta previa accreta was reported to arrive pulseless in the hospital, with no fetal heart activity.61 After failed resuscitation attempts, both the mother and fetus were confirmed deceased. A stillbirth was reported on admission in 1 case.37 A primary hysterectomy was performed in 33 cases (80.5%). Conservative management with uterine preservation was successful in 6 cases (14.6%). Maternal intraoperative death owing to uncontrollable bleeding was reported in 1 case.31 Moreover, 2 hysterectomies were performed postmortem.

Table 4 presents the histopathologic findings reported in the 41 case reports included in the review. There was no gross image available in 13 cases. The remaining 28 cases included intraoperative images in 10 cases,25,35,40,45,48,52,55,59,61,63 immediate postoperative images of hysterectomy specimens in 2 cases,33,57 laboratory gross images in 10 cases,26,30,36,39,42,43,46,47,50,56 and combined intraoperative and postoperative images in 6 cases.7,49,51,54,58,62 The most common macroscopic description (13 of 28 cases [46.4%]) was that of uterine rupture with bulging of the

### TABLE 2

Distribution for the placenta accreta spectrum grading based on the intraoperative findings in the 101 cases of the cohort using the International Federation of Gynecology and Obstetrics’ classification1 and final histopathologic diagnosis in the 80 cases that required a hysterectomy or partial myometrial resection placenta accreta spectrum

<table>
<thead>
<tr>
<th>FIGO grade</th>
<th>Observer A, n (%)</th>
<th>Observer B, n (%)</th>
<th>Final histopathologic diagnosis, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No evidence of PAS</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>15 (14.9)</td>
</tr>
<tr>
<td>Grade 1 Creta: uterus macroscopically normal. No separation with synthetic oxytocin and gentle controlled cord traction or attempts at manual removal of the placenta results in heavy bleeding from the placenta implantation site requiring mechanical or surgical procedures.</td>
<td>15 (14.9)</td>
<td>14 (13.9)</td>
<td>9 (8.9)</td>
</tr>
<tr>
<td>Grade 2 Increta: bluish purple coloring and distension of the uterine wall over the placental bed with significant amount of hypervascularity. Gentle cord traction results in the uterus being pulled inward without separation of the placenta. No placental tissue seen invading through the surface of the uterus.</td>
<td>42 (41.6)</td>
<td>33 (32.7)</td>
<td>56 (55.5)</td>
</tr>
<tr>
<td>Grade 3 Percreta: same as increta with placental tissue seen to be invading through the surface of the uterus.</td>
<td>—</td>
<td>—</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Grade 3a: Limited to the uterine serosa.</td>
<td>23 (22.8)</td>
<td>33 (32.7)</td>
<td>—</td>
</tr>
<tr>
<td>Grade 3b: Placental villi are seen invading into the bladder but not into other organs, and clear surgical plane cannot be identified between the bladder and uterus.</td>
<td>19 (18.8)</td>
<td>13 (12.8)</td>
<td>—</td>
</tr>
<tr>
<td>Grade 3c: Placental villi are seen invading into the broad ligament, vaginal wall, pelvic sidewall, or any other pelvic organ (with or without invasion of bladder)</td>
<td>2 (1.9)</td>
<td>8 (7.9)</td>
<td>—</td>
</tr>
</tbody>
</table>

FIGO, International Federation of Gynecology and Obstetrics; PAS, placenta accreta spectrum.

placenta or both placenta and fetus. Ruptures were reported as fundal in 3 cases and cervical in 1 case. The other descriptions included areas of placenta protruding through the uterine wall or invading the entire anterior wall to the serosa or laterally into the parametrium or bladder or ileum. In 10 cases, the review of the published macroscopic images identified dehiscence of the uterine wall covered by an intact serosa shell.

Chorionic villi invading or infiltrating the full thickness of the uterine wall or deep into the myometrium, close to the serosa, was the most common (19 of 41 cases [46.3%]) reported histologic feature (Table 4). The depth of the trophoblastic invasion and villi attached to the myometrium without intervening decidua or Nitabuch layer was reported by 7 and 5 authors, respectively, as their main criteria for the diagnosis of placenta percreta. The review of the published microscopic images found chorionic villi directly apposed to a morphologically normal myometrium in 13 cases, to a scarred uterine myometrium in 9 cases, and to both normal and scarred myometrial tissues in 4 cases. In 2 cases, the villi were apposed on the cervical stroma, and in 3 cases, the villi were bounded by fibrinoid. In 1 case, EVTs might be present in the bowel fat tissue outside a scarred uterine wall after myomectomy. Overall, microscopic examination found no evidence supporting the diagnosis of PAS in 12 cases.

Comment
Principal findings of the study
Our cohort study and systematic review of case reports described as placenta percreta in the literature found no documentation of villous tissue invading the full thickness of the myometrium; in particular, no histologic sample or literature image showed transmural villous invasion. The main intraoperative features and histologic findings suggested that most, if not all, cases reported as
placenta percreta in the literature were the consequence of a complete or partial uterine rupture, dehiscence, or adhesions mainly between the anterior lower uterine segment and posterior wall of the bladder (Figure 1). Furthermore, these findings suggested that in women with a history of previous CD presenting with an anterior low-lying placenta or placenta previa, which currently account for 90% of all cases of PAS reported in the literature, the macroscopic features will often lead to a false-positive diagnosis of PAS in general and placenta percreta in particular.

**Comparison with existing literature**

PAS was first defined by Luke et al.

50 years ago to include both abnormally adherent and invasive placentas. Furthermore, Luke et al.

suggested that the depth of villous invasiveness is rarely uniform and that all 3 grades of villous invasiveness coexist in the same accreta placenta; however, the authors did not describe the histologic changes associated with placenta percreta. More recent histopathologic studies have described placenta percreta using one of the following criteria: placental villi directly attached to a thin uterine wall composed of a layer of dense connective tissue and little or no muscular tissue, a deficient maternal decidua at the implantation site with abnormal behavior of cells of the nonvillous trophoblast, a decidua replaced with hyaline connective tissue over a thinned uterine wall made of myometrial fibers often hyalinized, or chorionic villi anchored by a broad band of fibrin to the connective tissue of the peritoneum. Our systematic review has confirmed the heterogeneity in the criteria used to describe the microscopic finding in case reports of placenta percreta (Table 4). Overall, these descriptions combine the original criteria proposed by Irving and Hertig with the microscopic changes of the uterine wall associated with the scarification process after surgery or other medical treatments, such as radiotherapy. None of these studies describe the depth of invasiveness of the villous tissue.

The FIGO classification divides placenta percreta (grade 3) into 3 categories according to the depth of invasion of the chorionic villi on microscopic examination of samples from a hysterectomy specimen showing villous tissue within or breaching the uterine serosa (grade 3a), villous tissue breaching the uterine serosa and invading the bladder wall tissue or urothelium (grade 3b), and villous tissue breaching the uterine serosa and invading pelvic tissues/organs (grade 3c). In the present study, we found no evidence of chorionic villi invading the myometrium down to the serosa or beyond. Placental development over a scar may induce further remodeling that
The uterine wall with part of the basal plate of an anterior placenta previa becoming visible through dehiscence of the lower segment only covered by a thin serosal membrane (Figure 1). Using a new methodologic approach for clinicopathologic correlations in PAS, we have recently shown that the abnormal attachment of chorionic villi to the uterine wall is associated with thick fibrinoid deposition at the utero-placental interface with distortion of the “Nitabuch membrane,” which might explain the loss of parts of the physiological site of detachment of the placenta from the uterine wall. These changes are secondary to part of the definitive placenta getting its blood supply from deep uterine vessels with larger diameters than the spiral arteries. This results in high velocity flow entering the intervillous space from the beginning of the second trimester and abnormal excessive fibrinoid deposit at the level of the basal plate. Several authors of case reports and histopathologic studies referred to the depth of the EVT migration as a histologic criterion for the diagnosis of placenta percreta. Human placentation is physiologically invasive. In normal pregnancies, interstitial EVT cells invade the uterine wall as far as the inner third of the uterine myometrium or junctional zone (JZ), where they fuse to form multinucleated trophoblast giant cells. Not surprisingly, the focal loss of normal myometrium structure, including the JZ and factors that control trophoblastic migration, allows the migration of the EVT cells close to the uterine serosa. Within this context, there are similarities between tubal ectopic pregnancies where the blastocyst implants within the epithelium of the Fallopian tube and intrauterine scar placentation. Histopathologic studies of tubal ectopies have shown that EVT cells often reach tubal vessels, but the subsequent development of the placenta in the tube differs from that in the uterus, in so far as EVT migration inside the tubal tissues is unrestrained, with penetration of the trophoblast into the tubal serosa. Trophoblast migration into the cervical stroma as part of placenta previa with increta villi should be regarded as extrauterine implantation, as should implantation in the cornua when associated with rupture or surgical intervention (Table 4) and not as PAS. However, as found in our systematic review, these criteria have led to the diagnosis of percreta in cases of scar dehiscence with intraoperative rupture or in cases with injury to the bladder where histologic sections show EVT in scar tissue or adhesions.

In our systematic review, EVT cells were found in the fat tissue between a scarred uterine wall and the bowel wall in a case of a primigravida with a previous history of myomectomy. In this case, chorionic villi were found attached to a thin fibrin layer at the interface between the basal plate of the placenta and bowel wall. Furthermore, these microscopic features have been described in case reports of placenta percreta associated with bladder invasion or bowel invasion but were not readily identified in our review of the corresponding histologic images. In areas of accreta, EVT was sparse in the myometrium deep to the inner layer, and deeper thick-walled vessels remained unconverted. Conversion of deep myometrial vessels associated with immune cells, whose composition resembles that seen in normal implantation, has been reported in the adjacent myometrium. These histologic changes in areas designated grossly as placental invasion closely resembled those on normal implantation rather than the usual microscopic hallmarks of neoplastic invasion without desmoplastic stroma or neovascularization. EVT has not generally been part of the histologic definition of percreta.
expert panel convened recently to recommend terminology and reporting elements for the pathology diagnosis of PAS specimens has concluded that the evaluation of the EVT migration patterns is not typically necessary for diagnosis.²

### Clinical implications

A recent analysis of the data of an international database using the FIGO classification reported an incidence of placenta percreta of 55%.⁷⁹ Here, using the same clinical criteria, we found a false-positive diagnosis for placenta percreta in more than 40% of the cases in the cohort (Table 2), including cases that showed no evidence of abnormal placental attachment at delivery (Figure 1). A recent national US study of the trends, characteristics, and outcomes of PAS using the World Health Organization (WHO) International Classification of Disease, Tenth Revision, reported an incidence of placenta increta and percreta of 9.5% and 13.2%, respectively.⁸⁰ The WHO classification provides no clinical description of the condition and, in particular, no clue on the differential diagnosis among PAS grades. Furthermore, it does not require the diagnosis to be validated by histopathologic examination. However, this model is problematic in that most cases of PAS that require surgical intervention are associated with low-lying placenta in the area of a previous CD scar often with dehiscence of the lower segment and adhesions with other pelvic structures. In practice, as we observed in our systematic review, this model has led to a diagnosis of percreta in case of uterine rupture during pregnancy, even when these defects are fundal and away from the placental implantation site or involve ectopic placenta in the proximal or cornual portion of the fallopian tube.²⁶,²³ Myofiber disarray, tissue edema, inflammation, and elastosis have all been described in human uterine scar tissue after surgery.⁸¹ Furthermore, the smooth muscle volume density was reported to decrease in the lower uterine segment after CD, and the number of apoptotic nuclei remained increased up to 3 years after surgery.⁸² The density of the myofibers and thickness of the uterine wall decreased in the lower segment toward the cervix where the wall is made up of dense connective tissue with only approximately 10% of smooth muscle fibers.⁸³ Thus, the lower segment is prone to major remodeling, including scar defect and progressive dehiscence during pregnancy. Adhesions between the uterine wall and bladder and/or other pelvic structures below the peritoneal reflection are common findings in women with multiple previous CDs with and without accreta placenta.⁸⁴–⁸⁶ Remodeling of the lower uterine segment after CDs will be associated with abnormalities of the uterine contour on prenatal ultrasound imaging, such as loss of clear zone, myometrial thinning, and bulgelike appearance.⁸⁵ We have recently shown that the lower uterine segment in women with previous multiple CDs presenting with an anterior low-lying placenta or placenta previa, shows major anatomic changes because of scarification both on ultrasound examination and at delivery, independently of the presence of accreta villous tissue on microscopic examination.⁸⁶ This can explain the high rate of a false-positive diagnosis of placenta percreta in our study when the diagnosis is based exclusively on intraoperative clinical features (Table 2). Furthermore, this can explain why the performance of ultrasound and magnetic resonance imaging to discriminate mild from severe PAS disorders remains poor.⁸⁷

Over 90% of cases of PAS are found in women with a prior CD presenting with a placenta previa.⁶⁵–⁶⁷ However, cases of PAS have been described in primigravida women with no surgical history but presenting with a uterine pathology, such as a bicornuate uterus, adenomyosis, submucous fibroids, or myometopic dystrophy,⁶⁵ and as found in our systematic review, after radiotherapy.²⁵,²⁸ A recent literature review of

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**TABLE 3**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean (SD)</th>
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<tbody>
<tr>
<td>Mean maternal age (y)</td>
<td>32.5 (6.1)</td>
</tr>
<tr>
<td>Mean gravidity</td>
<td>3.4 (1.9)</td>
</tr>
<tr>
<td>Mean parity</td>
<td>1.7 (1.2)</td>
</tr>
<tr>
<td>Mean number of previous cesarean delivery</td>
<td>1.2 (1.2)</td>
</tr>
<tr>
<td>Mean gestational age at delivery (wk)</td>
<td>26.1 (8.5)</td>
</tr>
<tr>
<td>Presenting symptoms n (%)</td>
<td></td>
</tr>
<tr>
<td>Sudden severe pain (pelvic-suprapubic-abdominal)</td>
<td>17 (41.5)</td>
</tr>
<tr>
<td>Vaginal bleeding or antepartum hemorrhage</td>
<td>10 (24.5)</td>
</tr>
<tr>
<td>Vaginal bleeding and pain</td>
<td>3 (7.3)</td>
</tr>
<tr>
<td>Preterm labor or premature rupture of membranes</td>
<td>3 (7.3)</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Pulseless on arrival</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>None reported (asymptomatic)</td>
<td>6 (14.6)</td>
</tr>
<tr>
<td>Surgical outcome n (%)</td>
<td></td>
</tr>
<tr>
<td>Primary hysterectomy</td>
<td>33 (80.5)</td>
</tr>
<tr>
<td>Conservative management</td>
<td>6 (14.6)</td>
</tr>
<tr>
<td>Secondary hysterectomy</td>
<td>2 (4.9)</td>
</tr>
</tbody>
</table>

SD, standard deviation.

133 cases of PAS of the upper uterine segment reported during a 70-year period (1949–2019) found that a quarter of cases were diagnosed in primipara and that more than half presented with signs of uterine rupture before the end of the second trimester of pregnancy. We recently reported on the vascular changes in the uteroplacental and intervillous circulations in 27 ongoing CD scar pregnancies, including 2 patients who presented with uterine rupture requiring laparotomy and hysterectomy at 13 weeks and 15 weeks. In both cases, a residual myometrial thickness <1 mm was found at 6 to 10 weeks of gestation, suggesting that this parameter is pivotal to evaluate the risks of uterine rupture in the early second trimester of pregnancy.89 In addition, bladder injury is not uncommon with uterine rupture, in particular in women with previous uterine surgery.90 This could explain the presence of hematuria44,31,33 in cases of partial uterine rupture of a dehiscent area in the third trimester of pregnancy.

The classic symptoms described for uterine rupture included acute onset abdominal pain and vaginal bleeding.91 Sudden severe pelvic, suprapubic, or abdominal pain and bleeding ranging from simple vaginal bleeding to APH were the most common presenting symptoms in the 41 cases included in our systematic review (Table 3). In contrast, only 3 patients in the cohort required emergent delivery owing to APH associated with a placenta previa, but they had no other symptom. A uterine rupture can allow a part of the fetus, placenta, amniotic cavity, or umbilical cord to enter the peritoneal cavity or broad ligament. If the placenta implants and develops under the area of rupture, it will appear through the uterine wall at laparotomy and may mislead the surgeon into believing that it is a case of placenta percreta. The findings of our study and, in particular, the absence of villous tissue invading the whole uterine wall in any of the cases of the cohort and case reports included in the review suggested that the finding of the placenta protruding through the entire uterine wall with the placental basal plate directly attached to pelvic organs is mechanical and not directly related to invasive accreta placenta. In those cases, the placental villi may be only separated from the wall of the bladder or bowel by a thin serosal layer, suggesting extrauterine villous invasion.

**Strengths and limitation of the study**

The evaluation of the clinical criteria proposed by the FIGO, in a large prospective cohort of cases of PAS, confirmed by detailed histopathologic examination of those cases requiring a hysterectomy or partial myometrial resection.

<table>
<thead>
<tr>
<th><strong>TABLE 4</strong></th>
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</table>

Histopathologic main findings described by the authors of 41 case reports included in the systematic review

<table>
<thead>
<tr>
<th>Macroscopic descriptions (n=28)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine rupture, perforation, or defect of the uterus with bulging of the placenta or of the placenta and fetus</td>
<td>13 (46.4)</td>
</tr>
<tr>
<td>Areas of placenta protruding through uterine wall</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>Placental invasion of the entire anterior wall to the serosal layer</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Placental invasion toward the parametrium, lateral, or broad ligament</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>Placenta invading the cervix, ileum, or bladder</td>
<td>3 (10.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Microscopic descriptions (n=41)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorionic villi invading or infiltrating the full thickness of the uterine wall or deep into the myometrium or close to the serosa</td>
<td>19 (46.3%)</td>
</tr>
<tr>
<td>Trophoblastic cells invading or proliferating inside the uterine wall or invading into the serosa</td>
<td>7 (17.1)</td>
</tr>
<tr>
<td>Villi attached to the myometrium without intervening decidua or Nitabuch layer</td>
<td>5 (12.4)</td>
</tr>
<tr>
<td>Villi and intermediate trophoblastic cells close to the illeal serosa or infiltrating the intestinal wall through the uterine serosa</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td>Villi invading the uterine wall and serosa of the bladder</td>
<td>2 (4.9)</td>
</tr>
<tr>
<td>Placental infiltration into the subadventitial tissues of the anterior cervix</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Villi within endocervical stroma with hemorrhage and necrosis</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Placenta percreta with chorioamnionitis and dilated blood vessels</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>villi and syncytiotrophoblastic cells mixed with fibrinoid and inflammatory exudates at serosal surface</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Placenta percreta with degeneration and hyalinization of the myometrium</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Ruptured uterine site with infarcted villi and organized thrombus</td>
<td>1 (2.4)</td>
</tr>
</tbody>
</table>

resection, and a thorough literature search with in-depth data analysis and review of the histopathologic findings of case reports describing a placenta percreta, represented the main strengths of our study. Immediate postoperative dissection of all hysterectomy specimens in the cohort allowed us to guide the sampling for histologic examination, and thus provided accurate grading for the depth and extent of abnormal villous attachment. The main limitation of our study was the heterogeneity of the gross and histologic data reported in the case reports and the variable quality of the images included in the text. In addition, the cohort included only patients referred to the MDT in the third trimester of pregnancy, and none of the patients presented with a uterine rupture before the planned date for their delivery, restricting the comparison of the data from the systematic review.

Conclusions

The results of our study have provided evidence that PAS is not an invasive disorder of placentation but primarily the consequence of postoperative surgical remodeling or a preexisting uterine pathology. Our findings have challenged the existence of placenta percreta as defined by histopathology and the theory that the severity of PAS is linked to the abnormal invasiveness of the villous tissue. Histopathologic findings in PAS may not have much impact on the management of the individual patient but are essential for a better understanding of the epidemiology, pathophysiology, and management of complex CDX, whether or not associated with abnormal placental attachment (Video).

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SUPPLEMENTAL FIGURE
Outcome flowchart of the cases included in the cohort

Cohort study (n= 101)

Surgical management
- Hysterectomy (n= 73)
- Partial myometrial resection (n= 7)

PAS (n= 65 cases)
  - Creta (n= 9)
  - Increta (n= 56)
  - Percreta (n= 0)

Non-PAS (n= 15)

CD with no evidence of PAS at delivery (n= 21)

CD, cesarean delivery; PAS, placenta accreta spectrum.

SUPPLEMENTAL TABLE
Electronic search strategy (August 1982 and April 2021)

<table>
<thead>
<tr>
<th>Search strategy</th>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case reports of women diagnosed with a placenta percreta during the second or third trimester of pregnancy and/or at birth</td>
</tr>
<tr>
<td></td>
<td>Original publication with data on the histopathologic findings, including histologic images</td>
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</table>

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<tr>
<th>Search strategy</th>
<th>Exclusion criteria</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Reviews, opinions, letters, protocols, and conference proceedings</td>
</tr>
<tr>
<td></td>
<td>Case series and cohorts of placenta accreta spectrum</td>
</tr>
<tr>
<td></td>
<td>Articles published before 1982</td>
</tr>
<tr>
<td></td>
<td>Articles in languages other than English</td>
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<td></td>
<td>Nonhuman studies</td>
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