

## Clinical Article

# Ultrasound and histopathologic diagnosis of placenta accreta spectrum: An inter-observer agreement study

**Nurit Zosmer<sup>1</sup>, Eric Jauniaux<sup>2</sup>, Catey Bunce<sup>3</sup>, Jenie Panaiotova<sup>1</sup>, Hizbullah Shaikh<sup>4</sup>, Kypros H Nicholaides<sup>1</sup>**

<sup>1</sup>Harris Birthright Research Centre for Fetal Medicine, Kings College Hospital, London, UK.

<sup>2</sup>EGA Institute for Women's Health, Faculty of Population Health Sciences, University College London (UCL), London, UK.

<sup>3</sup>Department of Primary Care & Public Health Sciences, Kings College London, London UK.

<sup>4</sup>Department of Histopathology, Kings College Hospital, London, UK.

**Corresponding author:** *Professor Eric Jauniaux, Academic Department of Obstetrics and Gynaecology, Institute for Women's Health, University College London, 86-96 Chenies Mews, London WC1E 6HX, UK.*  
Tel No: +44/207/3908113/Fax: +44/207/3908115/E-mail: [e.jauniaux@ucl.ac.uk](mailto:e.jauniaux@ucl.ac.uk)

**Key Words:** Placenta accreta; placenta increta; placenta percreta; ultrasound; prenatal diagnosis; histopathology; interobserver agreement.

**Synopsis:** High interobserver degree of agreement was found for most ultrasound signs and for histopathologic examination in placenta accreta spectrum.

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## **Abstract**

**Objective:** To evaluate the agreement between observers in assessing ultrasound signs and histopathologic findings in the prenatal diagnosis and postnatal correlation of placenta accreta spectrum (PAS).

**Methods:** A retrospective study of ultrasound and histopathologic findings on 25 cases of PAS for which ultrasound images, clinical data and detailed histopathologic examination were available. The incidence of each ultrasound sign on grey-scale imaging and colour Doppler imaging (CDI) and the proportion of agreement for both ultrasound and histologic findings were calculated.

**Results:** The study group included 11 cases of placenta creta (adherenta), 10 cases of increta and four cases of percreta. Interobserver degree of agreement for ultrasound imaging in the second and third trimester and histologic diagnosis of PAS was good to excellent. The highest level of interobserver degree of agreement for ultrasound signs was found for the loss of clear zone, myometrial thinning substantial on grey-scale imaging and the presence of lacunar feeder vessels on 2-dimensional (D) and crossing vessels and lacunae on 3D CDI, respectively.

**Conclusions:** Most of the ultrasound signs described in recent international standardised protocols could be useful in the screening of women at risk of PAS and the corresponding ultrasound images could be remotely evaluated by experts.

## Introduction

Placenta accreta is a histopathologic term which refers to a spectrum of abnormally deep uterine placentations. Placenta accreta spectrum (PAS) was defined by Lukes et al 50 years ago to include both abnormally adherent and invasive placentas [1]. PAS has been separated into three categories according to the depth of villous invasiveness inside the uterine wall: placenta creta (PC) or adherenta where the placental villi are directly attached to the myometrium without interposing decidua; placenta increta (PI) where the villi penetrate the myometrium up to the uterine serosa; and placenta percreta (PP) where the villi penetrates through the serosa and invade surrounding tissues and organs such as the bladder [2-4]. 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 [1].

PAS and in particular its invasive forms are secondary to a decidua basalis defect due to a failure of normal re-epithelialization in the area of a uterine scar allowing trophoblastic infiltration beyond the superficial myometrium and villous development inside or beyond the uterine wall during subsequent placentation [3,5-9]. In the 1960s only half of the cases of PAS had an history of prior caesarean delivery (CD) [1]. The vast majority of PAS are now found in women presenting with a previous history of caesarean delivery (CD) and a placenta praevia [9-11]. Several epidemiological studies have also found that the strongest risk factor for placenta praevia is a prior CD [10-13] suggesting that poor vascularisation and tissue oxygenation in the area of a previous uterine scar is associated with a local failure of re-epithelialization and thus decidualization which has an impact on both implantation and placentation [3,6-8].

When unsuspected at delivery, PAS is associated with major haemorrhage and an increasing need for emergency hysterectomy [11,13]. In particular, its invasive forms will require major surgical procedures and the involvement of a multidisciplinary team [14]. Despite more than 30 years of experience and more than 1000 cases of PAS diagnosed prenatally reported in the international literature [4], more than 50-70% of the cases are still missed by routine ultrasound examination in the general population [12,15]. In a recent systematic review, we found that 23 out of 53 prenatal diagnosis series describing 1078 cases of PAS, did not provide data on the depth of villous myometrial invasion on ultrasound imaging or at delivery [4]. We also found that, due to wide heterogeneity in terminology used and study design, no ultrasound sign or a combination of ultrasound signs were specific of the depth of accreta placentation. Standardised evidence-based approaches were recently proposed for the ultrasound signs [16,17], clinical grading [18] and histopathological examination [19]. The aim of the present study is to evaluate the interobserver variability for ultrasound signs and histopathologic findings in the diagnosis of PAS in order to determine their potential for improving the prenatal screening and confirm the diagnosis at delivery.

## Materials and Methods

We conducted a retrospective study of 25 patients diagnosed with PAS over a 5-year period for which ultrasound images, clinical data and detailed histopathologic examination were available. In all cases, the diagnosis was made prenatally by expert maternal-fetal medicine physicians using both transabdominal and transvaginal ultrasound transducers with 3-dimensional (3D) imaging facilities (GE Voluson® 730, GE Medical System, Zipf, Austria). Magnetic resonance imaging (MRI) was performed in three cases of PP by experienced radiologists to evaluate the lateral extension of villous tissue outside the uterine wall.

All patients attending the Harris Birthright Research Centre for Fetal Medicine are informed that ultrasound images and clinical data are used for clinical studies approved by the local ethical committee. Retrospective patient consent and specific ethics committee approval was not required for this study as all prenatal ultrasound records were examined within the research centre, basic clinical were collected using a standard clinical audit protocol and all images and histological slides were anonymised for data analysis.

For the review of ultrasound images, we used ultrasound signs from the standardized descriptions proposed recently by the European Working Group on Abnormally Invasive Placenta (EW-AIP) and the AIP international expert group [16,17]. These signs are summarized in table 1. In addition, when available we also reviewed the three-dimensional (3D) ultrasound images of the placental bed and serosa-bladder interface obtained using the technique previously described by Cali et al [20].

For the histopathologic examination, a standard methodology was used as previously described by placental pathologists [1,2]. Between 10 and 15 samples

were taken from the accreta area, as identified by the clinical and macroscopic examination. All samples were processed as per the protocol of the Department of Histopathology and slides were stained with Haematoxylin and Eosin (H&E) for microscopic examination.

### ***Statistical analysis***

StatGraphic-plus Version 3 data analysis and statistical software package (Manugistics, Rockville, MD) was used to analyse the demographic data and calculate relationships between linear parameters. Continuous data are presented as mean and standard deviation (SD) and categorical variables are expressed as frequencies and percentages.

For both the ultrasound images (observers NZ and EJ) and histological slides (observer HS and EJ), observer B was blind to the examination results of observer A. Interobserver variability rates were based on each observer's first examination. 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 [21]. Because of the uneven distribution of values amongst cells some of the kappa values are unstable as indicated by negative values despite high agreement and we have used the percentage agreement as previously described [22]. Cross tabulations and agreement analysis was performed using Stata version 14.1m StataCorp LP, TX, USA. A binomial test of significance was conducted to assess whether there was evidence of higher agreement in the third than the second trimester. A P value <0.05 was considered significant.

## Results

The study group included 11 cases of PC, 10 cases of PI and four cases of PP confirmed clinically and by histopathological examination. Sixteen women (4 PC, 10 PI & 2PP) were first referred for expert ultrasound examination during the second trimester. The other nine women were referred between 28 and 36. In all cases, the placenta was also previa. The patient clinical characteristics are displayed in Table 2. A primary caesarean hysterectomy was performed in 17 (64%) cases including six of the PC cases, eight of the PI cases and the three cases of PP. The remaining eight cases were managed conservatively with partial myometrial resection. Twelve patients (5 PC, 4 PI & 3PP) were delivered before 37 weeks including two before 28 weeks of gestation because of major prenatal bleeding. A positive correlation was found between the number of prior CD and the gestational age at delivery ( $F= 6.78$ ;  $R= 22.8$ ;  $P=0.016$ ) but not for the number of prior CD and gestational diagnosis or for the gestational age at diagnosis and gestational at delivery.

Both investigators examined independently 105 ultrasound studies. Tables 3 and 4 present the distribution of the different ultrasound signs at the first ultrasound examination for the women referred in the second trimester and for the study group in the third trimester, respectively. Both observers reported a loss of clear zone, myometrial thinning and placental lacunae as the most common signs found in PAS with grey-scale imaging. Hypervascularity of utero-vesical interface and crossing vessels and lacunae were the most common signs on 2D and 3D CDI respectively.

Tables 5 and 6 shows and compares the interobserver agreement analysis for the ultrasound signs in the second and third trimester, respectively. Excellent agreement was found for the loss of clear zone, myometrial thinning substantial and

the presence of lacunar feeder vessels on grey-scale imaging and 2D CDI, respectively. Excellent agreement was also found for crossing vessels and lacunae on 3D CDI. For some markers, agreement was higher during the second than the third trimester but for others the reverse was found. There was no evidence that the overall agreement was better during the third than the second trimester ( $p = 0.527$ ).

The interobserver agreement analysis of the histopathologic grading of the different depth of villous invasion showed a 76% agreement. There were six cases where there was a difference between the observers in the final diagnosis. In five cases of PI one observer described them as PC and in the case of PP both observers described it as PI. In 16 cases, including all the cases of PI and two of the three PP cases, villous tissue was found to be both adherent and invasive. Infiltration of chorionic villi into myometrial vascular spaces was observed in three of the PI cases and 2 of the PP cases. The highest degree of invasion was used for the final classification of the 25 cases reviewed in this study.

## Discussion

This study is the first to provide data on the interobserver variability for both ultrasound imaging and histopathology in the perinatal diagnosis of PAS. High reproducibility and low interobserver variability of ultrasound imaging of invasive placentation assessments of quantitative data are important strengths of this technique in clinical practice and in particular in its role in the management of PAS.

The issue of interobserver variability in ultrasound prediction of PAS response assessments have only been previously evaluated by Bowman et al [23]. Their multivariate analysis found that true positives were more likely to have loss of subplacental clear zone placental lacunae or vascular abnormalities on CDI. In a recent systematic review using the standardised ultrasound signs (Table 1), we also found that a loss of clear zone, placental lacunae and subplacental hypervascularity on CDI were the most common signs in both cases report and cohort studies [15]. In the 72 cases, for which the authors provided detailed correlations between ultrasound findings and PA grading, loss of clear zone and bridging vessels was found 62.1% and 71.4% of PC cases, respectively whereas loss of clear zone (84.6%) and subplacental hypervascularity (60%) were the most common signs in PI whereas placental lacunae (82.4%) and subplacental hypervascularity (54.5%) were the most common signs for PP. There were no ultrasound sign or combination of ultrasound signs that were specific of the depth of accreta invasion [15].

In the present study, a loss of clear zone, myometrial thinning, placental lacunae (Figure 1) on grey-scale imaging and hypervascularity of utero-vesical interface (Figure 2) on 2D CDI were the most common signs found in PAS by both observers in the second and third trimester. 3D CDI also identified

hypervascularization patterns below the placental bed or subplacental zone and within the placenta (Figure 3) in 70-80% of the cases (Tables 3 and 4). The interobserver agreement for these signs was excellent suggesting that they could be included in screening protocol of women at high risk of PAS. We also found a significant positive correlation between the number of prior CD and the risk of preterm delivery when the subsequent pregnancy was complicated by placenta previa accreta. Prior CD is the main risk factor for the development of placenta previa accreta in subsequent pregnancies and the number of previous CD increases the risks of scar defects and dehiscence [3-6,10-13]. This can explain why a loss of clear zone and myometrial thinning has been reported by all authors of case reports and cohort series on the prenatal diagnosis of PAS [4]. In isolation, these ultrasound signs are probably of limited clinical use and are associated with a high false-positive rate.

The accuracy of both grey-scale and CDI in diagnosing placenta previa accreta in the second trimester in women presenting with a low placenta or placenta previa with one or more previous CD is high [9]. However, the results of well conducted prospecting cohort studies by Finberg et al [24] and Comstock et al [25] have shown that the sensitivity and specificity of grey-scale imaging alone in diagnosing for placenta previa accreta are high when performed by experience operators suggesting that CDI and 3D ultrasound are not essential to the screening of PAS [25]. The ultrasound appearance of most ultrasound signs used in the diagnosis of PAS are influenced by gestational age and technical artefacts such as the location of the placenta inside the uterine cavity, direct pressure of the ultrasound probes and/or the filling of the bladder [6]. The anatomy of the utero-placental interface may also be obscured by the amount of scar tissue present and the amount

of blood flow between the myometrium and bladder or between the placental basal plate and the bladder wall will be influenced by myometrial contractions [6]. Unlike MRI, ultrasound imaging is operator-dependent and thus this can explain why we found quantitative differences between expert observers for the presence of placenta lacunae, bladder wall interruption on grey-scale imaging and vascularity changes between the placenta basal plate and the myometrium on 2D CDI.

Bladder wall interruption or loss or irregularity are often an artefact secondary to ultrasound dropout from the angle of insonation [6]. Subplacental hypervascularity and lacunae feeder vessels are secondary to the dilatation of the utero-placental circulation beyond the spiral arteries and their features may vary depending on the position of the placenta inside the uterine cavity, whether near to or far from the main uterine arteries, and on the remodelling of the myometrial circulation around the scar area [6]. The findings of the present study suggest that in placenta previa accreta the hypervascularity of the utero-vesical interface and subplacental area on 2D CDI should be included in the same category of ultrasound signs and are better evaluated with 3D CDI. However, this latter technique requires advanced ultrasound equipment and additional expertise which mainly available in specialist centres.

Detailed correlation between ultrasound and histopathological examination using standard protocols is essential to improve the prenatal screening and diagnosis and thus management of women with PAS. The differential diagnosis between retained placenta and abnormally adherent can be difficult, in particular in the absence of pathological examination. The different diagnosis between PC and PI can also be difficult after manual placental delivery and/or post-partum uterine curettage [1-3]. In these cases, the utero-placental interface is inevitably damaged leaving often no myometrial tissue and thus impairing the quality of histological

examination. Modern pathological studies have also shown that the degree of villous adhesion or invasion is rarely uniform across the accreta area of placental bed and that many cases of PAS present with creta (adherenta) and increta zones [1,2,6]. This can explain, the discrepancy for depth of accreta invasion in histological classification in six cases out of 25 cases in the present series.

Excellent or good interobserver agreement for most the ultrasound signs described in recent international standardised protocols suggest that ultrasound images could be remotely evaluated by experts for centres that do not have the expertise in the diagnosis of PAS. Similarly, histological slides obtained using the standardised protocols [19] could be review remotely by perinatal pathology experts. Multicentric prospective studies are needed to further evaluated this concept.

## **Author contributions**

All authors contributed to the study design were involved in the critical discussion and approved this final version for publication. NZ and EJ performed the ultrasound signs interobserver study and HS and EJ performed the histopathology interobserver study. CB and EJ carried out the data analysis. EJ and NZ drafted the manuscript. EJ is the guarantor of the study.

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## **Conflict of interest**

The authors have no conflicts of interest to declare.

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**Table 1.** Ultrasound signs from the standardized descriptions proposed recently by the European Working Group on Abnormally Invasive Placenta (EW-AIP) and the AIP international expert group [16,17].

**Grey-scale imaging**

- 1) Loss of the clear zone in the myometrium under the placental bed (“subplacental clear zone”);
- 2) Myometrial thinning to <1mm or undetectable;
- 3) Intra-placental lacunae often large and irregular (“moth eaten” areas);
- 4) Bladder wall interruption or loss (hyperechoic line between serosa and bladder lumen);
- 5) Placental bulge distorting the extrauterine organs; and
- 6) Focal exophytic mass of placental tissue extending beyond the serosa.

**Colour Doppler imaging (CDI)**

- 7) Utero-vesical hypervascularity between the myometrium and the posterior wall of the bladder;
- 8) Subplacental hypervascularity (placental bed);
- 9) Bridging vessels across the myometrium and beyond the serosa;
- 10) Lacunae feeder vessels with high velocity (turbulent) flow from the arterial vasculature of myometrium.

**Table 2:** Patient clinical characteristics.

**Variables**

	Mean (SD)
Maternal age (Years)	36.1 (4.7)
Gesity	4.6 (1.8)
Parity	2.6 (1.6)
No of prior CD	2.1 (1.5)
Gestational age at diagnosis (weeks)	22.2 (8.6)
Gestational age at delivery (weeks)	34.9 (3.6)

CD= Caesarean delivery; PI= Placenta increta; PP= placenta percreta; EI=elective; Em= emergent.

**Table 3:** Distribution of the ultrasound signs found in the 16 cases according to depth of villous invasiveness at the second trimester ultrasound examination for observer A and B.

Ultrasound signs	PC n=4		PI n=10		PP n=2		Total n= 16	
	A n	B n	A n	B n	A n	B n	A n(%)	B n(%)
<u>Grey-scale Parameters</u>								
1.Loss of clear zone	4	4	10	10	2	2	16(100)	16(100)
2.Myometrial thinning	4	4	10	10	2	2	16(100)	16(96)
3.Placental lacunae	2	4	8	10	1	2	11(56)	16(96)
4.Bladder wall interruption	2	4	3	6	1	2	6(36)	12(72)
5.Placental bulge	0	0	1	0	0	1	1(4)	1(4)
6.Focal exophytic mass	0	0	1	1	0	0	1(8)	1(8)
<u>CDI Parameters</u>								
7.Utero-vesical HV	3	3	6	10	2	2	11(68.7)	15(93.7)
8.Subplacental HV	2	4	4	8	1	2	7(43.7)	14(87.5)
9.Bridging vessels	1	2	2	6	0	2	3(18.7)	10(62.5)
10.Lacunae feeder vessels	2	2	3	3	0	0	5(31.2)	5(31.2)
11.3D crossing vessels	3	3	7	8	2	2	12(75)	13(81.2)
12.3D lacunae	3	3	7	7	2	2	12(75)	12(75)

CDI= Color Doppler Imaging; PI= Placenta increta; PP= placenta percreta; HV= hypervascularity.

**Table 4:** Distribution of the ultrasound signs found in the 23 cases according to depth of villous invasiveness at the third trimester ultrasound examination for observer A and B.

Ultrasound signs	PC n=7		PI n=13		PP n=3		Total n= 23	
	A n	B n	A n	B n	A n	B n	A n(%)	B n(%)
<u>Grey-scale Parameters</u>								
1.Loss of clear zone	7	7	13	13	3	3	23(100)	23(100)
2.Myometrial thinning	7	7	13	13	3	3	23(100)	23(100)
3.Placental lacunae	4	6	11	13	1	3	16(69.5)	22(95.6)
4.Bladder wall interruption	3	5	9	11	2	3	14(60.8)	19(82.6)
5.Placental bulge	0	0	2	0	0	1	2(8.6)	1(4.3)
6.Focal exophytic mass	0	0	2	1	0	0	2(8.6)	2(8.6)
<u>CDI Parameters</u>								
7.Utero-vesical HV	4	7	11	13	3	3	18(78.2)	23(100)
8.Subplacental HV	3	5	6	12	3	3	12(52.1)	20(86.9)
9.Bridging vessels	2	3	2	8	0	3	4(12.6)	14(76.7)
10.Lacunae feeder vessels	2	2	4	4	1	1	7(30.4)	7(30.4)
11.3D crossing vessels	7	6	10	10	2	2	19(82.6)	18(78.2)
12.3D lacunae	7	6	7	9	2	2	16(69.5)	17(73.9)

CDI= Color Doppler Imaging; PI= Placenta increta; PP= placenta percreta; HV= hypervascularity

**Table 5:** Interobserver agreement for the ultrasound signs used in the diagnosis of in the second trimester.

<b>Ultrasound signs</b>	<b>Agreement %</b>
<u>Grey-scale Parameters</u>	
1.Loss of clear zone	100
2.Myometrial thinning	96
3.Placental lacunae	68
4.Bladder wall interruption	64
5.Placental bulge	92
6.Focal exophytic mass	92
<u>CDI Parameters</u>	
7.Utero-vesical HV	64
8.Subplacental HV	56
9.Bridging vessels	56
10.Lacunae feeder vessels	100
11.3D crossing vessels	92
12.3D lacunae	95

CDI= Color Doppler Imaging; PI= Placenta increta; PP= placenta percreta; HV= hypervascularity.

Signs	1		2		3		4		5		6	
Observer	B		B		B		B		B		B	
A	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Yes	16	0	16	1	10	0	0	5	0	1	1	0
No	0	0	0	0	6	1	8	4	1	15	0	16

Signs	7		8		9		10		11*		12*	
Observer	B		B		B		B		B		B	
A	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Yes	11	1	8	0	3	0	4	0	12	0	12	0
No	5	0	2	2	6	8	0	13	2	0	0	2

\* In 3 cases neither observer could record a value

**Table 6:** Inter-observer agreement for the ultrasound signs used in the diagnosis of in the third trimester.

Ultrasound signs	Agreement %
<u>Grey-scale Parameters</u>	
1.Loss of clear zone	100
2.Myometrial thinning	100
3.Placental lacunae	74
4.Bladder wall interruption	70
5.Placental bulge	87
6.Focal exophytic mass	87
<u>CDI Parameters</u>	
7.Utero-vesical HV	78
8.Subplacental HV	65
9.Bridging vessels	55
10.Lacunae feeder vessels	100
11.3D crossing vessels	95
12.3D lacunae	86

CDI= Color Doppler Imaging; PI= Placenta increta; PP= placenta percreta; HV= hypervascularity.

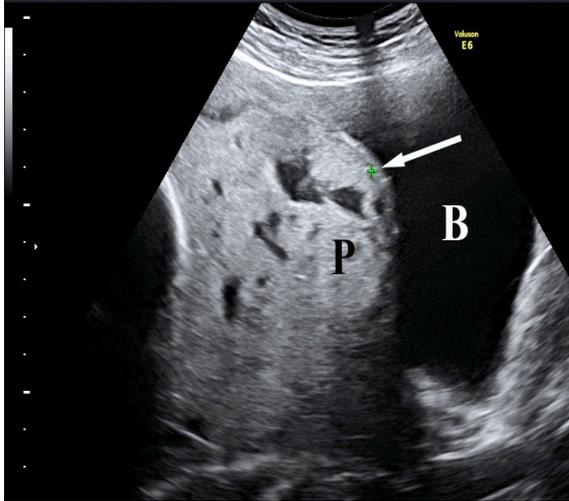
Signs	1		2		3		4		5		6	
Observer	B		B		B		B		B		B	
A	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Yes	23	0	23	0	16	6	13	1	0	1	0	1
No	0	0	0	0	6	1	6	3	2	20	1	20

Signs	7		8		9*		10		11**		12**	
Observer	B		B		B		B		B		B	
A	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Yes	18	5	12	0	4	0	7	0	18	1	15	1
No	0	0	8	3	10	8	0	16	0	2	2	3

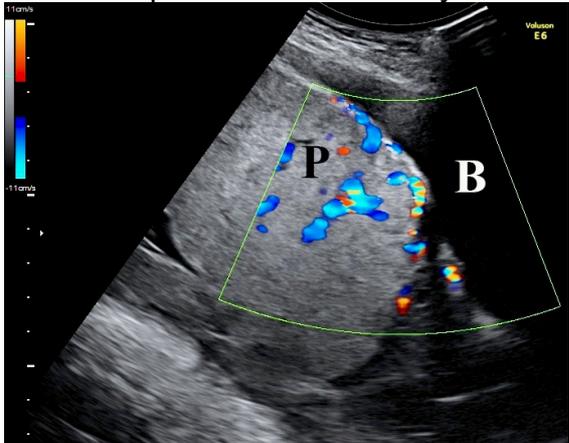
\* In 1 cases neither observer could record a value, \*\* 2 cases neither observer recorded a value

## Figure legends

**Fig 1:** Transabdominal ultrasound view of a placenta (P) previa creta at 30 weeks showing: loss of the clear zone under the placental bed and myometrial thinning (arrow) and intra-placental lacunae. B= Bladder.



**Fig 2:** Transabdominal color flow mapping of a placenta (P) previa increta at 32 weeks showing bridging and lacunae feeder vessels. Note the loss of the clear zone under the placental bed and myometrial thinning.



**Fig 3:** Transvaginal color flow mapping and 3D reconstruction of the utero-placental circulation in a placenta previa increta at 20 weeks showing the neovascularization of the uterine serosa-bladder (B) interface.

