HUSSEIN AHMED M. (Orcid ID: 0000-0002-0003-2366) Bhide Amarnath (Orcid ID: 0000-0003-2393-7501) Thabet Mohamed (Orcid ID: 0000-0003-0604-1420)

The impact of preoperative ultrasound and intraoperative findings on surgical outcomes in patients at high-risk of placenta accreta spectrum

Ahmed M. Hussein^a, MD, Karin Fox^b, MD, Amar Bhide^c, MD, Rasha A. Elbarmelgy^a, MD, Rana M. Elbarmelgy^a, MD, Mohamed M Thabet^a, MD, Eric Jauniaux^d, MD, PhD

^aDepartment of Obstetrics and Gynecology, University of Cairo, Cairo, Egypt. ^bDivision of Maternal–Fetal Medicine, Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, Texas, USA ^cFetal Medicine Unit, Department of Obstetrics and Gynecology, St George's Hospital, London, UK ^dEGA Institute for Women's Health, Faculty of Population Health Sciences, University College London (UCL), London, UK.

Running title: Pre- and intraoperative features of placenta accreta spectrum

Correspondence: Ahmed M. Hussein, Department of Obstetrics and Gynecology, University of Cairo, Cairo, Egypt. Email: ahmed_mhussein@live.com

Text word count: 3450

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1471-0528.17286

ABSTRACT

Objective To assess whether preoperative ultrasound imaging and intraoperative features predict surgical outcomes in patients at high-risk for placenta accreta spectrum (PAS).

Design Cohort study.

Setting Cairo University Maternity, Egypt.

Population or sample Pregnant patients with one or more prior cesarean delivery presenting with a low-lying/placenta previa with or without PAS confirmed by histopathology.

Methods Logistic regression and multivariable analyses.

Main outcomes measures Need for primary cesarean hysterectomy, numbers of red blood cell (RBC) units transfused and patients requiring transfusion of > 5 units. **Results** Ninety consecutive records were reviewed including 58 (64.4%) PAS cases. Sixty (66.7%, 95%CI 56-76%) required hysterectomy. Odds of hysterectomy were significantly (P=.005) increased with complete previa. Significantly higher odds of hysterectomy were associated with subplacental hypervascularity (7.23, 95% CI 2.72;19.2, P<.001), lacunar scores 2+ and 3+ (12.6, 95% CI 4.15;38.5) P<.001), lacunar feeder vessels (5.69, 95% CI 1.77;18.3, P=.004) or bridging vessels (2.00, 95% CI 1.29;3.10, P=.002) on ultrasound, and increased lower segment vascularization at laparotomy (5.42, 95% CI 2.09;14.1, P=.001). Transfusion > 5 RBC units was associated with number of lacunae (OR 1.48, 95% CI 1.14;1.93, P=.004) and presence of feeder vessels (OR 1.62, 95% CI 1.24;2.11, P=.001). The multivariable analysis indicated that parity, placental location and PAS were significantly (P=.007; P=.01; P<.001, respectively) associated with hysterectomy.

Conclusions Preoperative ultrasound imaging can assist in triaging and counselling patients regarding the odds of PAS, intraoperative blood losses and need for hysterectomy whereas intraoperative features can assist the surgeon in evaluating the need for multidisciplinary support.

Keywords Placenta accreta spectrum, increta, percreta, ultrasound, uterine dehiscence.

Tweetable abstract Ultrasound findings and/or intraoperative gross features in cases at high-risk of PAS can identify patients requiring cesarean hysterectomy and multidisciplinary support at delivery.

Introduction

Placenta accreta spectrum (PAS) is an anomaly of placentation characterized by various degrees of abnormal attachment of the placental villous tissue to the uterine wall.¹ A cesarean scar increases both the risks of placenta previa and accreta² and over 90% of cases of PAS are now found in women presenting with a low-lying or placenta previa and a history of prior cesarean delivery (CD).^{3,4} After multiple lowersegment CDs, the anterior uterine wall becomes thinner and largely consists of fibrotic scar tissue^{5,6} Deep cesarean scar defect (CSD) or niches have been reported after CD in 56 to 84% of cases.⁷ There is increasing evidence that implantation and development of a gestational sac inside a scarred lower segment can lead to PAS.^{8,9} In large defects, the normal uterine anatomical layers are permanently lost, including the junctional zone allowing the migrating extravillous trophoblast to reach the deep uterine arterial circulation.¹ As pregnancy advances, abnormally high velocity blood flow enters the placenta,^{1,6} leading to thick fibrinoid deposition at the utero-placental interface¹⁰, preventing the physiological detachment of the placenta at delivery¹. Attempts to manually remove accreta villous tissue at delivery typically provoke rapid massive obstetric haemorrhage.¹²,¹³

Patients with PAS diagnosed prenatally and managed by a multidisciplinary team (MDT) are less likely to require large-volume blood transfusion and reoperation within 7 days of delivery for bleeding complications compared with patients managed by standard obstetric care,¹⁴ even in cases of unexpected PAS.¹⁵ Prenatal diagnosis decreases the risk of complications at delivery¹⁶ and diagnostic accuracy of ultrasound imaging by experts has been reported to be around 90%.¹⁷ However, large national population studies have shown that PAS remains undetected before delivery in half^{18,19} to two-thirds of the cases.²⁰ Up to 46% of patients with placenta previa accreta may deliver urgently and face increased risk compared to those who deliver in a scheduled manner, even in experienced centers.²¹

Avoiding transection of the placenta during hysterotomy, leaving the placenta in situ after fetal delivery, and repairing the hysterotomy in a manner that secures the amnion to the myometrium to permit delayed or secondary hysterectomy have been proposed for the management of complex cases of PAS.²² The objective of this study was to evaluate the role of preoperative ultrasound imaging and/or the finding of gross features at laparotomy suggesting PAS in predicting the likelihood of primary hysterectomy and need for intraoperative blood transfusion aiming to improve management and outcome.

Methods

Population and sample

This was an analysis of prospectively collected data from 90 consecutive pregnant patients at high-risk of PAS recorded in an electronic database who were referred for management by an expert specialist MDT at the Department of Obstetrics and Gynecology, University of Cairo over an 20-month period up to 1st of September 2021. All patients had singleton pregnancies between 32-37 weeks, history of one or more prior CD and were diagnosed prenatally with an anterior, low-lying placenta or previa. Patients with multiple gestations or who required unscheduled or emergent delivery were excluded from the study group. This study is part of an ongoing prospective cohort study on the diagnosis and management of PAS (Research Registry study No 6541; <u>www.researchregistry.com</u>). 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 after delivery. Basic clinical data were collected using a standard clinical audit protocol and all data and images were fully anonymised for further analysis.

Transabdominal and transvaginal sonographic examinations of the placenta, uterus and pelvis were performed (GE Voluson E10, GE Medical System, Zipf, Austria) in all cases, within 48 hours before planned surgical delivery using standardised protocols for placental location²² and the ultrasound signs for the screening and diagnosis of PAS²⁴ i.e. loss of clear zone, myometrial thinning, placental lacunae; bladder wall interruption and placental bulge on grey scale imaging; and subplacental hypervascularity; lacunae feeder vessels and bridging vessels on colour Doppler imaging. Myometrial thinning was recorded when the myometrial thickness was < 1 mm and the minimal myometrial thickness was measured transabdominally at the level of the upper, middle and transvaginally at lower edges of the bladder-uterine wall junction. Additionally, we used the Finberg and Williams lacunar scoring system (0= none; 1+=1-3; 2+=4-6; 3+=>6).²⁵

All patients were managed surgically according to local protocol.²⁶ A primary hysterectomy was performed when intraoperative macroscopic features indicated an extensive area of placental involvement, a large or extended area of dehiscence of the lower segment without sufficient myometrial tissue above the cervix to permit reconstruction, or in cases of uncontrolled bleeding from the placental bed. In cases

of focal PAS with limited lower segment dehiscence, a focal myometrial resection of the affected area with subsequent repair was attempted.

Intraoperative gross pelvic features at laparotomy and macroscopic findings of hysterectomy specimens were photographed using a digital camera (Figure 1), as previously described.²⁷ Intraoperative findings included dehiscence (focal if involving < 30% of the lower segment surface, large if involving 30-50% of the lower segment and extensive if involving >50 %), increased vascularity (dense tangled bed of vessels and multiple vessels running cranio-caudally and laterally in the anterior uterine serosa over the placental bed or in the parametria) and placental bulge. Hysterectomy and partial myometrial resection specimens were examined in the operating theatre by the surgical team, areas of the placental bed that could not be digitally separated from the uterine wall were sampled, and processed for histopathologic examination.²⁷ Histologic grading was performed using the Society for Pediatric Pathology Task Force guidelines for the pathology diagnosis of PAS.²⁸ Hysterectomy specimens from non-PAS cases i.e. complete placental delivery during the surgical procedure were examined using a routine gynaecology histopathology protocol.

Anonymized ultrasound and gross intraoperative photographic images were reviewed retrospectively and independently by PAS experts (AB for ultrasound images and KF for intraoperative features). Both were blinded to clinical histories, surgical outcomes and histopathologic diagnoses. The expert reviewing the ultrasound images was asked to identify the (standardised) signs of PAS²⁴ and to differentiate between PAS and non-PAS cases whereas the expert examining the gross intraoperative photos was asked to identify the cases using the International

Federation of Gynecology and Obstetrics classification (FIGO)²⁹ and the need to involve an MDT in the surgical management.

Exposures and outcomes

The primary exposure is the surgical management and its complications at delivery. Primary outcomes are the number of patients managed by primary cesarean hysterectomy or conservative management including focal myometrial resection and repair. Secondary outcomes are the median number of packed red blood cells (PRBC) units transfused and the number of patients requiring transfusion of > 5 PRBC units.

Analyses

Stata/IC version 15.0 (StataCorp LLC, TX, USA) was used for analysis. Standard Kurtosis analysis indicated non-normal distribution and therefore data are presented as median and interquartile range (IQR). Continuous variables between PAS (n= 58) and non-PAS (n=32) subgroups were compared using the Wilcoxon rank test at the 95% confidence interval (CI) whereas categorical variables were compared using the Chi-square test. A logistic regression and multivariable analyses were performed to elucidate associations between the patient, ultrasound and intraoperative factors with outcomes. The size of associations between each factor and hysterectomy or packed red blood cell transfusion are expressed as odds ratios (OR) and presented with the corresponding 95% CI. A P value <.05 was considered significant.

Results

Of the 90 included patients, seven (7.8%) had a history of one prior cesarean

delivery, 32 (35.6%) had had two prior cesarean deliveries and 51 (56.6%) had had \geq 3 prior cesarean deliveries. Transvaginal ultrasound confirmed ten (11.1%) lowlying placentae, 15 (16.7%) marginal placenta previas and 65 (72.2%) partial or complete placenta previas. The median maternal age at the time of delivery was 32 (IQR 28;35) years and median parity was 3.0 (IQR 2.4;4.0). Abnormal villous attachment to the uterine wall on histology was found in 58 (64.4%) cases (PAS subgroup). There was no evidence of villous tissue entering the uterine serosa or beyond the uterine wall in any of the cases. There were 32 (35.6%) cases with no evidence accreta placental tissue on histopathologic examination (non-PAS subgroup).

Comparison of demographic and outcomes in PAS and non-PAS

Table 1 compares the maternal demographic characteristics, ultrasound signs, intraoperative findings and main outcomes according to the final histopathologic diagnosis. The median maternal age, gravidity, parity and number of prior cesarean deliveries were significantly (P=.032; P=.001; P<.001; P=.005, respectively) higher in the PAS than in the non-PAS subgroup. There was no difference between the subgroups for median gestational age at delivery and median birthweight. The distribution of placental location and median cervical length was similar on transvaginal ultrasound. All cases in both subgroups presented with a loss of clear zone. Myometrial thinning was found in at least one area of the anterior lower segment in all cases. No patients had a myometrial thickness <1 mm at all three levels and the distribution of myometrial thinning was similar in both subgroups. The incidence of placental bulge was significantly (P=.006) higher in the PAS than in the non-PAS subgroup. The incidence of ultrasound signs associated with vascular

changes of the utero-placental interface i.e. subplacental hypervascularity; lacunae score 2+ and 3+, lacunae feeder vessels and bridging vessels was significantly higher in the PAS compared to the non-PAS subgroup (P<.001; P<.001; P<.001; P=.005, respectively).

Sixty (66.7%, 95%CI 56-76%) patients were managed by primary cesarean hysterectomy and 30 (33.3%) were managed conservatively, including seven by partial myometrial resection and uterine reconstruction in the PAS subgroup (Table 1). The distribution of surgical outcomes was significantly (P<.001) different, with 51 (87.9%) cases in the PAS subgroup requiring a primary hysterectomy compared to nine (28.1%) in the non-PAS subgroup. In the non-PAS subgroup, patients required hysterectomy when there was insufficient supracervical myometrial tissue to reconstruct the anterior lower segment after delivery of the placenta and removal of scar tissue, or due to excessive bleeding during repair of the lower segment. Some degree of uterine lower segment anterior wall dehiscence was found at laparotomy in all patients, with 69 (76.6%) presenting with a large (n= 30; 33.3%) or extended (n=39; 43.3%) areas of dehiscence. The corresponding distribution was significantly (P=.033) different between the subgroups with 47 (81.0%) and 22 (68.8%) presenting with a large or extended dehiscence in the PAS and non-PAS subgroup, respectively. There were 59 (65.6%) patients with increased vascularization of the lower segment at laparotomy with a significantly (P<.001) higher incidence in the PAS than in the non-PAS subgroup.

The subgroups did not differ significantly in the median number of red blood cells units transfused nor the number of patients requiring > 5 units of packed red blood cells during the surgery, despite a significantly higher estimated blood loss in

PAS compared to non-PAS subgroup(P=.032). Median preoperative and postoperative hemoglobin levels did not differ. One patient in the PAS subgroup required a second laparotomy due to persistent postoperative intraabdominal bleeding. Eleven (12.2%) patients were diagnosed intraoperatively with bladder injury (Table 1).

Impact of preoperative ultrasound findings and intraoperative features on surgical outcomes

Table 2 shows the results of the univariate analysis of factors associated with cesarean hysterectomy. A significantly higher risk of cesarean hysterectomy was found for maternal gravidity (P<.001), parity (P<.001), and number of prior cesarean deliveries (P=.001). Over 90% of women with a gravidity of \geq 5 or higher had a hysterectomy compared to only 29% of those with a gravidity of 3 or less (Table 2). Odds of hysterectomy were > 20 times higher for those with the highest parity (OR 20.8 95% CI 4.17;104) compared to the lowest group. Odds of hysterectomy were significantly (P=.005) increased for women presenting with a complete placenta previa than for those with a low-lying or marginal previa. Significantly higher odds of hysterectomy were found with the presence of subplacental hypervascularity (7.23, 95% CI 2.72;19.2, P<.001), lacunar scores 2+ and 3+ (12.6, 95% CI 4.15;38.5) P<.001), lacunar feeder vessels (5.69, 95% CI 1.77;18.3, P=.004) and bridging vessels (2.00, 95% CI 1.29;3.10, P=.002) on ultrasound. Increased vascularization of the lower segment at laparotomy (5.42, 95% CI 2.09;14.1, P=.001) was also significant. The univariate analysis indicated a significant association with the number of lacunae (OR 1.48, 95% CI 1.14;1.93, P=.004) and presence of feeder vessels (OR 1.62, 95% CI 1.24;2.11, P=.001) with the need to transfuse > 5 units of

red blood cells. The multivariable analysis (Table 3) indicated that parity, placental location and PAS were significantly (P=.007; P=.01; P<.001, respectively) associated with cesarean hysterectomy. After adjusting for these three factors, there was no additional effects of gravidity, number of prior CDs, subplacental hypervascularity, lacunae, feeder vessels, bridging vessels and increased vascularisation, all of which were found to be significant in the univariable analyses.

Expert review of preoperative ultrasound findings and intraoperative features

The review of the ultrasound images led to a correct diagnosis of PAS in 41 (70.7%) of the 58 cases confirmed by histopathology. In two cases confirmed as PAS, the intraoperative images were judged insufficient for an accurate evaluation and they were excluded from this analysis. The review of the intraoperative images correctly identified 50 (89.3%) of 56 histopathology confirmed PAS cases and incorrectly identified 19 (59.4%) of the 32 cases with no evidence of accreta placentation on histopathologic examination. The predicted surgical outcome in the 88 cases reviewed, was immediate caesarean hysterectomy in 50 cases (56.8%) including urology support in 34 of these cases and 41 (82%) of which required a primary hysterectomy. Of the remaining 38 cases, ten had a predicted conservative management but required a hysterectomy, one for focal PAS and nine for insufficient supracervical myometrial tissue to reconstruct the anterior lower segment after delivery of a non-PAS placenta.

Discussion

Main findings

Our data indicates that preoperative ultrasound examination and intraoperative features at laparotomy can identify patients at high risk of PAS who may require a support of an MDT for complex CD including a primary hysterectomy and massive transfusion during delivery, independently of the findings consistent with PAS on histologic examination.

Strengths and limitations

Our study had several strengths. We used a pragmatic approach that used both preoperative ultrasound imaging and gross intraoperative features to determine surgical approach and compared them to outcomes, rather than simply a retrospective analysis limited to patients identified with PAS on histopathology alone, which by design excludes patients with clinically relevant risk factors and those managed with uterine sparing and conservative measures. We also used a standardized protocol for the recording of ultrasound findings and intraoperative gross images, limiting ascertainment bias. We have found that while the predicted vs. actual outcomes based on independent review was high, it was not without limitations. In particular, photos provides views of a 3-dimensional structure in a 2-dimensional plane, which limits the surgeon point of view such as from an oblique angle under the skin allowing visualization of parametrial extension or bulging and cannot discern tissue elasticity or movement. Finally, our study was conducted by a MDT with 10-years of experience who manages an average of 100 cases at high-risk of PAS per year. This and exclusion of cases requiring emergency delivery prior to

planned surgery limits the generalizability of our results.

Interpretation and implications

Ultrasound signs suggestive of PAS can be separated into 1) abnormalities of uterine contour including loss of clear zone, myometrial thinning and a bulge-like appearance of the anterior lower segment; and 2) of the utero-placental circulation including hypervascularity of the retroplacental space and the presence of placental lacunae, lacunae feeder vessels and bridging vessels.^{1,6,24,30} We found no difference in the distribution of myometrial thickness at different levels of the anterior uterine wall between the PAS and non-PAS subgroups (Table 1). Furthermore, odds of a hysterectomy were not increased by myometrial thinning or the presence of a placental bulge on ultrasound (Table 2). These findings support the concept that abnormalities of the uterine contour are secondary to scarification and remodelling of the anterior lower uterine segment^{1,31} and thus not specific to a histopathologic diagnosis of PAS.

Overall, a placental bulge alone is evidence of architectural myometrial disruption, whether parts of the placenta are accreta or not and this sign is more strongly associated with intrapartum hemorrhage than PAS. However, antenatal detection of dehiscence alone still carries a high surgical risk, even when the overlying placenta is not PAS. Conversely, the incidence of all vascular ultrasound signs was significantly higher in the PAS than in the non-PAS subgroups (Table 1). Women with lacunar scores 2+ or 3+ on ultrasound had the highest odds of needing hysterectomy and \geq 5 units of blood transfusion when compared to those with either lacunar score of 0 or 1+ or other sonographic vascular anomalies (Table 2).

Accepted Articl

The odds of a hysterectomy for patient presenting with a complete placenta previa were 5 times higher than for those with a low-lying or marginal previa (Table 2). These findings highlight the need for standardized ultrasound examination protocol²⁴ for both antenatal and preoperative examinations. Independent of the presence of PAS, over 80% of patients with prior multiple CDs and an anterior lowlying or placenta previa will present with large areas of dehiscence and adhesions requiring complex surgical dissection and hysterectomy.³¹ This presents a surgical challenge that often requires the support of an MDT, even if the placenta is not accreta. The fact that intraoperative image review "overcalled" the need for hysterectomy and MDT management may serve as a protective strategy, if photographs are used to increase the presence of resources at the time of delivery, or to decide to transfer a stable patient to an appropriate referral center, even if a PAS or dehiscence is identified only at the time of laparotomy. A recent study using telemedicine for the diagnosis and MDT management of PAS in the rural state of Arkansas, has shown that this approach improves the management of patients at high-risk of PAS.³⁸

Lack of experience in managing complex obstetric surgical cases and lack of access to hematology and intensive care support is associated with a high risk of maternal death.³² Within this context, our findings that hypervascularization of the lower segment at laparotomy increased the odds of hysterectomy by over 5-fold, should alert the surgeon that such findings at laparotomy herald the need for expert support and to delay the hysterectomy until such support arrives or until the patient is transported to an appropriate nearby facility.²²

We have previously shown that the interobserver agreement for antenatal ultrasound imaging in cases confirmed as PAS by histopathology is good-toAccepted Articl

excellent.³³ We have also demonstrated that these ultrasound images can be used for training and that the level of inter-observer agreement, the numbers agreed as PAS and diagnostic sensitivity increased after training.³⁴ A recent study has reported that the combined antenatal imaging and intraoperative assessment is useful to determine which patients may benefit from use of aortic balloon occlusion.³⁵ In the present study, we found that the review of intraoperative images using the FIGO classification lead to the overdiagnosis in the number of cases of PAS, mainly of socalled cases of placenta percreta. When the placenta is visible through the serosa of a dehiscent lower segment, the villous tissue is almost always contained within the thin shell of serosa or scarring, and it is the surgical manipulation and dissection that leads to false diagnosis of placenta percreta³⁶ and in those cases there is no histological evidence for transmural villous invasion.³⁷ In the present study, the histologic examination of samples obtained from abnormally attached areas at birth also failed to identify villous tissue invading the entire uterine wall, including cases described intraoperatively as "percreta" (Figure 1).

While the actual clinical severity and pathology has likely not changed over the last century, our findings lend support to the concept that "through and through" villous invasion, as described in invasive hydatidiform moles, does not apply to accreta placentation. The physical destruction and remodelling of the myometrium from previous surgeries, followed by mechanical disruption and bulging of the scar, combined with large vascular recruitment and fibrosis, makes placental delivery hazardous and surgical resection technically difficult especially when located low within the pelvis. These findings suggest that including preoperative ultrasound images and intraoperative photography in PAS database could be useful to improve standardization for future comparative clinical research amongst centers but also training and management.

Conclusion

The changes associated with uterine remodelling following cesarean section are not pathognomonic of accreta placentation but when associated with abnormalities of uteroplacental circulation on ultrasound and of vascularization of the lower segment at laparotomy increase the odds of cesarean hysterectomy and should alert the surgeon for the need of expert, multidisciplinary support. When PAS is not diagnosed prior to surgery, delaying hysterectomy until additional support arrives or for transport to an appropriately equipped facility may be considered for stable patients.

Disclosure of interests

Completed disclosure of interests form available to view online as supporting information. The views expressed in this document reflect the opinion of the individuals and not necessarily those of the institutions that they represent.

Contribution to authorship

AMH and EJ conceived the study. RAE, RME and MMT collected the data and contributed to the data analysis. EJ and AMH drafted the manuscript. All authors were involved in the critical discussion and approved the final article prior to publication.

Details of ethics approval

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 preoperative ultrasound images and photographs obtained during surgery.

Funding

Dr Fox is partly supported by grant funding from the Eunice Kennedy Shriver NICHD R01 HD09434745: Molecular and Vascular MRI of Placenta Accreta

Acknowledgements

The authors wish to thank Mr Paul Bassett, M.Sc. (Stats consultancy Ltd, Bucks, UK) for his help with the statistical analysis.

References

- Jauniaux E, Jurkovic D, Hussein AM, Burton GJ. New insights into the etiopathology of placenta accreta spectrum. Am J Obstet Gynecol. 2022 Mar 3:S0002-9378(22)00167-3. doi: 10.1016/j.ajog.2022.02.038.
- Keag OE, Norman JE, Stock SJ. Long-term risks and benefits associated with cesarean delivery for mother, baby, and subsequent pregnancies: Systematic review and meta-analysis. *PLoS Med* 2018;15:e1002494.
- Jauniaux E, Chantraine F, Silver RM, Langhoff-Roos J; FIGO Placenta accreta diagnosis and management Expert Consensus Panel. FIGO consensus guidelines on placenta accreta spectrum disorders: Epidemiology. *Int J Gynaecol Obstet* 2018;140:265-273.
- Jauniaux E, Silver RM. Rethinking prenatal screening for anomalies of placental and umbilical cord implantation. *Obstet Gynecol* 2020;136:1211-1216.
- 5. Roeder HA, Cramer SF, Leppert PC. A look at uterine wound healing through a histopathological study of uterine scars. *Reprod Sci* 2012;19:463-73.
- Jauniaux E, Zosmer N, Subramanian D, Shaikh H, Burton GJ. Ultrasoundhistopathologic features of the utero-placental interface in placenta accreta spectrum. *Placenta* 2020;97:58-64.
- 7. Bij de Vaate AJ, van der Voet LF, Naji O, Witmer M, Veersema S, Brölmann HA, Bourne T, Huirne JA. Prevalence, potential risk factors for development and symptoms related to the presence of uterine niches following Cesarean section: systematic review. *Ultrasound Obstet Gynecol* 2014;43:372-82.

- Timor-Tritsch IE, Monteagudo A, Cali G, Palacios-Jaraquemada JM, Maymon R, Arslan AA, Patil N, Popiolek D, Mittal KR. Cesarean scar pregnancy and early placenta accreta share common histology. *Ultrasound Obstet Gynecol* 2014;43:383-395.
- Zosmer N, Fuller J, Shaikh H, Johns J, Ross JA. Natural history of early firsttrimester pregnancies implanted in cesarean scars. *Ultrasound Obstet Gynecol* 2015;46:367–375.
- 10. Jauniaux E, Zosmer N, De Braud LV, Ashoor G, Ross J, Jurkovic D.
 Development of the utero-placental circulation in cesarean scar pregnancies: a case-control study. *Am J Obstet Gynecol* 2022;226:399.e1-399.e10.
- 11. Jauniaux E, Hussein AM, Elbarmelgy RM, Elbarmelgy RA, Burton GJ. Failure of placental detachment in accreta placentation is associated with excessive fibrinoid deposition at the utero-placental interface. *Am J Obstet Gynecol* 2022, 226:243.e1-243.e10.
- 12. Silver RM, Branch DW. Placenta Accreta Spectrum. *N Engl J Med* 2018;378:1529-36.
- 13. Fitzpatrick K, Sellers S, Spark P, Kurinczuk J, Brocklehurst P, Knight M. The management and outcomes of placenta accreta, increta, and percreta in the UK: a population-based descriptive study. *BJOG* 2014;121:62-71.
- 14. Bartels HC, Rogers AC, O'Brien D, McVey R, Walsh J, Brennan DJ. Association of Implementing a multidisciplinary team approach in the management of morbidly adherent placenta with maternal morbidity and mortality. *Obstet Gyneco* 2018;132:1167-76.

- 15. Erfani H, Fox KA, Clark SL, Rac M, Rocky Hui SK, Rezaei A, Aalipour S, Shamshirsaz AA, Nassr AA, Salmanian B, Stewart KA, Kravitz ES, Eppes C, Coburn M, Espinoza J, Teruya J, Belfort MA, Shamshirsaz AA. Maternal outcomes in unexpected placenta accreta spectrum disorders: single-center experience with a multidisciplinary team. *Am J Obstet Gynecol* 2019;221:337.e1-337.e5.
- 16. Buca D, Liberati M, Calì G, Forlani F, Caisutti C, Flacco ME, Manzoli L, Familiari A, Scambia G, D'Antonio F. Influence of prenatal diagnosis of abnormally invasive placenta on maternal outcome: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2018;52:304-309.
- 17. Jauniaux E, Bhide A. Prenatal ultrasound diagnosis and outcome of placenta previa accreta after cesarean delivery: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2017;217:27-36.
- 18. Fitzpatrick KE, Sellers S, Spark P, Kurinczuk JJ, Brocklehurst P, Knight M. Incidence and risk factors for placenta accreta/increta/percreta in the UK: a national case-control study. *PLoS One* 2012;7:e52893.
- 19. Bailit JL, Grobman WA, Rice MM, Reddy UM, Wapner RJ, Varner MW, Leveno KJ, lams JD, Tita ATN, Saade G, Rouse DJ, Blackwell SC; Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network. Morbidly adherent placenta treatments and outcomes. *Obstet Gynecol* 2015;125:683-9.
- 20. Thurn L, Lindqvist PG, Jakobsson M, Colmorn LB, Klungsoyr K, Bjarnadóttir RI, Tapper AM, Børdahl PE, Gottvall K, Petersen KB, Krebs L, Gissler M, Langhoff-Roos J, Källen K. Abnormally invasive placenta-prevalence, risk factors and

antenatal suspicion: results from a large population-based pregnancy cohort study in the Nordic countries. *BJOG* 2016;123:1348-1355.

- 21. Shamshirsaz AA, Fox KA, Erfani H, Clark SL, Shamshirsaz AA, Nassr AA, et al. Outcomes of planned compared with urgent deliveries using a multidisciplinary team approach for morbidly adherent placenta. *Obstet Gynecol* 2018;131:234-241.
- 22. Zuckerwise LC, Craig AM, Newton JM, Zhao S, Bennett KA, Crispens MA. Outcomes following a clinical algorithm allowing for delayed hysterectomy in the management of severe placenta accreta spectrum. *Am J Obstet Gynecol* 2020;222:179.e1-179.e9.
- 23. Reddy UM, Abuhamad AZ, Levine D, Saade GR; Fetal Imaging Workshop Invited Participants. Fetal imaging: executive summary of a joint Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American Institute of Ultrasound in Medicine, American College of Obstetricians and Gynecologists, American College of Radiology, Society for Pediatric Radiology, and Society of Radiologists in Ultrasound Fetal Imaging Workshop. *J Ultrasound Med* 2014;33:745-757.
- 24. Jauniaux E, Bhide A, Kennedy A, Woodward P, Hubinont C, Collins S; FIGO Placenta accreta diagnosis and management expert consensus panel. FIGO consensus guidelines on placenta accreta spectrum disorders: Prenatal diagnosis and screening. *Int J Gynaecol Obstet* 2018;140:274-280.
- 25. Finberg HJ, Williams JW. Placenta accreta: prospective sonographic diagnosis in patients with placenta previa and prior cesarean section. *J Ultrasound Med* 1992;11:333-343.

- Accepted Article
- 26. Hussein AM, Kamel A, Raslan A, Dakhly DMR, Abdelhafeez A, Nabil M, Momtaz M. Modified cesarean hysterectomy technique for management of cases of placenta increta and percreta at a tertiary referral hospital in Egypt. *Arch Gynecol Obstet* 2019;299:695-702.
- 27. Jauniaux E, Hussein AM, Zosmer N, Elbarmelgy RM, Elbarmelgy RA, Shaikh H, Burton GJ. A new methodologic approach for clinico-pathologic correlations in invasive placenta previa accreta. *Am J Obstet Gynecol* 2020; 222:379.e1-379.e11369.
- 28. Hecht JL, Baergen R, Ernst LM, Katzman PJ, Jacques SM, Jauniaux E, et al. Classification and reporting guidelines for the pathology diagnosis of placenta accreta spectrum (PAS) disorders: recommendations from an expert panel. *Mod Pathol* 2020;33:2382-2396.
- 29. Jauniaux E, Ayres-de-Campos D, Langhoff-Ross J, Fox KA, Collins SL, FIGO Placenta accreta diagnosis and management expert consensus panel. FIGO classification for the clinical diagnosis of placenta accreta spectrum disorders. *Int J Gynecol Obstet* 2019;146:20-4.
- 30. Shainker SA, Coleman B, Timor-Tritsch IE, Bhide A, Bromley B, Cahill AG, et al. Special Report of the Society for Maternal-Fetal Medicine Placenta Accreta Spectrum Ultrasound Marker Task Force: Consensus on definition of markers and approach to the ultrasound examination in pregnancies at risk for placenta accreta spectrum. *Am J Obstet Gynecol* 2021;224:B2-B14.
- 31. Hussein AM, Elbarmelgy RA, Elbarmelgy RM, Thabet MM, Jauniaux E. Prospective evaluation of the impact of post-cesarean section uterine scarification in the perinatal diagnosis of placenta accreta spectrum. *Ultrasound Obstet Gynecol* 2022;59:474-482.

- Accepted Articl
- 32. Nieto-Calvache AJ, Palacios-Jaraquemada JM, Osanan G, Cortes-Charry R, Aryananda RA, Bangal VB, et al; Latin American group for the study of placenta accreta spectrum. Lack of experience is a main cause of maternal death in placenta accreta spectrum patients. *Acta Obstet Gynecol Scand* 2021 Apr 25. doi: 10.1111/aogs.14163.
- 33. Zosmer N, Jauniaux E, Bunce C, Panaiotova J, Shaikh H, Nicholaides KH. Interobserver agreement on standardized ultrasound and histopathologic signs for the prenatal diagnosis of placenta accreta spectrum disorders. *Int J Gynaecol Obstet* 2018;140:326-331.
- 34. Dimitrova I, Jauniaux E, Zosmer N, De Stefani LB, Andrade W, Bourmpaki E, Bunce C, Nicholaides KH. Development of a training program for the ultrasound screening of placenta accreta spectrum disorders. *Int J Gynaecol Obstet* 2019;147:73-77.
- 35. Nieto-Calvache AJ, Palacios-Jaraquemada JM, Aryananda RA, Rodriguez F, Ordoñez CA, Messa Bryon A, et al. How to identify patients who require aortic vascular control in placenta accreta spectrum disorders?

Am J Obstet Gynecol MFM 2022;4:100498.

- 36. Einerson BD, Comstock J, Silver RM, Branch DW, Woodward PJ, Kennedy A. Placenta accreta spectrum disorder: uterine dehiscence, not placental invasion. *Obstet Gynecol* 2020;135:1104-1111.
- 37. Jauniaux E, Hecht JL Elbarmelgy RA, Elbarmelgy RM, Thabet MM, Hussein AM. Searching for placenta percreta: A prospective study cohort and

systematic review of case reports. *Am J Obstet Gynecol* 2021 Dec 29:S0002-9378(21)02694-6. doi: 10.1016/j.ajog.2021.12.030. **Table 1.** Comparison of maternal demographic characteristics, ultrasound signs, intraoperative findings and main outcomes in the PAS and non-PAS subgroups.

Veriebles	PAS	Non-PAS	Р
Variables	n=58	n=32	
Median (IQR) maternal age (years)	32.0 (28.0;36.0)	31.0 (28.0;33.0)	.032
Median (IQR) gravidity	5.0 (4.0;6.0)	4.0 (3.0;4.5)	.001
Median (IQR) parity	3.0 (3.0;4.0)	2.0 (2.0;3.0)	<.001
Median (IQR) No of prior CD	3.0 (2.0;4.0)	2.0 (2.0;3.0)	.005
Median (IQR) GA at delivery (weeks)	36.3 (36.0;37.0)	36.3 (36.0;37.0)	.956
Median (IQR) birthweight (g)	2900 (2750;3100)	2950 (2775;3145)	.345
Placental location (n)			
- Low-lying	6 (10.3%)	4 (12.5%)	.246
- Marginal previa	7 (12.1%)	8 (25.0%)	
- Complete previa	45 (77.6%)	20 (62.5%)	
Median (IQR) cervical length (mm)	39.5 (32;48)	43 (40;52)	.112
<u>Ultrasound signs (n)</u>			
Myometrial thinning (< 1mm)	43 (74.1%)	23 (71.9%)	.816
1 level	15 (25.9%)	9 (28.1%)	
2 levels			
Placental Bulge	34 (58.6%)	9 (28.1%)	.006
Subplacental hypervascularity	51 (87.9%)	6 (18.8%)	<.001
Lacunae			
1+	7 (12.1%)	5 (16.6%)	<.001
2+	21 (36.2%)	0	
3+	29 (50.0%)	0	
Feeder vessels	32 (55.2%)	0	<.001
Bridging vessels	21 (36.2%)	2 (6.3%)	.002
Intraoperative findings (n)			
Anterior wall dehiscence			
<30%	11 (19.0%)	10 (31.3%)	.033

30-50%	16 (27.6%)	14 (43.7%)	
>50%	31 (53.4%)	8 (25.0%)	
Increased vascularity	51 (87.9%)	8 (25.0%)	<.001
Placental bulge	15 (25.9%)	9 (28.1%)	.816
Primary outcome (n)			
Cesarean hysterectomy	51 (87.9%)	9 (28.1%)	<.001
Conservative management	7 (12.1%)	23 (71.9%)	
Secondary outcome			
Median number PRBC units transfused	2.0 (2.0;4.0)	2.0 (2.0;3.0)	.315
Transfusion > 5 PRBC units (n)	9 (15.5%)	1 (3.1%)	.073
Other surgical data			
Median estimated blood loss (mL)	1850 (1500;2600)	1575 (1425;1950)	.033
Median preoperative Hb (g/dL)	10.7 (10.2;11.5)	10.6 (9.9;11.4)	.732
Median postoperative Hb (g/dL)	9.6 (9.1;10.4)	9.9 (9.4;10.7)	.099
Bladder injury (n)	9 (15.5%)	2 (6.3%)	.199

CD= Cesarean delivery; IO= Internal os; PRBC= packed red blood cells; 1 level or 2 level= myometrium thickness < 1mm at 1 or 2 levels of the 3 levels measured.

Table 2: Univariable analysis of factors associated with cesarean hysterectomy

Variable	Category	Hysterectomy n/N (%)	Odds Ratio (95% CI)	Р
Maternal age (*)	-		1.31 (0.80;2.13)	.29
	≤ 3	7/24 (29%)	1	<.001
Gravidity	4	14/23 (61%)	3.78 (1.12;12.7)	
	5	20/22 (91%)	24.3 (4.44;132)	
	<u>></u> 6	19/21 (90%)	23.1 (4.21;127)	
	≤2	12/32 (38%)	1	<.001
Parity	3	23/31 (74%)	4.79 (1.63;14.1)	
	<u>></u> 4	25/27 (93%)	20.8 (4.17;104)	
No of prior CD	<u>≤</u> 2	18/39 (46%)	1	.001
	<u>></u> 3	42/51 (82%)	5.44 (2.09;14.2)	
GA at delivery (weeks)			1.03 (0.57;1.81)	.92
Birthweight (g) ^(***)			0.90 (0.77;1.05)	.20
Placental location	Covering previa	50/65 (77%)	1	.005
	Low-lying	4/10 (40%)	0.20 (0.05;0.80)	
	Marginal previa	6/15 (40%)	0.20 (0.06;0.65)	
Cervical length (mm) ^(**)			1.00 (0.69;1.44)	.98
<u>Ultrasound signs (n)</u>				
Myometrial thinning (<	1 level	43/65 (66%)	1	.87
1mm)	2 levels	17/25 (68%)	1.09 (0.41;2.91)	
Placental bulge	No	30/47 (64%)	1	.55
	Yes	47/57 (82%)	1.31 (0.54;3.16)	
Subplacental hypervascularity	No	13/33 (39%)	1	<.001
Lacunae	Yes	47/57 (82%)	7.23 (2.72;19.2)	
	0 or 1+	17/42 (40%)	1	<.001
Feeder vessels	2+ or 3+	43/48 (90%)	12.6 (4.15;38.5)	
	No	32/58 (55%)	1	.004
Bridging vessels	Yes	28/32 (88%)	5.69 (1.77;18.3)	

	No	41/67 (61%)	1	.002
	Yes	19/23 (83%)	2.00 (1.29;3.10)	
Intraoperative findings (n)				
Anterior wall dehiscence	<30%	13/22 (59%)	1	.10
	30-50%	17/30 (57%)	0.91 (0.30;2.76)	
	>50%	30/38 (79%)	2.60 (0.82;8.23)	
Increased vascularity	No	13/31 (42%)	1	.001
	Yes	47/59 (80%)	5.42 (2.09;14.1)	
Placental bulge	No	17/24 (71%)	1	.61
	Yes	43/66 (65%)	0.77 (0.28;2.13)	

(*) Odds ratio given for 5-year increase in variable

(**) Odds ratio given for a 10-unit increase in variable

(***) Odds ratio given for a 100-unit increase in variable

Table 3: Multivariable	analysis	of factors	associated wi	th hysterectomy

Variable	Category	Odds Ratio (95% CI)	Р
	≤2	1	
Parity	3	5.48 (1.26 23.7)	<.007
	<u>≥</u> 4	32.0 (3.07, 334)	
Placental location	Complete previa	1	
	Low-lying	0.16 (0.02, 1.02)	.01
	Marginal previa	0.08 (0.01, 0.55)	
PAS	No	1	
	Yes	19.6 (4.79, 79.8)	<0.001

Figure legend

Figure 1: Intraoperative views of placenta previa with evidence of abnormal placental attachment and deep villous implantation on histology (placenta increta). In both cases the bluish/purple coloring, distension of the anterior uterine wall over the placental covered by an adherent bladder (b) bed with significant amount of hypervascularity over the lower and upper segments. (A) at 34 weeks of gestation before bladder dissection showing focal areas of dehiscence (*); (B) at 36 weeks of gestation showing placental tissue (*) after bladder dissection.

Accepted Article



