Searching for Placenta Percreta: A prospective cohort and systematic review of case reports

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Condensation

Placenta percreta as described clinically does not correspond to a standardised histopathologic entity and is not associated with intramural villous invasion of the uterine wall.

Short title: Searching for histopathologic evidence of placenta percreta.

AJOG at a Glance

- **A. 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.

- **B. What are the 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 beyond into the pelvis.

- **C. What does this study add to what is already known?**
  This study provides meaningful clinical and histopathologic data indicating that placenta accreta spectrum is not an invasive disorder of placentation but the consequence of a primary or secondary abnormality of the uterine wall.
Abstract

Background

Placenta percreta is described as the most severe grade of placenta accreta spectrum (PAS) and accounts for a quarter of all cases of PAS 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 due to primary or secondary uterine abnormality rather than an abnormally invasive form of placentation.

Study design

We have evaluated the agreement between the intra-operative findings using the International Federation of Gynecology and Obstetrics (FIGO) classification with the postoperative histopathology diagnosis in a prospective cohort of 101 consecutive singleton pregnancies presenting with a low-lying/placenta previa, a history of at least one prior cesarean delivery (CD) and ultrasound signs suggestive of PAS. A systematic literature review of case reports of placenta percreta which included histopathologic findings and gross images was also performed.

Results
Samples for histologic examination were available in 80 out of 101 cases of the cohort which were managed by hysterectomy or partial myometrial resection. Microscopic examination showed evidence of PAS in 65 cases (creta n= 9; increta n=56) of these cases. Observer A and observer B graded as percreta 44 (43.5%) and 54 (53.5%) of the 101 cases included in the cohort, respectively. There was a moderate agreement between observers. Eleven out of the 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 gross images and the presenting symptomatology suggesting that the majority of these cases were the consequence of a uterine rupture. The microscopic descriptions were heterogeneous and all demonstrated histology of placenta creta rather than percreta.

**Conclusion**

Our study supports the concept that placenta accreta is not an invasive disorder of placentation, but the consequence of a primary or secondary 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 rupture; uterine adhesion; villous invasion
Introduction

Placenta percreta is described as 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.\textsuperscript{1,2} The term “placenta percreta” was first used in 1950 by Mc Carthy and Nichols\textsuperscript{3} and by 1956, only eight cases had been reported in the medical literature, all associated with a uterine rupture.\textsuperscript{4} Modern histopathologic cohort studies have reported on the different grades of villous invasion in accreta placentation i.e. placenta creta or adherenta, placenta increta and placenta percreta\textsuperscript{5-10} and suggested that they can co-exist in the same specimen.\textsuperscript{5} Similarly, authors of textbooks on the pathology of the human placenta describe in detail individual cases of placenta percreta.\textsuperscript{11,12} However, reported histologic criteria for percreta are heterogeneous, with most authors describing injury or remodelling of the underlying uterine wall, or extension of the trophoblastic cells into tissues other than the uterine smooth muscle\textsuperscript{5,7,11,12} 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.\textsuperscript{13}

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\textsuperscript{5-12} and textbook descriptions are illustrated by diagrams showing placental villi protruding into the peritoneal cavity after crossing the myometrium and uterine serosa.\textsuperscript{7} These diagrams have been used until today by many authors of diagnostic\textsuperscript{14,15} and management\textsuperscript{16} studies to describe the different grades of PAS. Lukes et al\textsuperscript{6}, 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 on the 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 shell 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.¹⁷

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.¹⁸,¹⁹ Not surprisingly, the incidence of placenta percreta reported in those studies ranges between 6.6 and 51.9% (average 22.1%) in general population studies¹⁸ and 2.4 and 35.3% (average 13.4%) in diagnostic studies of placenta previa accreta.¹⁹ 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.¹ The main objective of the present study was to prospectively evaluate the agreement between a diagnosis of FIGO grade 3 (percreta) based on intraoperative clinical assessment, and the final pathology report diagnosis. The findings of a systematic review of case reports of placenta percreta will be used to illustrate problematic areas in the current PAS classifications.
Materials and Methods

Cohort study

This is a prospective study of 101 consecutive women who presented with a singleton pregnancy, a low-lying/placenta previa, a history of at least one prior cesarean delivery (CD) and ultrasound signs suggestive of PAS between 20th March 2019 and 30th of June 2021 for management by the multidisciplinary team (MDT) at the Department of Obstetrics and Gynecology, University of Cairo. The MDT manages an average of three patients per week with potentially complex CD. All patients are managed according to a local protocol including elective delivery at 35-37 weeks in women with no major antenatal complications, mainly ante-partum hemorrhage (APH) and/or premature labour.

Macroscopic features during surgery and gross examination of the hysterectomy specimens were recorded using an image capture digital photographic protocol as previously described.21 Depending on the size of the adherent area, between 2-6 samples of the full thickness of the uterine wall with a third of the placental thickness were obtained from the areas of abnormal attachment, processed for histologic examination and stained with hematoxylin and eosin (H&E).

Two specialist research fellows in obstetrics and gynaecology (RAE and RME), with 3-year experience in the MDT, reviewed the intra-operative gross findings of the whole cohort independently and graded them using the FIGO classification. They were blinded to the surgical outcome, histopathology data and to the examination results of each other. All records were examined within the research centre and all images
were anonymised for data analysis. Institutional Scientific and Research Ethical
Committee approval (RSEC 021001) was obtained prior to the start of this study and all
patients were consented for 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 al22
and April 2021 (supplementary table A). The search protocol was designed a priori and
data reported as per PRISMA 2009 guidelines (www.prisma-statement.org). The
overall search strategy was inclusive of MeSH 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”. Title, abstracts and full-text were independently assessed by the authors
(EJ and RAE) 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 (EJ and RME) selected studies in two stages. The
abstracts of all potentially relevant papers were individually examined for suitability.
Papers were only ruled out at this stage if they obviously did not meet the inclusion criteria. The remainder were obtained in full text and were independently assessed for content, data extraction and analysis. Disagreements between the two original reviewers were resolved by discussion with the third investigator (AH). We excluded studies published before July 1982, cohort studies and case reports containing no microscopic images of the histologic diagnosis.

**Data extraction**

Study characteristics were subsequently extracted independently by two reviewers (MMT and AH) using a predesigned data extraction form including for 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 the intra-operative 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, structure of the uterine wall underneath the basal plate of the placenta (EJ & JH) using the new classification and reporting guidelines for the pathology diagnosis of PAS.²

**Statistical analysis**
Stata/IC version 15.0 (StataCorp LLC, TX, USA) was used to analyse the data. A standard Kurtosis analysis indicated that the demographic values were normally distributed and the data are therefore presented as mean and standard deviation (SD).

Intra-operative findings were graded using the FIGO classification. Due to the ordered categorical nature of the outcome, the inter-observer agreement was assessed using the weight a kappa method which measures the agreement over and above that which would be expected due to chance. The kappa analyses were first performed using the five individual categories of the Figo classification. The analysis was then repeated combining the grade 3 categories (3a, 3b and 3c) together into one category. Kappa statistics and percentage agreement are reported according to Landis and Koch and 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.23

Results

Cohort study

Table 1 displays the maternal demographic characteristics and main outcomes of the 101 patients included in the cohort study. Three patients were ≥ 40 years of age. Forty-five (44.6%) were grand multiparous (≥ 5 births). Nine (8.9%) patients had a history of one prior CS, 33 (32.7%) had two prior CDs and 59 (58.4%) patient had 3 or more prior CDs. The mean gestational age at delivery was 36.1 weeks. All patients were delivered after 35 weeks except three who were delivered at 27, 32 and 34 weeks, respectively due to APH on placenta previa.
Samples for histologic examination were available in 80 cases including the 73 cases who required a cesarean hysterectomy and in 7 cases managed conservatively with partial myometrial resection followed by reconstruction of the lower uterine segment (supplementary Figure A). There was histologic evidence of placenta creta i.e. villi attached directly to the superficial myometrium with no interposing decidua in 9 cases and placenta increta i.e. villi deeply implanted within the uterine wall in 56 cases. In the latter subgroup, there was also evidence of creta villi and myometrial scarification i.e. disrupted hyalinized myometrial fibers by fibrous and edematous tissue in a thinned uterine wall in at least one sample in all cases. Evidence of myometrial scarification was found in all the samples from areas of abnormal placenta attachment. Clusters of extravillous trophoblast (EVT) cells close to the serosal surface of the uterus were observed in 37 of those cases.

Table 2 presents the distribution of the PAS grading based on the gross intraoperative findings of the 101 cases included the cohort using the FIGO classification. Observer A graded 44 (43.5%) as percreta and observer B graded 54 (53.5%) cases as percreta. Kappa values were 0.53 (95% CI 0.41;0.66) and 0.53 (95% CI 0.37;0.68), respectively depending on whether the grade 3 categories were examined separately or whether they were combined together, indicating a “moderate” agreement between the two observers.

Eleven cases that were classified as percreta 3a (n= 9), 3b (n=1), 3c (n=1) by both observers intraoperatively (Figure 1 and 2) were found to be placenta previa non-accreta 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 exclusion of duplicates 805 remained. On screening the titles and abstracts, a further 637 were excluded as the reported outcomes were not relevant (cohort studies, letters, expert reviews) leaving 168 articles which 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 containing 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.\(^{24-64}\) In 24 cases, the patient had a history of at least one cesarean delivery and five were primiparous including two with a prior radiotherapy for childhood cancer, one for sarcoma\(^ {32}\) and one for leukemia\(^ {38}\) and one had had a prior myomectomy.\(^ {64}\) In one case, the patient had a prior 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%). One patient with a history of 2 prior cesarean deliveries and ultrasound features of placenta previa accreta was reported to arrive pulseless in hospital, with no fetal heart activity.\(^ {61}\) After failed resuscitation attempts both mother and fetus were confirmed deceased. A stillbirth was reported on admission in one other case.\(^ {37}\) A primary hysterectomy was performed in 33 cases (80.5%). Conservative management with uterine preservation was successful in six cases.
(14.6%). A maternal intraoperative death due to uncontrollable bleeding was reported in one case. Two hysterectomies were performed post-mortem.

Table 4 presents the histopathologic findings reported in the 41 case reports included in the review. There were no gross images available in 13 cases. The remaining 28 cases included intra-operative images in ten cases, immediate post-operative images of hysterectomy specimens in two cases, laboratory gross images in ten cases, and combined intra-operative and post-operative images in six cases. The most common macroscopic description (n=13 out of 28 cases; 46.4%), was that of uterine rupture with bulging of the placenta or of both placenta and fetus. In three of the cases, the rupture was reported as fundal and in one case as cervical. 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 into the bladder or ileum. In ten of these cases, the review of the published macroscopic images identified dehiscence of the uterine wall covered by an intact serosa shell.

Chorionic villi invading/infiltrating the full-thickness of the uterine wall or deep into the myometrium, close to the serosa was the most commonly (n= 19 out of 41 cases; 46.3%) reported main histologic features (Table 4). The depth of the trophoblastic invasion and villi attached to the myometrium without intervening decidua or Nitabuch’ layer was reported by seven and five authors, respectively, as their main criteria for the diagnosis of placenta percreta. The review of the published microscopic images found chorionic villi directly appose to a morphologically normal myometrium in 13 cases, to a scarred uterine myometrium in nine cases.
and to both normal and scarred myometrial tissues in four cases. In two cases, the villi were found to be appose on the cervical stoma and in three cases the villi were bounded by fibrinoid. In one case, EVTs might be present in the bowel fat tissue outside a scarred uterine wall following myomectomy. Overall, the microscopic examination found no evidence of 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 samples or images showed transmural villous invasion. The main intra-operative features and histologic findings suggest that the majority if not all cases reported as placenta percreta in the literature are the consequence of a complete or partial uterine rupture, dehiscence or adhesions mainly between the anterior lower uterine segment and the posterior wall of the bladder (Figure 1). These findings also suggest that in women with a history of prior CD presenting with an anterior low-lying/placenta previa which currently account to 90% of all cases of PAS reported in the literature, the macroscopic features will often lead to the false positive diagnosis of PAS in general and of placenta percreta in particular.

Comparison with existing literature
PAS was first defined by Lukes et al 50 years ago to include both abnormally adherent and invasive placentas. Lukes et al also suggested that the depth of villous invasiveness is rarely uniform and that all three grades of villous invasiveness may co-exist in the same accreta placenta but 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 non-villous trophoblast; or a decidua replaced by 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. The present systematic review confirms 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 following surgery or other medical treatments such as radiotherapy and not the depth of invasiveness of the villous tissue.

The FIGO classification divides placenta percreta (grade 3) into 3 categories according to depth of invasion of the chorionic villi on microscopic examination of samples from 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.

Rather, placental development over a scar may induce uterine further remodeling that thins the uterine wall with part of the basal plate of an anterior placenta previa becoming visible through a dehiscence of the lower segment only covered by serosa (Figure 1).

Using a new methodologic approach for clinico-pathologic correlations in PAS\textsuperscript{21}, 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’s membrane” which might explain the loss of parts of the physiological site of detachment of the placenta from the uterine wall.\textsuperscript{68} These changes are secondary to the definitive placenta recruiting deep uterine vessels with larger diameter from the beginning of the second trimester, resulting in high velocity flows entering the intervillous space during the rest of the pregnancy.

Several authors of case reports\textsuperscript{26,27,31,32,33,38,58} and histopathologic studies\textsuperscript{7} refers to the depth of the EVT migration as a histologic criterion for the diagnosis of placenta percreta. Human placentation is physiologically invasive.\textsuperscript{69} 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 (MNGCs).\textsuperscript{70} Not surprisingly, the focal loss of normal myometrium structure including the junctional zone and the factors that control trophoblastic migration, leads to migration of the EVT cells close to the uterine serosa.\textsuperscript{71-75} 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.\textsuperscript{76} Histopathologic studies of tubal ectopics have shown that extravillous trophoblastic cells invade tubal
vessels but subsequent development of the placenta in the tube differs from that in the uterus, in so far as invasion of the tubal tissues is unrestrained, with penetration of the trophoblast into the tubal serosa.\textsuperscript{77} Trophoblast infiltration of the cervical stroma as part of placenta previa with increta villi should be regarded as extrauterine implantation\textsuperscript{27,39}, as should implantation in the cornua when associated with rupture\textsuperscript{26,53} or surgical intervention (Table 4) and not as PAS. However, as found in the present systematic review, these criteria have led to diagnosis of percreta in cases of scar dehiscence with intraoperative rupture, or in cases with injury to the bladder where histologic sections often show intermediate trophoblast in scar tissue or adhesions.

In the present systematic review, EVT cells were also found in the fat tissue between a scarred uterine wall and the bowel wall in a case of a primigravida with a prior history of myomectomy.\textsuperscript{64} In this case, chorionic villi were found attached to a thin fibrin layer at the interface between the basal plate of the placenta and the bowel wall. These microscopic features have also been described in case reports of placenta percreta associated with bladder invasion\textsuperscript{5,31,54,63} or bowel invasion\textsuperscript{34,56} but were not readily identified in our review of the corresponding histologic images. In areas of accreta, interstitial trophoblast is sparse in the myometrium deep to the inner layer, and deeper thick-walled vessels remain unconverted.\textsuperscript{71,75} Conversion of deep myometrial vessels associated with immune cells, whose composition resembles that seen in normal implantation, has been reported in the adjacent myometrium.\textsuperscript{78} These histologic changes in areas designated grossly as placental invasion, closely resemble those on normal implantation rather than the usual microscopic hallmarks of neoplastic invasion without desmoplastic stroma or neovascularization. Extravillous trophoblast has not
generally been part of the histologic definition of percreta. An 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 data base using the FIGO classification reported an incidence of placenta percreta of 55%.\(^{79}\) In the present study, using the same clinical criteria, we found a false positive diagnosis for placenta percreta in over 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 (ICD-10) 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 between PAS grades. It also 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 placentation in the area of a prior cesarean 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 placentation in the proximal/cornual portion of the fallopian tube.\(^{26,53}\)
Myofiber disarray, tissue edema, inflammation and elastosis have all been described in human uterine scar tissue following surgery.\textsuperscript{81} The smooth muscle volume density was also reported to decrease in the lower uterine segment after CD and the number of apoptotic nuclei remains increased up to 3 years after surgery.\textsuperscript{82} The density of the myofibers and the thickness of the uterine wall decrease in the lower segment towards the cervix where the wall is made up of dense connective tissue with only around 10\% of smooth muscle fibers.\textsuperscript{83} Thus, the lower segment is prone to major remodeling including scar defect and progressive dehiscence during pregnancy. Together with adhesions between the uterine wall and the bladder and/or other pelvic structures below the peritoneal reflection, these are a common finding in women with multiple prior CDs with and without accreta placentation.\textsuperscript{84-86} Remodelling of the lower uterine segment will be associated with abnormalities of the uterine contour on prenatal ultrasound imaging such as loss of clear zone, myometrial thinning and a bulge-like appearance.\textsuperscript{85} We have recently showed that the lower uterine segment in women with prior multiple CDs presenting with an anterior low-lying/placenta previa, shows major anatomical changes due to scarification on both ultrasound examination and at delivery, independently of the presence of accreta villous tissue on microscopic examination.\textsuperscript{86} This can explain the high rate of false positive diagnosis of placenta percreta in the present study when the diagnosis is based exclusively on intra-operative clinical features including (Table 2). This can also explain why the performance of ultrasound and magnetic resonance imaging to discriminate mild from severe placenta accreta spectrum disorders remains poor.\textsuperscript{87}

Cases of PAS have been described in primigravida women with no surgical history, but presenting with a uterine pathology such as bicornuate uterus,
adenomyosis, submucous fibroids or myotonic dystrophy and as found in the present systematic review, following radiotherapy. A recent literature review of 133 cases of PAS of the upper uterine segment reported during a 70-year period (1949-2019) found that a quarter were diagnosed in primipara and that more than half presented with signs of uterine rupture before the end of the second trimester. We recently reported on the vascular changes in the utero-placental and intervillous circulations in 27 ongoing cesarean scar pregnancies including two patients who presented with uterine rupture requiring laparotomy and hysterectomy at 13 weeks and 15 weeks. In both cases a residual myometrial thickness (RMT) < 1mm was found at 6-10 weeks suggesting that this parameter pivotal to evaluate the risks of uterine rupture in the early second trimester and PAS later in pregnancy. In addition, bladder injury is not uncommon with uterine rupture, in particular in women with prior uterine surgery and this could explain the presence of hematuria in cases of partial uterine rupture of a dehiscent area in the third trimester.

The classic symptoms described for uterine rupture include acute onset abdominal pain and vaginal bleeding. 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 the present systematic review (Table 3). By contrast, only three patients in the cohort required emergent delivery due to APH associated with a placenta previa but they had no other symptoms. A uterine rupture can allow a part of the fetus, placenta, amniotic cavity, or the 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 in believing that it is a case of placenta percreta. The findings of the present 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 suggest 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 placentation. In those cases, the placental villi may be only separated from the 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 and a thorough literature search with in depth data analysis and review of the histopathologic findings of case reports describing a placenta percreta represent the main strengths of the present study. Immediate post-operative dissection of all hysterectomy specimens in the cohort allowed us to guide the sampling for histological examination and thus provided accurate grading for the depth and extent of abnormal villous attachment. The main limitation of our study is 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 presented with a uterine rupture before the planned date for their delivery restricting the comparison with the data from systematic review.

**Conclusions**
The results of our study provide evidence that PAS is not an invasive disorder of placentation but primarily the consequence of a primary or secondary uterine pathology. Our findings challenge 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 for the management of complex cesarean deliveries associated or not with abnormal placental attachment.

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FIGURE LEGENDS

Figure 1. Diagram showing a large area of dehiscence (dark grey) and adhesion (orange) between the lower segment of the uterus and the bladder. A & B Intra-operative views at 37 weeks of gestation before and after bladder dissection in a case of placenta previa with no evidence of abnormal placental attachment at delivery showing an extended area of uterine dehiscence covered by an adherent bladder through which the placenta can be seen occupying the entire anterior wall of the lower segment after dissection; C & D: Intra-operative views at 36 weeks of gestation before bladder dissection in a case of placenta previa with evidence of abnormal placental attachment and deep villous implantation on histology (placenta increta) showing an extended dehiscence of lower segment partially covered by an adherent bladder, through which the placenta becomes more visible after bladder dissection. Note in both cases the bluish/purple coloring, distension of the uterine wall over the placental bed with significant amount of hypervasularity.

M= Myometrium; P= Placenta; AC= Amniotic cavity; Cx= Cervix.

Figure 2: Intraoperative views of 10 previa non-accreta cases which like one of the cases in Figure 1 (A&B) were classified intraoperatively as percreta by both observers.

Figure 3: Flow diagram showing the selection of case reports included in the systematic review.

Supplementary Figure: Outcome flow chart of the cases included in the cohort.
**Table 1.** Maternal demographic characteristics and main outcomes of the cohort study (n= 101).

<table>
<thead>
<tr>
<th>Variables</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean maternal age (years)</td>
<td>31.3</td>
</tr>
<tr>
<td>Mean gravidity</td>
<td>4.7</td>
</tr>
<tr>
<td>Mean parity</td>
<td>3.1</td>
</tr>
<tr>
<td>Mean no of prior CD</td>
<td>2.8</td>
</tr>
<tr>
<td>Mean Gestational age at delivery (weeks)</td>
<td>36.1</td>
</tr>
<tr>
<td><strong>Surgical outcome</strong></td>
<td></td>
</tr>
<tr>
<td>Cesarean section hysterectomy</td>
<td>73</td>
</tr>
<tr>
<td>Conservative management</td>
<td>28</td>
</tr>
<tr>
<td><strong>Results of histologic examination (n= 80)</strong></td>
<td></td>
</tr>
<tr>
<td>PAS Creta</td>
<td>9</td>
</tr>
<tr>
<td>PAS Increta</td>
<td>56</td>
</tr>
<tr>
<td>No evidence of PAS</td>
<td>15</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD); CD= cesarean delivery; PAS= placenta accreta spectrum
Table 2. Distribution for the PAS grading based on the intra-operative findings in the 101 cases of the cohort using the FIGO classification\(^1\) and final histopathologic diagnosis in the 80 cases that required a hysterectomy or partial myometrial resection.

<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>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>2 INCRETA: bluish/purple coloring, distension of the uterine wall over the placental bed with significant amount of hypervascularity. Gentle cord traction results in the uterus being pulled inwards 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>3 PERCRETA: same as increta with placental tissue seen to be invading through the surface of the uterus.</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3a Limited to the uterine serosa</td>
<td>23 (22.8%)</td>
<td>33 (32.7%)</td>
<td></td>
</tr>
<tr>
<td>3b Placental villi are seen to be invading into the bladder but no 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>3c Placental villi are seen to be 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>
Table 3. Maternal demographic characteristics, presenting symptoms and main outcomes of 41 case reports included in the systematic review.

**Variables**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean maternal age (years)</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 no of prior CD</td>
<td>1.2 (1.2)</td>
</tr>
<tr>
<td>Mean Gestational age at delivery (weeks)</td>
<td>26.1 (8.5)</td>
</tr>
<tr>
<td>Presenting symptoms</td>
<td></td>
</tr>
<tr>
<td>Sudden severe pain (Pelvis-Suprapubic-Abdominal)</td>
<td>17 (41.5%)</td>
</tr>
<tr>
<td>Vaginal bleeding/APH</td>
<td>10 (24.5%)</td>
</tr>
<tr>
<td>Vaginal bleeding and pain</td>
<td>3 (7.3%)</td>
</tr>
<tr>
<td>Preterm labour/PROM</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</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>

CD= cesarean delivery; APH= antepartum hemorrhage; PROM= premature rupture of membranes
Table 4. 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/defect of the uterus with bulging of the placenta(^{25,28,30,33,39,40,46,48,50,51,57}) or of the placenta and fetus(^{37,42})</td>
<td>13 (46.4%)</td>
</tr>
<tr>
<td>- Areas of placenta protruding through uterine wall(^{35,58,59,61,62})</td>
<td>5 (17.9%)</td>
</tr>
<tr>
<td>- Placental invasion of the entire anterior wall to the serosal layer(^{43,49,54,55})</td>
<td>4 (14.3%)</td>
</tr>
<tr>
<td>- Placental invasion towards the parametrium/laterally/broad ligament(^{45,47,52})</td>
<td>3 (10.7%)</td>
</tr>
<tr>
<td>- Placenta invading cervix(^{36}), ileum(^{56}) or bladder(^{63})</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/infiltrating the full-thickness of the uterine wall or deep into the myometrium or close to the serosa(^{24,25,29,30,37,41-43,44,45,48,50-53,55,57,60,62})</td>
<td>19 (46.3%)</td>
</tr>
<tr>
<td>- Trophoblastic cells invading or proliferating inside the uterine wall or invading to the serosa(^{26,27,31,32,33,38,58})</td>
<td>7 (17.1%)</td>
</tr>
<tr>
<td>- Villi attached to the myometrium without intervening decidua or Nitabuch' layer(^{28,35,44,46,47})</td>
<td>5 (12.4%)</td>
</tr>
<tr>
<td>- Villi and intermediate trophoblastic cells close to ileal serosa(^{34}) or infiltrating the intestinal wall through the uterine serosa(^{64})</td>
<td>2 (4.9%)</td>
</tr>
<tr>
<td>- Villi invading the uterine wall and serosa of the bladder(^{54,63})</td>
<td>2 (4.9%)</td>
</tr>
<tr>
<td>- Placental infiltration to the sub-adventitial tissues of the anterior cervix(^{36})</td>
<td>1 (2.4%)</td>
</tr>
<tr>
<td>- Villi within endocervical stroma with hemorrhage and necrosis(^{39})</td>
<td>1 (2.4%)</td>
</tr>
<tr>
<td>- Placenta percreta with chorioamnionitis and dilated blood vessels(^{49})</td>
<td>1 (2.4%)</td>
</tr>
<tr>
<td>- Villi and syncytiotrophoblastic cells mixed with fibrinoid and inflammatory exudates at serosal surface(^{56})</td>
<td>1 (2.4%)</td>
</tr>
<tr>
<td>- Placenta percreta with degeneration and hyalinization of myometrium(^{59})</td>
<td>1 (2.4%)</td>
</tr>
<tr>
<td>- Ruptured uterine site with infarcted villi and organized thrombus(^{61})</td>
<td>1 (2.4%)</td>
</tr>
</tbody>
</table>
Records identified from databases searching (n=819)

Additional records identified through references and other sources (n=14)

Records potentially eligible (n=833)

Duplicates excluded (n=28)

Records excluded (n=637)

Full-text articles included for in depth review (n=168)

Full-text articles excluded with reasons (n=127)

Studies included in review (n=41)