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Prenatal ultrasound staging system for placenta accreta spectrum disorders

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KEYWORDS: outcome; placenta accreta spectrum disorders; prenatal diagnosis

ABSTRACT

Objectives *To develop a prenatal ultrasound staging system for placenta accreta spectrum (PAS) disorders in women with placenta previa and to evaluate its association with surgical outcome, placental invasion and the clinical staging system for PAS disorders proposed by the International Federation of Gynecology and Obstetrics (FIGO).*

Methods *This was a secondary retrospective analysis of prospectively collected data from women with placenta previa. We classified women according to the following staging system for PAS disorders, based upon the presence of ultrasound signs of PAS in women with placenta previa: PAS0, placenta previa with no ultrasound signs of invasion or with placental lacunae but no evidence of abnormal uterus–bladder interface; PAS1, presence of at least two of placental lacunae, loss of the clear zone or bladder wall interruption; PAS2, PAS1 plus uterovescical hypervascularity; PAS3, PAS1 or PAS2 plus evidence of increased vascularity in the inferior part of the lower uterine segment potentially extending into the parametrial region. We explored whether this ultrasound staging system correlates with surgical outcome (estimated blood loss (EBL, mL), units of packed red blood cells (PRBC), fresh frozen plasma (FFP) and platelets (PLT) transfused, operation time (min), surgical complications defined as the occurrence of any damage to the bladder, ureters or bowel, length of hospital stay (days) and admission to intensive care unit (ICU)) and depth of placental invasion. The correlation between the present ultrasound staging system and the clinical grading system proposed by FIGO was assessed. Prenatal and surgical management were not based on the proposed prenatal ultrasound staging system. Linear and multiple regression models were used.*

Results *Two-hundred and fifty-nine women were included in the analysis. Mean EBL was 516 ± 151 mL in women with PAS0, 609 ± 146 mL in those with PAS1, 950 ± 190 mL in those with PAS2 and 1323 ± 533 mL in those with PAS3, and increased significantly with increasing severity of PAS ultrasound stage. Mean units of PRBC transfused were 0.05 ± 0.21 in PAS0, 0.10 ± 0.45 in PAS1, 1.19 ± 1.11 in PAS2 and 4.48 ± 2.06 in PAS3, and increased significantly with PAS stage. Similarly, there was a progressive increase in the mean units of FFP transfused from PAS1 to PAS3 (0.0 ± 0.0 in PAS1, 0.25 ± 1.0 in PAS2 and 3.63 ± 2.67 in PAS3). Women presenting with PAS3 on ultrasound had significantly more units of PLT transfused (2.37 ± 2.40) compared with those with PAS0 (0.03 ± 0.18), PAS1 (0.0 ± 0.0) or PAS2 (0.0 ± 0.0). Mean operation time was longer in women with PAS3 (184 ± 32 min) compared with those with PAS1 (153 ± 38 min) or PAS2 (161 ± 28 min). Similarly, women with PAS3 had longer hospital stay (7.4 ± 2.1 days) compared with those with PAS0 (3.4 ± 0.6 days), PAS1 (6.4 ± 1.3 days) or PAS2*

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(5.9 ± 0.8 days). On linear regression analysis, after adjusting for all potential confounders, higher PAS stage was associated independently with a significant increase in EBL (314 (95% CI, 230–399) mL per one-stage increase; $P < 0.001$*), units of PRBC transfused (1.74 (95% CI, 1.33–2.15) per one-stage increase;* $P < 0.001$*), units of FFP transfused (1.19 (95% CI, 0.61–1.77) per one-stage increase;* $P < 0.001$*), units of PLT transfused (1.03 (95% CI, 0.59–1.47) per one-stage increase;* $P < 0.001$*), operation time (38.8 (95% CI, 31.6–46.1) min per one-stage increase;* $P < 0.001$*) and length of hospital stay (0.83 (95% CI, 0.46–1.27) days per one-stage increase;* $P < 0.001$*). On logistic regression analysis, increased severity of PAS was associated independently with surgical complications (odds ratio, 3.14 (95% CI, 1.36–7.25);* $P = 0.007$*), while only PAS3 was associated with admission to the ICU (*$P < 0.001$*). All women with PAS0 on ultrasound were classified as having Grade-1 PAS disorder according to the FIGO grading system. Conversely, of the women presenting with PAS1 on ultrasound, 64.1% (95% CI, 48.4–77.3%) were classified as having Grade-3, while 35.9% (95% CI, 22.7–51.6%) were classified as having Grade-4 PAS disorder, according to the FIGO grading system. All women with PAS2 were categorized as having Grade-5 and all those with PAS3 as having Grade-6 PAS disorder according to the FIGO system.*

Conclusion *Ultrasound staging of PAS disorders is feasible and correlates with surgical outcome, depth of invasion and the FIGO clinical grading system.*

INTRODUCTION

Placenta accreta spectrum (PAS) disorders encompass a heterogeneous group of anomalies characterized by abnormal adhesion or invasion of the trophoblastic tissue into the myometrium[1–3]. Advances in prenatal imaging techniques and improved knowledge of the natural history of these anomalies have led to an increase in the prenatal detection rate of PAS disorders[4]. Prenatal diagnosis of a PAS disorder is fundamental as it has been shown to reduce the burden of maternal morbidity by allowing preplanned treatment in centers with high expertise in surgical management of this condition[5,6].

The large majority of studies on prenatal diagnosis of PAS disorders have focused on the diagnostic performance of ultrasound in detecting these anomalies, without assessing whether the risk of severe maternal morbidity can be stratified.

PAS disorders are commonly classified according to depth of trophoblastic invasion into the myometrium, with the most severe type, placenta percreta, being associated with a higher risk of massive hemorrhage, need for blood transfusion and admission to intensive care unit (ICU)[7]. However, although depth of invasion represents one of the major determinants of surgical outcome in PAS disorders, large variability in the clinical course of women presenting with the same degree of placental invasion has been observed[8,9].

In oncology, stratification of the severity of cancer, which is based upon several characteristics of the tumor, such as size, spread and cellular abnormalities, helps in classifying the disease, estimating its severity, making an informed prediction of prognosis, planning the most appropriate treatment and identifying clinical trials that may be applicable in treating an individual.

The International Federation of Gynecology and Obstetrics (FIGO) introduced recently a clinical grading system for PAS[3]. However, despite its importance, this grading is performed at delivery and cannot be used to counsel women prenatally. Only a few studies have looked at the feasibility of a prenatal staging system for the assessment of the presence and severity of PAS disorders[10–12].

The aims of this study were to develop an ultrasound staging system for PAS disorders in women with placenta previa and to evaluate its association with surgical outcome, placental invasion and the clinical staging system for PAS disorders proposed by FIGO.

METHODS

This was a secondary retrospective analysis of a prospective longitudinal study on the diagnostic performance of ultrasound in detecting PAS disorders, which included women presenting with placenta previa between 2009 and 2018[13]. All women had bimonthly assessments in the second and third trimesters of pregnancy, as per local guidelines, in order to detect a PAS disorder. STROBE guidelines were followed[14].

Ultrasound assessment was performed using transvaginal and transabdominal ultrasound in all cases. All examinations were performed using a 4.0–6.0-MHz curved transabdominal or 5.0–7.0-MHz transvaginal transducer (GE Voluson® 730, GE Medical Systems, Zipf, Austria and Samsung WS80A with Elite, Samsung Healthcare, Samsung Electronics, Milan, Italy). When using color Doppler ultrasound, the pulsed rate frequency was set initially at 1.3 kHz, but it was then lowered in order to identify the presence of placental lacunar flow.

Prenatal diagnosis of PAS disorders was performed using recently proposed standardized descriptors of ultrasound markers for PAS disorders, based on the following ultrasound signs[15] (Figures S1–S3): (1) loss of the clear zone, defined as loss or irregularity of the hypoechoic plane in the myometrium underneath the placental bed; (2) placental lacunae, defined as the presence of numerous lacunae, often containing turbulent flow visible on grayscale or color Doppler ultrasound; (3) bladder wall interruption, defined as loss or interruption of the bright bladder wall (hyperechoic band or 'line' between the uterine serosa and bladder lumen); (4) uterovescical hypervascularity, defined as a striking amount of color Doppler signal seen between the myometrium and the posterior wall of the bladder,

including 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; and (5) increased vascularity in the parametrial region, defined as the presence of hypervascularity extending beyond the lateral uterine walls and involving the region of the parametria[16].

We propose the following staging system of PAS disorders (Figure 1) based on the presence of ultrasound signs of PAS in women presenting with placenta previa: PAS0, placenta previa with no ultrasound signs of invasion or placenta previa with placental lacunae but no evidence of abnormal uterus–bladder interface (i.e. no loss of the clear zone and/or bladder wall interruption); PAS1, presence of at least two of placental lacunae, loss of the clear zone and bladder wall interruption; PAS2, PAS1 plus uterovesical hypervascularity; PAS3, PAS1 or PAS2 plus evidence of increased vascularity in the inferior part of the lower uterine segment extending into the parametrial region. The last ultrasound examination prior to surgery was used to assess the presence and distribution of ultrasound signs of PAS and to build the staging system.

The association between the PAS disorder stage and surgical outcome was assessed. The outcomes explored were: estimated blood loss (EBL; mL); units of packed red blood cells (PRBC) transfused; units of fresh frozen plasma (FFP) transfused; units of platelets (PLT) transfused; operation time (min); surgical complications, defined as the occurrence of any damage to the bladder, ureters or bowel; length of hospital stay (days); and admission to the ICU.

The correlation between the present ultrasound staging system and the clinical grading system for PAS disorders proposed recently by FIGO[3] and assessed at delivery was also explored. According to this clinical staging system, PAS disorders can be categorized into subgroups as follows. Grade 1: at Cesarean or vaginal delivery, there is complete placental separation at the third stage and normal adherence of the placenta. Grade 2: at Cesarean section/laparotomy, no placental tissue is seen invading through the surface of the uterus, there is incomplete separation with uterotonics and gentle cord traction, and manual removal of placenta is required for remaining tissue, and parts of the placenta are thought to be abnormally adherent; at vaginal delivery, manual removal of placenta is required and parts of the placenta are thought to be abnormally adherent. Grade 3: at Cesarean section/laparotomy, no placental tissue is seen invading through the surface of the uterus, there is no separation with uterotonics and gentle cord traction, and manual removal of placenta is required, and the whole placental bed is thought to be abnormally adherent; at vaginal delivery, manual removal of placenta is required and the whole placental bed is thought to be abnormally adherent. Grade 4: at Cesarean section/laparotomy, placental tissue is seen to have invaded through the serosa of the uterus but a clear surgical plane can be identified between the bladder and uterus to allow non-traumatic reflection of the urinary bladder at surgery. Grade 5: at Cesarean section/laparotomy, placental tissue is seen to have invaded through the serosa of the uterus and a clear surgical plane cannot be identified

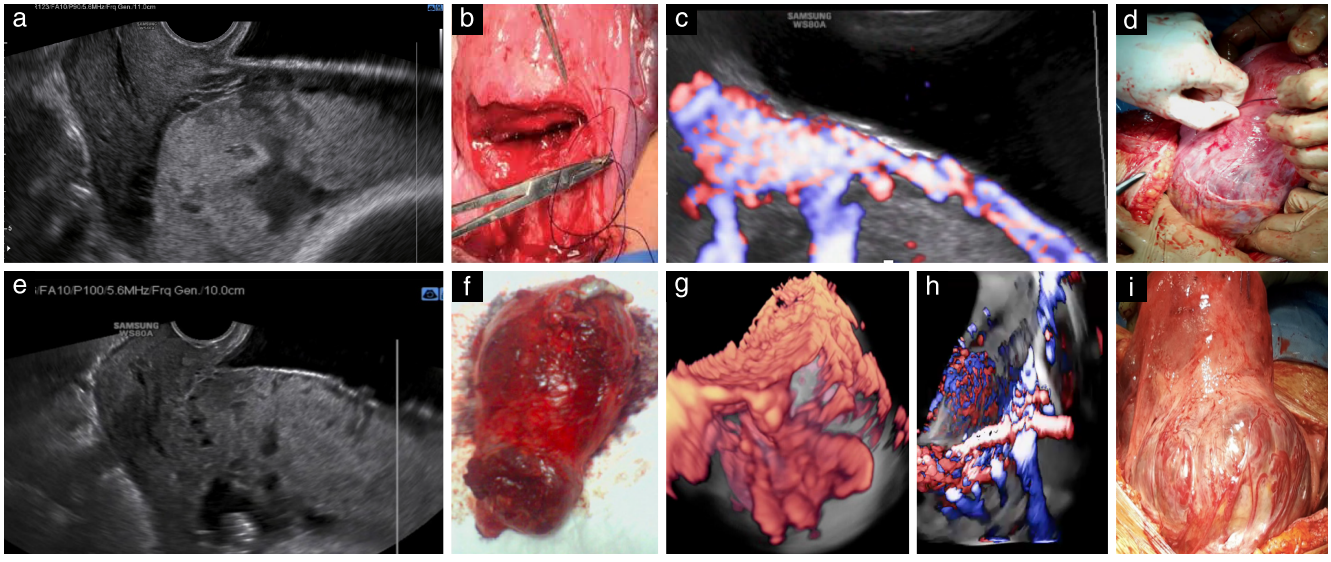

Figure 1 Ultrasound and surgical images in four women with placenta previa, classified prenatally using ultrasound staging system for placenta accreta spectrum (PAS) disorders. (a,b) In woman with PAS0, placenta showed lacunae but no other signs of invasion on ultrasound (a); at surgery, lower uterine segment seemed unaffected and there was no macroscopic evidence of PAS disorder (b). (c,d) In woman with PAS1, placenta showed presence of lacunae and abnormal bladder interface but no uterovesical hypervascularity on ultrasound (c); at surgery, there was placental adherence but no sign of macroscopic invasion through uterine serosa could be identified (d). (e,f) In woman with PAS2, there were signs of uterovesical hypervascularity on ultrasound (e); at surgery, there was placenta percreta invading upper and lower uterine segments but no evidence of parametrial invasion (f). (g–i) In woman with PAS3, there was increased vascularity in inferior part of lower uterine segment extending into parametrial region on ultrasound (g,h); at surgery, there was evidence of parametrial invasion (i).

between the bladder and uterus to allow non-traumatic reflection of the urinary bladder at surgery. Grade 6: at Cesarean section/laparotomy, placental tissue is seen to have invaded through the serosa of the uterus and be infiltrating the parametrium or any organ other than the urinary bladder.

The association between PAS ultrasound stage and depth of placental invasion was also assessed. Depth of placental invasion was defined as the degree of trophoblastic invasion into the myometrium, as assessed on histopathological analysis of the removed uterus for those cases undergoing hysterectomy. Placenta accreta was diagnosed when anchoring placental villi were attached to the myometrium rather than the decidua, but without completely invading it. Placenta increta was diagnosed when chorionic villi penetrated the myometrium, while the diagnosis of placenta percreta was considered when chorionic villi penetrated through the myometrium to the uterine serosa and/or adjacent organs. All uterine specimens were assessed by the same research pathologist who was blinded to the ultrasound and surgical findings. Furthermore, because different degrees of placental invasion may coexist in the same uterus, cases were labeled according to the maximum depth of placental invasion observed. Conversely, in women not undergoing hysterectomy, the presence of a PAS disorder was defined according to the FIGO clinical grading system and cases with PAS0 as those presenting with complete placental separation at the third stage of labor[3].

For the purposes of the analysis, we used the data from ultrasound assessments performed at 30–32 weeks of gestation. We have demonstrated previously that the distribution of PAS disorder ultrasound signs in affected women is similar between the second and third trimesters of pregnancy[17]. In the authors' collective experience, assessment of parametrial invasion is performed more accurately at 30–32 weeks of gestation. Early assessment may not allow a proper assessment of abnormal vascularization in the parametrial region, while late assessment may be affected technically by the increase in uterine size and difficulties in visualizing parametrial regions.

The correlation between the present staging system and the FIGO clinical grading system of PAS disorders was assessed by analyzing retrospectively the surgical notes of each woman, because, at the time the study was conducted, the FIGO staging system of PAS disorders was not yet available.

Clinical management of PAS disorders

All women presenting with at least two ultrasound signs suggestive of a PAS disorder were treated with Cesarean hysterectomy and preoperative temporary occlusion of the internal iliac arteries with balloon catheters. For those cases showing ultrasound evidence of a PAS disorder but no clear placental invasion on direct visualization, after delivery of the fetus and clamping of the cord, the balloon catheters were inflated and expulsion of the placenta attempted by administering carbetocin and by controlled cord traction. In the event of failed placental detachment, hysterectomy was performed, preserving the adnexa and leaving the placenta *in situ*. Conversely, for cases showing placental tissue protruding through the uterine serosa, a longitudinal incision on the uterine fundus was performed to deliver the fetus, followed by Cesarean hysterectomy without any attempt to remove the placenta. Finally, women presenting with placenta previa with no ultrasound evidence of a PAS disorder had Cesarean delivery with an incision performed on the lower uterine segment without the use of interventional radiology techniques. The multidisciplinary team remained the same throughout the study period.

No attempt was made to leave the placenta *in situ* in order to delay surgery and no women undergoing a conservative surgical technique (including TRIPLE-P or one-step conservative surgery) were included in the study in order not to bias the analysis.

There was no difference in the management of women according to the ultrasound grading of PAS with regards to prenatal follow-up, timing of delivery or surgical technique.

Data analysis

The relationship between selected maternal and gestational characteristics and six continuous and two categorical outcomes was investigated, according to PAS disorder stage, ranging from PAS0 (the least severe form) to PAS3 (the most severe form). The continuous outcomes were: (1) EBL during delivery; (2) units of PRBC transfused; (3) units of PLT transfused; (4) units of FFP transfused; (5) length of operation time; and (6) length of hospital stay. The categorical outcomes were: (1) occurrence of maternal surgical complications; and (2) admission to the ICU. Depth of placental invasion according to presentation with PAS1, PAS2 or PAS3 was assessed. Finally, the proportion of women classified into each FIGO grade according to PAS stage on ultrasound was assessed.

The potential association between all recorded maternal and gestational characteristics and the continuous outcomes was evaluated by, first, using standard univariate analyses (Spearman's correlation test for continuous parameters and Kruskal–Wallis test for categorical ones), and then fitting six multiple regression models. All recorded covariates, which were tested previously for multicollinearity, were included *a priori* and potential transformation, interaction and/or quadratic/cubic terms were investigated[18]. Parity, gravidity and number of previous Cesarean sections were collinear, as were PAS disorder ultrasound stage and histopathological diagnosis. We thus chose to include the most relevant covariates from a clinical point of view, namely parity and PAS disorder stage. Parity and PAS disorder stage were treated as both continuous and ordinal variables, identifying three categories for parity (nulliparous, primiparous and multiparous) and four for PAS disorder ultrasound stage (PAS0 to PAS3). All remaining outcomes were included as covariates in all models, with the exception of the

model predicting the amount of blood loss, in which the units of PRBC, FFP and PLT transfused were excluded because they are a consequence of blood loss. The validity of each final regression model was assessed as follows: the assumption of constant error variance was checked graphically, plotting Pearson residuals against fitted values, and formally, using the Cook–Weisberg test for heteroscedasticity. High leverage observations were identified by computing Pearson, standardized and studentized residuals, and Cook's D influence. In all models, we found fewer than 10 high-leverage observations, the exclusion of which resulted in no substantial changes.

The potential association between the recorded maternal and gestational parameters and the two categorical outcomes was first evaluated using standard univariate analyses (chi-square test for categorical variables and Kruskal–Wallis test for continuous variables), and then by fitting two logistic regression models. Both models were built using a forward stepwise process, including only significant covariates and maternal age. To reduce potential overfitting due to the small number of events (19 women with surgical complications and 17 women admitted to the ICU), the number of covariates was limited to four in every phase of both models' fitting[19]. The goodness-of-fit was assessed using the Hosmer–Lemeshow test, and the predictive power was assessed using C-statistics (area under the receiver–operating characteristics curve). Standard post-estimation tests were used to check the validity of both final models, performing multicollinearity and influential observation analyses (using standardized residuals, change in Pearson and deviance chi-square).

We further explored the relationship between pregnancy outcome and PAS severity by comparing the distribution of all recorded outcomes and gestational parameters between the different PAS disorder stages.

Statistical significance was defined as a two-sided P-value < 0.05 for all analyses, which were carried out using Stata, version 13.1 (Stata Corp., College Station, TX, USA, 2013).

RESULTS

Two-hundred and fifty-nine women were included in the analysis. General characteristics of the study population are reported in Table 1. Mean maternal age at diagnosis was 31.6 ± 5.6 years and mean gestational age at birth was 35.6 ± 1.7 weeks. Hysterectomy was performed in all women affected by PAS1, PAS2 or PAS3 and in none of those presenting with PAS0. None of the included cases was treated by leaving the placenta *in situ*

Table 1 Maternal and pregnancy characteristics and outcome in study population of 259 women with placenta previa, overall and according to placenta accreta spectrum (PAS) disorder stage on prenatal ultrasound (US)

Variable	*All (n = 259)*	*US stage of PAS disorder*			
		PAS0 (n = 150)	*PAS1 (n = 39)*	*PAS2 (n = 16)*	*PAS3 (n = 54)*
Maternal age (years)	31.6 ± 5.6	29.3 ± 5.4	35.0 ± 4.5*	33.8 ± 3.7*	35.0 ± 3.8*
Gestational age at delivery (weeks)	35.6 ± 1.7	36.4 ± 1.1	35.1 ± 1.6*	34.7 ± 1.1*	33.9 ± 1.9*†
Parity					
Nulliparous	73 (28.2)	73 (48.7)	0 (0.0)	0 (0.0)	0 (0.0)
Primiparous	51 (19.7)	24 (16.0)	11 (28.2)	4 (25.0)	12 (22.2)
Multiparous	135 (52.1)	53 (35.3)	28 (71.8)*	12 (75.0)*	42 (77.8)*
Number of prior Cesarean sections					
None	72 (27.8)	72 (48.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	55 (21.2)	25 (16.7)	13 (33.3)*	4 (25.0)	13 (24.1)
2	84 (32.4)	31 (20.7)	17 (43.6)*	9 (56.3)*	27 (50.0)*
≥ 3	48 (18.5)	22 (14.7)	9 (23.1)	3 (18.8)	14 (25.9)
Histopathological diagnosis					
Placenta previa without PAS	150 (57.9)	150 (100)	0 (0.0)	0 (0.0)	0 (0.0)
Placenta accreta	23 (8.9)	0 (0.0)	23 (59.0)	0 (0.0)	0 (0.0)
Placenta increta	16 (6.2)	0 (0.0)	16 (41.0)	0 (0.0)	0 (0.0)
Placenta percreta	70 (27.0)	0 (0.0)	0 (0.0)	16 (100)	54 (100)
Presence of comorbidities	5 (1.9)	3 (2.0)	1 (2.6)	1 (6.3)	0 (0.0)
Type of anesthesia					
General	15 (5.8)	0 (0.0)	2 (5.1)*	1 (6.3)*	12 (22.2)*†
Epidural	244 (94.2)	150 (100)	37 (94.9)*	15 (93.8)*	42 (77.8)*†
Outcome					
Estimated blood loss (mL)	725 ± 427	516 ± 151	609 ± 146*	950 ± 190*†	1323 ± 533*†‡
Units of red blood cells transfused	1.05 ± 2.05	0.05 ± 0.21	0.10 ± 0.45	1.19 ± 1.11*†	4.48 ± 2.06*†‡
Units of fresh frozen plasma transfused	0.80 ± 1.92	0.05 ± 0.21	0.0 ± 0.0	0.25 ± 1.0*	3.63 ± 2.67*†‡
Units of platelets transfused	0.51 ± 1.45	0.03 ± 0.18	0.0 ± 0.0	0.0 ± 0.0	2.37 ± 2.40*†‡
Operation time (min)	104.6 ± 60.5	57.6 ± 8.6	153 ± 38*	161 ± 28*	184 ± 32*†‡
Length of hospital stay (days)	4.8 ± 2.1	3.4 ± 0.6	6.4 ± 1.3*	5.9 ± 0.8*	7.4 ± 2.1*†‡
Surgical complication	19 (7.3)	0 (0.0)	0 (0.0)	4 (25.0)*†	15 (27.8)*†
Admission to intensive care unit	17 (6.6)	0 (0.0)	0 (0.0)	0 (0.0)	17 (31.5)

Data are mean ± SD or *n* (%). Chi-square test for categorical variables and *t*-test and Kruskal–Wallis test for normally distributed and non-normally distributed continuous variables, respectively; $P < 0.05$ on comparison with: *PAS0, †PAS1, ‡PAS2.

or using a partially resective surgical technique. Mean EBL was 725 ± 427 mL, while mean units of PRBC, FFP and PLT transfused were 1.1 ± 2.1, 0.8 ± 1.9 and 0.5 ± 1.5, respectively. Surgical complications occurred in 7.3% (95% CI, 4.8–11.2%; 19/259), while 6.6% (95% CI, 4.1–10.3%; 17/259) of women were admitted to the ICU (Table 1). On histopathological or clinical assessment, placenta accreta was diagnosed in 8.9% (95% CI, 6.0–13.0%; 23/259) of women, placenta increta in 6.2% (95% CI, 3.8–9.8; 16/259) and placenta percreta in 27.0% (95% CI, 22.9–32.8; 70/259) of included cases, while 57.9% (95% CI, 51.8–64.0%; 150/259) did not show any sign of a PAS disorder.

According to the presence of ultrasound signs of PAS disorders, 57.9% (95% CI, 51.6–64.0%; 150/259) of women were classified as PAS0, 15.1% (95% CI, 11.2–19.9%; 39/259) as PAS1, 6.2% (95% CI, 3.8–9.8%; 16/259) as PAS2 and 20.8% (95% CI, 18.2–26.4%; 54/259) as PAS3. Women with PAS0 were significantly younger (mean maternal age, 29.3 ± 5.4 years) than those with PAS1 (35.0 ± 4.5 years), PAS2 (33.8 ± 3.7 years) and PAS3 (35.0 ± 3.8 years), with no significant differences in maternal age between those with PAS1, PAS2 and PAS3. Similarly, women with PAS0 delivered at a later gestational age (36.4 ± 1.1 weeks) compared with those with PAS1 (35.1 ± 1.6 weeks), PAS2 (34.7 ± 1.1 weeks) and PAS3 (33.9 ± 1.9 weeks).

Mean EBL was 516 ± 151 mL in women with PAS0, 609 ± 146 mL in those with PAS1, 950 ± 190 mL in those with PAS2 and 1323 ± 533 mL in those with PAS3, and increased significantly with increasing severity of PAS ultrasound stage (Table 1). Mean units of PRBC transfused were 0.05 ± 0.21 in PAS0, 0.10 ± 0.45 in PAS1, 1.19 ± 1.11 in PAS2 and 4.48 ± 2.06 in PAS3, and increased significantly with increasing severity of PAS ultrasound stage. Similarly, there was a progressive increase in the mean units of FFP transfused from PAS1 to PAS3 (0.0 ± 0.0 in PAS1, 0.25 ± 1.0 in PAS2 and 3.63 ± 2.67 in PAS3) (Table 1). There was no difference in the mean units of PLT transfused between women with PAS0 (0.03 ± 0.18), PAS1 (0.0 ± 0.0) and PAS2 (0.0 ± 0.0), while those presenting with PAS3 on ultrasound had significantly more units of PLT transfused (2.37 ± 2.40) compared with those with PAS0, PAS1 or PAS2.

Mean operation time was longer in women with PAS1 (153 ± 38 min) and those with PAS2 (161 ± 28 min) compared with those with PAS0 (57.6 ± 8.6 min), while it was longer in women with PAS3 (184 ± 32 min) than in those with PAS0, PAS1 or PAS2 (Table 1). Similarly, length of hospital stay was longer in women with PAS1 (6.4 ± 1.3 days) and those with PAS2 (5.9 ± 0.8 days) compared with those with PAS0 (3.4 ± 06 days), while length of hospital stay in women presenting with PAS3 (7.4 ± 2.1 days) was longer than in those with PAS0, PAS1 or PAS2 (Table 1).

Surgical complications involving bladder, ureteral or bowel damage occurred in none of the cases with PAS0 or PAS1 and in 25.0% and 27.8% of those with PAS2 and PAS3, respectively, while 31.5% of women with PAS3 were admitted to the ICU compared with none of those with PAS0, PAS1 or PAS2 (Table 1). Finally, there was no case of neonatal complication in the study population.

On linear regression analysis, after adjusting for all potential confounders, increased severity of PAS ultrasound stage was associated independently with a significant increase in EBL (314 (95% CI, 230–399) mL per one-stage increase; $P < 0.001$), units of PRBC transfused (1.74 (95% CI, 1.33–2.15) per one-stage increase; $P < 0.001$), units of FFP transfused (1.19 (95% CI, 0.61–1.77) per one-stage increase; $P < 0.001$), units of PLT transfused (1.03 (95% CI, 0.59–1.47) per one-stage increase; $P < 0.001$), operation time (38.8 (95% CI, 31.6–46.1) min per one-stage increase; $P < 0.001$) and length of hospital stay (0.83 (95% CI, 0.46–1.27) days per one-stage increase; $P < 0.001$) (Tables S1–S6). Likewise, on logistic regression analysis, increased PAS disorder severity was associated independently with incidence of surgical complications (odds ratio, 3.14 (95% CI, 1.36–7.25); $P = 0.007$), while only PAS3 was associated with admission to the ICU ($P < 0.001$) (Tables S7 and S8).

When assessing the depth of placental invasion in the different groups, 59% (95% CI, 42.1–74.4%) of cases with PAS1, compared with none of those with PAS2 or PAS3, had placenta accreta, while all cases with PAS2 and PAS3 had placenta percreta detected on histopathological analysis.

Correlation between the present ultrasound staging system of PAS and the clinical grading system proposed recently by FIGO was affected by the retrospective nature of the analysis because, at the time the study was conducted, the FIGO grading system had not yet been published. All women classified as PAS0 based on the ultrasound staging system were categorized as having Grade-1 PAS disorder according to the FIGO grading system. Conversely, of the women presenting with PAS1 on ultrasound, 64.1% (95% CI, 48.4–77.3%) were classified as having Grade-3, while 35.9% (95% CI, 22.7–51.6%) were classified as having Grade-4 PAS disorder, according to the FIGO clinical grading system. Finally, all women with PAS2 according to the ultrasound staging system were categorized as having Grade-5 and all those with PAS3 as having Grade-6 PAS disorder, according to the FIGO grading system (Tables 2 and 3).

Table 2 Correlation between proposed prenatal ultrasound staging system and clinical staging system of International Federation of Gynecology and Obstetrics (FIGO) for placenta accreta spectrum (PAS) disorders in study population

FIGO grade	*PAS0 (n = 150)*	*PAS1 (n = 39)*	*PAS2 (n = 16)*	*PAS3 (n = 54)*
1	150 (100)	0 (0)*	0 (0)*	(0)*
2	0 (0)	0 (0)	0 (0)	0 (0)
3	0 (0)	25 (64.1)*	0 (0)†	0 (0)†
4	0 (0)	14 (35.9)*	0 (0) †	0 (0)†
5	0 (0)	0 (0)	16 (100)*†	0 (0)‡
6	0 (0)	0 (0)	0 (0)	54 (100)*†‡

Data are given as *n* (%). Chi-square test for categorical variables; $P < 0.05$ on comparison with: *PAS0, †PAS1, ‡PAS2.

Table 3 Prenatal ultrasound (US) staging system for placenta accreta spectrum (PAS) disorders and corresponding histopathological findings and grade of PAS disorder according to clinical grading system of International Federation of Gynecology and Obstetrics (FIGO)

US stage of PAS disorder	*US finding*	*Histopathology*	*FIGO grade*
PAS0	Placenta previa with no ultrasound signs of invasion or Placenta previa with placental lacunae but no evidence of abnormal uterus–bladder interface (loss of clear zone and/or bladder wall interruption)	Placenta previa without PAS	1–2
PAS1	Presence of at least two ultrasound signs among: • Placental lacunae • Loss of clear zone • Bladder wall interruption	Placenta accreta/increta	3
PAS2	PAS1 plus uterovesical hypervascularity	Placenta percreta focal or diffuse	4–5
PAS3	PAS1 or PAS2 plus evidence of increased vascularity in inferior part of lower uterine segment extending into parametrial region	Placenta percreta invading inferior third of lower uterine segment and lateral pelvic walls (or parametria)	6

DISCUSSION

Main findings

The findings of this study show that prenatal ultrasound staging of PAS disorders is feasible. Increased severity of the ultrasound stage of PAS disorders was associated independently with a significant increase in EBL and units of PRBC, FFP and PLT transfused during surgery, operation time, length of hospital stay and surgical complications. When considering the depth of invasion, all women with PAS1 had placenta accreta or increta, while those with PAS2 or PAS3 had exclusively placenta percreta. Despite presenting with the same depth of placental invasion, women with PAS3 were at significantly higher risk of hemorrhage and need for transfusion compared with those with PAS2. Finally, the proposed ultrasound staging system of PAS disorders showed good correlation with the clinical grading system suggested by FIGO.

Comparison with previous studies

Only a few studies have attempted to explore the feasibility and diagnostic performance of an ultrasound-based scoring system in assessing the presence and severity of PAS disorders[10–12]. Tovbin *et al.*[11] reported that a scoring system including the number of placental lacunae and the presence of bladder wall interruption had a high diagnostic performance for PAS, with an area under the receiver–operating characteristics curve of 0.94 (95% CI, 0.86–1.0), while, in the study of Rac *et al.*[10], the combination of smallest sagittal myometrial thickness and presence of lacunae and bridging vessels, in addition to the number of previous Cesarean deliveries and placental location, yielded an area under the curve of 0.87 (95% CI, 0.80–0.95).

Strengths and limitations

The prospective data collection, large sample size and longitudinal assessment of the included women (from the first trimester of pregnancy in the large majority of included cases) represent the major strengths of this study. Furthermore, we evaluated the correlation of the proposed staging system for PAS disorders not only with surgical outcome but also with the depth of placental invasion and the FIGO grading system. Finally, all cases affected by PAS were managed by the same multidisciplinary team and treated with hysterectomy, thus reducing bias related to the operator's experience and type of surgical approach adopted.

The main limitation of the study is that we did not explore whether the application of this staging system in clinical practice may affect prenatal management and prognosis of women with PAS disorders, due to the study being a secondary retrospective analysis. Furthermore, the correlation between the present ultrasound staging system and the clinical grading system proposed by FIGO was affected by the retrospective nature of the analysis, because, at the time the study was conducted, the FIGO grading system was not yet available. Finally, we did not explore whether first-trimester assessment of gestational sac position can improve the risk stratification provided by the proposed staging system[20–24].

Implications for clinical practice and research

Risk stratification of women affected by a PAS disorder is challenging. Although advances in prenatal imaging have led to an increase in the detection rate of these anomalies, there is still limited evidence on how to identify cases at higher risk of severe surgical morbidity.

The depth of placental invasion is one of the major determinants of surgical outcome in women with a PAS disorder, with those affected by placenta percreta being at higher risk of intrasurgical complications such as massive hemorrhage, need for blood transfusion and damage to adjacent organs[7]. Nevertheless, there might be high variability in surgical outcome, even in women presenting with the same depth of placental invasion.

In the present study, women with PAS2 or PAS3 were affected exclusively by placenta percreta; however,

women with PAS3 carried a significantly higher risk of severe hemorrhage and need for transfusion than those with PAS2. These findings confirm that, although fundamental, the depth of placental invasion alone cannot be used to stratify the surgical risk in women affected by PAS.

The topography of placental invasion has been proposed recently to be a reliable predictor of surgical morbidity in women affected by a PAS disorder. Invasions in the inferior third of the lower uterine segment, posterior bladder and parametria carry a high risk of surgical morbidity, while upper invasions are commonly associated with a more favorable clinical outcome and a relatively easier vascular control surgery[9]. Assessment of the topography of invasion has been reported only on magnetic resonance imaging and it is still unclear whether such staging can be reproduced on ultrasound[9].

In the present study, all cases with PAS3 showed invasion of the inferior third of the lower uterine segment at surgery; more importantly, there was no case of parametrial invasion in cases classified as PAS2. Therefore, ultrasound evidence of increased vascularization in the lateral walls of the inferior part of the lower uterine segment may identify a subgroup of women with PAS disorders at higher risk of surgical morbidity due to invasion of the posterior bladder wall and parametrium.

Recently, FIGO proposed a clinical grading system that is assessed at delivery to determine the presence and severity of a PAS disorder. Despite having not yet been validated, the FIGO grading system represents one of the most robust attempts to categorize objectively PAS disorders. When exploring the correlation between the present ultrasound system and FIGO's clinical staging system, all women with PAS0 on ultrasound were classified as having Grade-1 PAS disorder according to the FIGO grading system; conversely, of the women presenting with PAS1 on ultrasound, 64.1% (95% CI, 48.4–77.3%) were classified as having Grade-3, while 35.9% (95% CI, 22.7–51.6%) were classified as having Grade-4 PAS disorder according to the FIGO clinical grading system. Finally, all women with PAS2 were categorized as having Grade-5 and all those with PAS3 as having Grade-6 PAS disorder according to the FIGO system. Despite being affected by the retrospective nature of the analysis, these findings show that the prenatal ultrasound staging system of PAS disorders may correlate with the intrapartum clinical grading system proposed by FIGO.

Conclusions

This study demonstrates that a prenatal ultrasound staging system of PAS disorders based upon the presence of different imaging signs is feasible and correlates with surgical outcome, irrespective of the depth of placental invasion. Further large prospective studies are needed in order to validate the present ultrasound staging system and to explore whether its inclusion in clinical practice may help in deciding the optimal surgical approach and improving the outcome of women affected by a PAS disorder.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Sonographic markers of placenta accreta spectrum disorder in woman with histologically proven placenta percreta after hysterectomy. Disappearance of 'clear space' is evident in all images. (a) 2D grayscale ultrasound demonstrating lacunae at 28 + 1 weeks of gestation. (b,c) 3D grayscale tomographic images using several sections in two scanning planes perpendicular to each other at 28 + 1 weeks. (d–f) Power and color Doppler images showing increased blood flow at placenta–bladder interface at 21 + 1 weeks; some distortion of bladder line is seen. After repeat Cesarean delivery, hysterectomy was performed and massive transfusion was necessary. (g–i) Ultrasound images showing massive involvement of cervix. (g) Grayscale ultrasound image showing large lacunae. Power (h) and color (i) Doppler images showing plume of flow in large lacunae.

Figure S2 (a–f) Serial transvaginal ultrasound images from 19 to 23 weeks of gestation and at 33 weeks in woman with placenta percreta confirmed by histology after Cesarean hysterectomy, demonstrating progressive cervical involvement, invasion of bladder (proven at surgery), lacunae, interruption of bladder line and loss of 'clear space'.

Figure S3 Doppler ultrasound images demonstrating distortion of bladder line by placental invasion. (a) 2D color Doppler showing bulge into bladder. (b–d) Three consecutive rotational stages around longitudinal axis of uterus using 3D surface rendering showing placental bulge into bladder. (e–g) Three consecutive rotational stages around longitudinal axis of same uterus using 3D color Doppler rendering showing placental blood vessels along incisional line of previous Cesarean section.

Tables S1–S6 Relationship between estimated blood loss (Table S1), units of packed red blood cells transfused (Table S2), units of packed fresh frozen plasma transfused (Table S3), units of packed platelets transfused (Table S4), length of surgery (Table S5) and length of hospital stay (Table S6) and selected maternal and pregnancy characteristics in 259 pregnancies complicated by placenta previa

Table S7 Univariate analyses evaluating relationship between pregnancy characteristics and surgical complications and admission to intensive care unit in 259 pregnancies complicated by placenta previa

Table S8 Logistic regression models evaluating potential predictors of surgical complications and admission to intensive care unit in 259 pregnancies complicated by placenta previa