Three-Dimensional Power Doppler Ultrasound for Diagnosing Abnormally Invasive Placenta and Quantifying the Risk

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Running title: Diagnosing Abnormally Invasive Placenta

Précis

The three-dimensional power Doppler ultrasound marker of the largest area of confluent power Doppler signal ($A_{con)}$ provides an objective quantitative means for both diagnosing abnormally invasive placenta and assessing its severity.

ABSTRACT

Objective

To test an objective ultrasound marker for diagnosing the presence and severity of abnormally invasive placenta.

Methods

Women at risk of abnormally invasive placenta underwent a three-dimensional (3D)-power Doppler ultrasound scan. The volumes were examined offline by a blinded observer. The largest area of confluent 3D-power Doppler signal (A_{con}:cm^2) at the utero-placental interface was measured and compared in women subsequently diagnosed with abnormally invasive placenta and controls who did not have abnormally invasive placenta. Receiver-operating characteristic (ROC) curves were plotted for prediction of abnormally invasive placenta and abnormally invasive placenta requiring cesarean hysterectomy.

Results

Ninety three women were recruited. Results were available for 89. Abnormally invasive placenta was clinically diagnosed in 42 women; 36 required hysterectomy and had abnormally invasive placenta confirmed histopathologically. Median and interquartile range for A_{con} was greater for abnormally invasive placenta (44.2 [31.4-61.7] cm^2) versus controls 4.5 cm^2 [2.9-6.6], p<0.001), and even greater in the 36 requiring hysterectomy (46.6 cm^2 [37.2-72.6] p<0.001). A_{con} rose with histopathological diagnosis: focal accreta 32.2cm^2 [17.2-57.3]), accreta 59.6cm^2 [40.1-89.9]) and percreta (46.6cm^2 [37.5-71.5), p<0.001 ANOVA for linear trend). ROC analysis for prediction of abnormally invasive placenta revealed that with an A_{con}≥12.4 cm2, 100% sensitivity (95%CI 91.6-100) could be obtained with 92% specificity (95%CI 79.6-97.6); area under the curve (AUC) is 0.99 (95%CI 0.94 to 1.0). For prediction of abnormally invasive placenta requiring hysterectomy, 100% sensitivity (95%CI 90.3-100) can be obtained with an A_{con} of ≥17.4 cm2, with 87% specificity (95%CI 74.7-94.5); AUC 0.98 (0.93-1.0).

Conclusion:

The marker A_{con} provides a quantitative means for diagnosing abnormally invasive placenta and assessing severity. If further validated, subjectivity could be eliminated from the diagnosis of abnormally invasive placenta.

INTRODUCTION

Abnormally invasive placentation, or placenta accreta, is a life threatening obstetric condition in which failure of placental separation at delivery can lead to catastrophic maternal haemorrhage. Prior cesarean delivery and placenta previa are the main risk factors.[1] The incidence of abnormally invasive placenta is increasing with the rise in cesarean delivery rates.

Maternal mortality and morbidity are reduced when women deliver in a tertiary hospital with a multidisciplinary team.[2,3] Antenatal diagnosis rests on 'typical' sonographic findings.[4] Magnetic resonance imaging has yet to clearly demonstrate an improvement in pregnancy outcomes.[5] Irrespective of the imaging modality, diagnosis is subjective with accuracy depending on the experience of the operator, which is limited by the rarity of the condition. Recent advances in three dimensional (3D) power Doppler (PD) imaging offered a new marker of 'numerous coherent vessels'.[6] However, it too remains subjective and experience-dependent.

While sensitivity is crucial, so too is the specificity of prenatal diagnosis. The price of a false-positive diagnosis is high. A vertical laparotomy proceeding straight to hysterectomy, is frequently employed when abnormally invasive placenta is anticipated.[7] Prophylactic occlusive balloons in the pelvic vasculature risk significant complications.[8-10] The American College of Obstetricians and Gynecologists currently states that combined maternal and neonatal outcome is optimized in stable patients with a planned delivery at 34 weeks, resulting in iatrogenic neonatal morbidity.[3,5,11,12]

95 The aim of this study was to investigate whether our novel ultrasound marker of largest area of
96 confluent 3D-power Doppler signal (A_{con}) can accurately predict both the presence and severity of
97 abnormally invasive placenta.
98

MATERIALS AND METHODS

Women were recruited from two referral centers: the Fetal Medicine Unit, John Radcliffe Hospital (Oxford, UK) and the Center for Abnormal Placentation at Hackensack University Medical Center (New Jersey, USA). Patients were referred by their primary healthcare provider if they suspected abnormally invasive placentation: diagnosis of a placenta previa and a history of previous uterine surgery or ultrasound findings suggestive of abnormally invasive placenta on routine ultrasound scan. Written informed consent was obtained with local research ethics approval. Exclusion criteria were multiple gestation, age <16 (UK) or <18 (USA) years and inability to provide informed consent.

The women were managed according to their local unit protocol. Pregnancy and delivery data were collected from antenatal records, operative and delivery notes, and postpartum records. The presence and severity of abnormally invasive placentation was assessed at delivery according to our clinical grading system (Table 1) by an attending obstetrician who had seen >10 cases of abnormally invasive placenta and from histopathology results where hysterectomy was performed. All histopathology was undertaken by senior pathologists in each unit who have special expertise in placentology.

Patients underwent diagnostic imaging according to the local unit protocol. In addition, static, transabdominal 3D power Doppler ultrasound volumes of the placental bed were obtained according to a pre-defined protocol, with the participant in a semi-recumbent position and a full bladder using a RAB4-8-D 3D/4D curved array abdominal transducer (4-8.5 MHz) on a Voluson E8™ (GE Healthcare, Milwaukee, WI, USA). Pre-determined machine settings were used (for details of all settings see Collins et al 2012).[13] To allow for differences in attenuation of the power Doppler signal due to variation in placental site and maternal adiposity, the sub-noise gain setting was selected according to a previously validated technique.[14,15] The participant was asked to remain as still as possible, and

volumes were excluded if any 'flash artefact' (secondary to fetal or transducer movement) was present. Initially a standard 85^{o} volume was collected in the sagittal plane, midline under the utero-vesical fold (presumed site of previous cesarean delivery scar and therefore most likely site of any abnormally invasive placenta). Subsequent volumes were then systematically collected until the entire basal plate of the placenta had been imaged, usually three to five volumes. The data was then stored anonymously using Sonoview and analysed after delivery, using the software package 4D View™ (GE Healthcare, Milwaukee, WI, USA).

All the static volumes were opened in 4D View™ and examined by one operator (SC). All images were coded (de-identified) and the analysis was conducted blinded to pregnancy outcome and previous imaging findings. The 3D volumes containing the utero-placental interface were transformed until only the PD signal around the utero-placental interface remained. This was performed according to the process shown in Figure 1. A 3-dimensional process is difficult to represent in 2-dimensions, therefore the images in Figure 1 have been adjusted to make the concept clearer. The settings were identical for all the patients including PD threshold and image magnification. The 3D-power Doppler signal was overlaid over the 3D B mode volume (Fig 1A & B). The volume was manipulated in three dimensions using the 4D View™ software and the PD signal was sequentially reduced using the software's 'magi-cut', colour-only function. Initially the PD signal representing the fetal circulation was removed (Fig 1C), then the remaining PD signal was removed until a 1cm deep volume was left: 0.5cm either side of the utero-placental interface (Fig 1D). The volume was then re-orientated until the plane of the utero-placental interface containing the PD signal of interest was perpendicular to the eye-line of the observer (Fig 1E). The vascularity at the utero-placental interface is thus viewed as if the observer was looking down through the flat placental bed from the myometrium towards the fetus. If the starting volume is initially in mid-sagittal view this is achieved by rotating by 90^{o} around the y-axis. The B mode was removed from view to improve visualisation of the PD signal. The largest area of confluent PD

signal (Area of confluence in cm^2, A_{con}) was then quantified using the 'generic area' measurement function provided by 4D View™ (Fig 1E).

Ten volumes were selected to be included in the intra and inter-observer study, five were randomly taken from the confirmed AIP group and five from the not AIP group. A_{con} was estimated by two observers (SC and GS) on three different occasions blinded to their previous estimates and each other's results. The two-way mixed intraclass correlation coefficients (ICCs) were calculated to assess intra and inter-observer variability.

Analyses of maternal/neonatal demographic characteristics were performed by Student's *t*-test or chi-square as appropriate. A_{con} was not normally distributed (Kolmogorov-Smirnov $p<0.001$), being right-skewed in both cases and controls. Therefore comparison of A_{con} between groups was conducted by non-parametric Mann-Whitney U and presented as box plots encompassing the 25^{th}-75^{th} centiles and whiskers indicating 5^{th}-95^{th} centiles.. A_{con} data analysed by diagnostic categories, whether histopathological or by clinical grade, were log-transformed and an ANOVA analysis of the linear trend between means was utilized. Regression analysis was used to examine the relationship between the log-transformed A_{con} and gestational age at the time of the scan. The receiver-operating characteristic (ROC) curves were plotted for the prediction of an abnormally invasive placenta by A_{con} (all abnormally invasive placenta, n=42) and the presence of abnormally invasive placenta resulting in cesarean hysterectomy (confirmed histopathologically, n=36) and area under the curve (AUC) was calculated with the exact binomial method employed to calculate the 95% confidence intervals. We report our data with sensitivity set, *a priori,* at 100%. Our goal in developing an objective screening test is to provide assurance with the highest possible accuracy that abnormally invasive placenta is not present. Statistical analyses were performed using SPSS (v19.0, IBM Corporation, NY, USA), and results were

graphed using Graph Pad Prism (Graph Pad Software, La Jolla, CA). Results were considered to be significant when $p<0.05$.

RESULTS

Ninety-three women were recruited over 2 years (4/2012 – 3/2014); two were lost to follow-up, one was excluded for an incomplete scan of the utero-placental interface and one was excluded because the woman was unable to fill her bladder sufficiently to adequately visualize the utero-vesical interface. Images and delivery data were available for 89 women (Table 2). Forty-seven women had no evidence of abnormally invasive placenta at delivery. Three of these women had a hysterectomy at the time for uterine atony unresponsive to conservative management, massive leiomyomas, and uterine-bowel adhesions. Subsequent histopathology confirmed no abnormally invasive placenta. Forty-two women had clinical evidence of abnormally invasive placenta at delivery, 36 of whom required hysterectomy. All 36 were histopathologically confirmed as abnormally invasive placenta (5 focal accreta, 9 accreta, and 22 percreta). All the women with abnormally invasive placenta had at least one previous cesarean delivery except for two who had complex histories of multiple uterine surgeries. The median gestation for all included scans was 32 weeks. There was no difference in the gestational age at USfor the women diagnosed with abnormally invasive placenta (median 32+1 weeks, range 17+1–33+6 weeks) and those without abnormally invasive placenta (32+4, range 15+2-39+2).

There were no differences in the BMI, ethnicity or parity of women with versus without abnormally invasive placenta (Table 2). The group diagnosed with abnormally invasive placenta had more total previa ($p<0.001$), underwent more hysterectomies ($p<0.001$) and were delivered earlier ($p<0.01$).

The intra-class correlation coefficient for the values of A_{con} estimated by the two different observers (inter-observer) was 0.92 (95% CI: 0.85-0.97). The ICCs for three repeated estimates by each observer (intra-observer) were 0.94 (GS: 0.89-0.99) and 0.95 (SC: 0.90-1.0).

196 A_{con} values were greater for the group clinically diagnosed with abnormally invasive placenta (n=42,
197 median 44.2, 25th-75th centile 31.4-61.7) than those without abnormally invasive placenta (4.5 [2.9-6.6],
198 Mann-Whitney U, p<0.0001; Figure 2A). A_{con} values were even greater in the subset of the AIP group
199 whose pathology was severe enough to require hysterectomy (46.6 [37.2-72.6]) compared to those
200 clinically diagnosed with abnormally invasive placenta but managed by placental removal without
201 hysterectomy (28.4, [21.9-33.6], p<0.005; Figure 2B). A_{con} rose with more severe histopathological
202 diagnosis (focal accreta 32.2cm^2 [17.2-57.3]), accreta 59.6 cm^2 [40.1-89.9]) and percreta (n=22, 46.6
203 cm^2 [37.5-71.5), p<0.0001, ANOVA test for linear trend between means). When the histopathological
204 diagnosis was compared between the 36 with abnormally invasive placenta and the 3 without
205 abnormally invasive placenta who underwent hysterectomy, A_{con} was greater for any form of accreta
206 (p<0.0001, Kruskal-Wallis with Dunn's multiple comparison; Figure 2C). Likewise, when A_{con} was
207 plotted against the clinical grade assigned to each case all grades had an elevated A_{con} relative to
208 control (p<0.0001, ANOVA test for linear trend between means, Figure 2D). . There was no correlation
209 between A_{con} and gestational age at the time of the ultrasound scan (r^2 for abnormally invasive placenta
210 = 0.12; for not abnormally invasive placenta r^2=0.08).

211 All 42 abnormally invasive placenta cases had A_{con} values ≥12.4 cm^2 while 4/47 controls had values
212 >12.4 cm^2 (false positives, range 12.8-29.7). The ROC curve for prediction of a clinical diagnosis of
213 abnormally invasive placenta (all grades) shows an AUC of 0.99 (0.94-1.0; Figure 3A, Table 3). With an
214 A_{con} of ≥12.4 cm^2 100% sensitivity could be achieved for the prediction of all clinically diagnosed
215 abnormally invasive placenta, with a 92% specificity and a positive predictive value (PPV) of 92% (8%
216 false-positive rate). Of greater clinical relevance, the AUC for abnormally invasive placenta requiring
217 hysterectomy compared with all other cases (including clinically diagnosed abnormally invasive
218 placenta managed conservatively) was 0.98 (0.93-1.0). Therefore an A_{con} of ≥17.4 cm^2 yielded 100%
219 sensitivity with 87% specificity and a 13% false-positive rate.

DISCUSSION

Abnormally invasive placenta is a dangerous pathology; it is difficult to manage clinically and is increasing worldwide[16]. Our results suggest that a quantitative measure, designated here as largest area of confluence (A_{con}), can differentiate between the presence and absence of abnormally invasive placenta, and is associated with the histopathological and clinical severity of abnormally invasive placenta. That 100% sensitivity was achieved with an 8% false-positive rate suggests that this technique could allow reliable prenatal diagnosis. This would enable adequate preparation and intervention for cases of abnormally invasive placenta, while minimizing the iatrogenic adverse events. However, care must be taken when interpreting this FPR as our sample was taken from a population with a high prevalence, women who were already considered to be at risk of abnormally invasive placenta. It would be inappropriate for this test to be employed as a screening tool on a low risk population due to the risk of the false positive paradox (the FPR being greater than the true positive rate due to the rarity of the condition).[17]

The observed increase in A_{con} with increasing severity, both clinical and histopathological, suggests that the numerical value of A_{con} may be able to predict not only the presence of abnormally invasive placenta but also the degree of clinical risk. In the absence of histopathological analysis a clinical grading system (Table 1) is required to compare severity of outcomes between centers. Without this we cannot compare the efficacy of diagnostic assessments. Most studies have not separated their cases into accreta, increta or percreta and some have minimal histopathological data with which to confirm a subjective diagnosis, despite large numbers of patients[18]. The use of a standardized clinical grading system would allow comparison both in research and clinical practice.

The strength of the study is the encouraging results despite the relatively small sample size. We acknowledge several weaknesses. This was a, 'proof of concept' pilot study, which combined the values for A_{con} gathered at a variety of gestations ranging from 19 to 39 weeks. Although there was no

strong correlation between the value of A_{con} and gestational age, the latter is still likely an important factor. Evaluation of A_{con} with larger numbers of at risk women and over an extended gestational age range are required to further evaluate the test and to determine gestation-appropriate values.

100% sensitivity was achieved with an 8% false positive rate. Although in many screening situations this would be too high, it is probably acceptable if it ensures no cases are missed in a condition where antenatal diagnosis has been shown to significantly decrease maternal mortality.[2]

The technique itself also has weaknesses and unknown factors. The manual process currently employed to obtain A_{con} using 4-D View™ requires considerable practice and must be undertaken by operators both experienced in placental imaging and manipulating 3D PD images in 4D View™. Although we have demonstrated high reproducibility, both operators were not only experienced in placental imaging but were also instrumental in designing the technique. This operator dependence can be decreased by use of existing image analysis tools, which reliably map the vasculature and morphometry of the placenta.[19-21] We have already developed a semi-automated technique to analyse the placenta, utero-placental interface, and its vasculature in the first trimester.[21,22] These techniques could be applied to facilitate semi-automated estimation of A_{con} thereby simplifying the process and decreasing operator dependence.

Little is known of the process underlying the development of the area of confluence. One theory is that it represents enlarged arterio-venous anastomoses located in the sub-placental myometrium[23], generating a large circulating pool which can be detected as an abnormal area of power Doppler signal in abnormally invasive placentas. This agrees with the findings of Tantbirojn et al. who showed trophoblast-induced remodelling deep in the myometrium.[24] How A_{con} develops over time remains unclear, but serial data across gestation may reveal not only the natural history, but whether abnormally invasive placenta progresses, for example, from an accreta to percreta. This is not trivial,

current ACOG recommendations suggest delivery at 34 weeks,.[12] While our data does not support a strong correlation between the size of A_{con} and gestational age, the majority of our data were collected in the late second and early third trimester. With a larger sample size, confidence intervals for A_{con} can be determined across gestation and in all grades of abnormally invasive placenta, thereby enabling establishment of clinically useful cut-off values that could reliably predict not only the presence of abnormally invasive placenta but also its likely clinical severity.

In summary we report a new, quantitative ultrasound technique enabling reliable prenatal identification of abnormally invasive placenta, a condition where prenatal diagnosis has been shown to reduce the high maternal mortality and morbidity[25]. The application of existing image analysis tools to automate calculation of A_{con} could eliminate operator dependence and permit its use for screening outside of specialized centers. Larger, longitudinal studies will allow exploration of the pathology of excess vascularity in abnormally invasive placenta, the optimal gestation for diagnosis and yield further information on the technique's performance.

Table 1: Clinical Grading System Used to Assess the Severity of the Abnormally Invasive Placenta

GRADE	DEFINITION
1	At cesarean or vaginal delivery: Complete placental separation at third stage. Not abnormally invasive placenta.
2	At cesarean delivery/laparotomy: No placental tissue seen invaded through the serosal surface of the uterus. Only partial separation with synthetic oxytocin and gentle controlled cord traction, manual removal of placenta required for remaining tissue AND parts of placenta thought to be abnormally adherent by a senior, experienced clinician. At vaginal delivery; manual removal of placenta required AND parts of placenta thought to be abnormally adherent by a senior, experienced clinician.
3	At cesarean delivery/laparotomy: no placental tissue seen invaded through the serosal surface of the uterus. No signs of any separation with synthetic oxytocin and gentle controlled cord traction, manual removal of placenta required AND the whole placental bed thought to be abnormally adherent by a senior, experienced clinician. At vaginal delivery: manual removal of placenta required AND the whole placental bed thought to be abnormally adherent by a senior, experienced clinician.
4	At cesarean delivery/laparotomy: Placental tissue seen to have invaded through the serosal surface of the uterus but NOT passing into any surrounding structures (including the posterior wall of the urinary bladder). A clear surgical plane can be identified between the bladder and uterus to allow non-traumatic reflection of the urinary bladder at hysterectomy.
5	At cesarean delivery/laparotomy: Placental tissue seen to have invaded through the serosal surface of the uterus AND invaded into the urinary bladder ONLY (consequently, a clear surgical plane cannot be identified between the bladder and uterus to allow non-traumatic reflection of the urinary bladder at hysterectomy).
6	At cesarean delivery/laparotomy: Placental tissue seen to have invaded through the serosal surface of the uterus AND invaded into the pelvic side wall or any organ other than the urinary bladder, +/- invasion into the urinary bladder.

NB For the purposes of this scale “uterus” includes the uterine body and uterine cervix.

293 **Table 2: Maternal characteristics and AIP risk factors**

294 (Means/median/proportions ± SD and range)

Maternal demographics	**Not AIP n = 47**	**AIP n = 42**	**P value**
BMI (Pre-pregnancy)	26.7 ± 5.4 (18.1 – 43.0)	26.1 ± 5.3 (17.9 – 43.4)	0.66
Ethnicity			
White (non Hispanic)	24 (50%)	22 (53%)	0.80
Hispanic	9 (19%)	11 (26%)	1.00
Black	4 (9%)	4 (9%)	0.70
Asian	3 (7%)	4 (9%)	0.20
Other (inc. mixed race)	7 (15%)	1 (2%)	0.06
Parity			
P0	5 (11%)	2 (5%)	0.40
P1	22 (47%)	15 (36%)	0.40
P2	12 (26%)	10 (24%)	0.60
P≥3	8 (17%)	15 (36%)	0.05
Gestational age (in weeks)			
at delivery	37+1 (28+2 - 42)	34+3 (21+5 – 26+4)	<0.01
at ultrasound scan	32+1 (17+1–33+6)	32+4 (15+2 – 39+2)	0.80
Hysterectomy performed	3 (6%)	36 (86%)	<0.001
Admission to ICU	0	3 (7%)	0.10
AIP risk factors			
Prior Cesarean (0-8)			
0	10 (21%)	2 (5%)	0.03
1	22 (47%)	21 (50%)	0.80
2	9 (19%)	9 (21%)	1.00
≥3	6 (13%)	10 (24%)	0.30
Placenta previa			
Major placenta previa	17 (36%)	32 (76%)	<0.001

(placenta over os)			295
Marginal placenta previa (≤ 2 cm from os)	7 (15%)	7 (17%)	1.00296
Cesarean scar and major placenta previa	11 (23%)	30 (71%)	<0.001
Previous Uterine Surgery			
Evacuation of Retained Products of Conception (ERPC)	9 (19%)	13 (31%)	0.23
Myomectomy	3 (6%)	2 (5%)	1.0
Trans-cervical resection of fibroids	1 (2%)	1 (2%)	1.0
Endometrial ablation	0	1 (2%)	0.10
Assisted Reproductive Technology	1 (2%)	3 (7%)	0.30

297 TABLE 3: Receiver-operating characteristic (ROC) curves for prediction of any AIP and AIP requiring
298 cesarean hysterectomy
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	A_{con} threshold value	Sensitivity (95%CI)	Specificity (95%CI)	AUC (95% CI)
Any AIP	12.4 cm^2	100% (91.6-100)	91.5% (79.6-97.6)	0.99 (0.94-1.00)
AIP requiring cesarean-hysterectomy	17.4 cm^2	100% (90.3-100)	86.8% (74.7-94.5)	0.98 (0.93-1.00)

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Figure Legends

Figure 1: 2D representation of the 3D method used to generate Area of confluence (A_{con})

A. The volume in B mode (lines have been drawn in on the 2D image to demonstrate the utero-placental interface (UPI) and the serosal surface of the uterus).
B. The B mode volume with the 3D power Doppler (PD) signal overlaid.
C. The PD signal after the fetal circulation has been removed.
D. Only the PD signal around the UPI is left.
E. The PD signal with the flattest plane of the UPI at 90° to the eye-line of the observer, the B mode signal removed and the largest area of PD confluence (A_{con}) estimated (shown by the yellow outline).

Figure 2: The median and 95% confidence intervals of the Area of confluence (A_{con}) in cm^2 for the following comparisons:

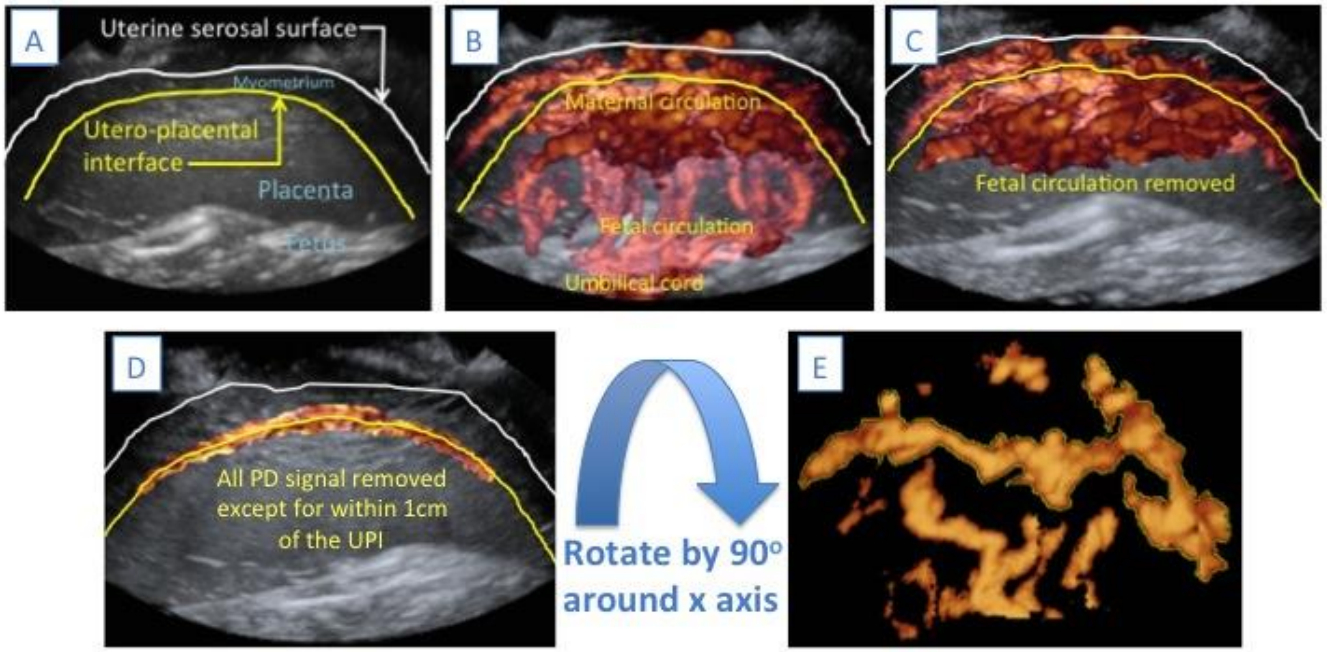
A. The clinical diagnosis of Not AIP (left, n=47, range 0.5-29.7 cm^2) versus AIP (right, n = 42, range 12.7-150,4 cm^2), p<0.0001.
B. Left two box-plots - Patients without AIP who did not have a hysterectomy (NO, n = 44, range 0.5-29.7 cm^2) or did have a hysterectomy (YES, n = 3, range 2.2-9.4 cm^2), p=NS. Right two box-plots - Patients with AIP who did not have a hysterectomy (NO, n = 6, range 12.7-33.6 cm^2) or did have a hysterectomy (YES, n = 36, range 18.7-150.4 cm^2, p<0.005).
C. Patients histopathologically confirmed as Not AIP (n=3), focal accreta (n = 5, range 18.7-61.1 cm^2), accreta (n = 9, range 23.9-102.6 cm^2) or percreta (n = 22, range 24.9-150.4 cm^2), p <0.0001 versus Not AIP).
D. Clinical grade (defined in Table 1) was greater for all grades relative to control (p<0.0001). Grade 2 (n = 12 median 32.2 cm^2, range 18.7-61.1), grade 3 (n = 6, median 54.7 cm^2, range 12.7-89.3), grade 4 (n = 15 median 45.7 cm^2, range 24.9-102.6), grade 5 (n = 8, median 59.6 cm2, range 43.0-150.4) and grade 6 (n=2, median 126.6 cm^2, range 113.3-141.8)

Figure 3: Receiver operator curves for the prediction of AIP using Area of confluence (A_{con})

A. ROC curve for any clinically diagnosed AIP (all grades) relative to controls. Area under the curve is 0.99, $p<0.0001$.

B. ROC curve for any histopathologically confirmed AIP significant enough to warrant hysterectomy relative to controls (not AIP and clinically diagnosed AIP managed with MROP). Area under the curve is 0.98, $p<0.0001$.

344 Figure 1:



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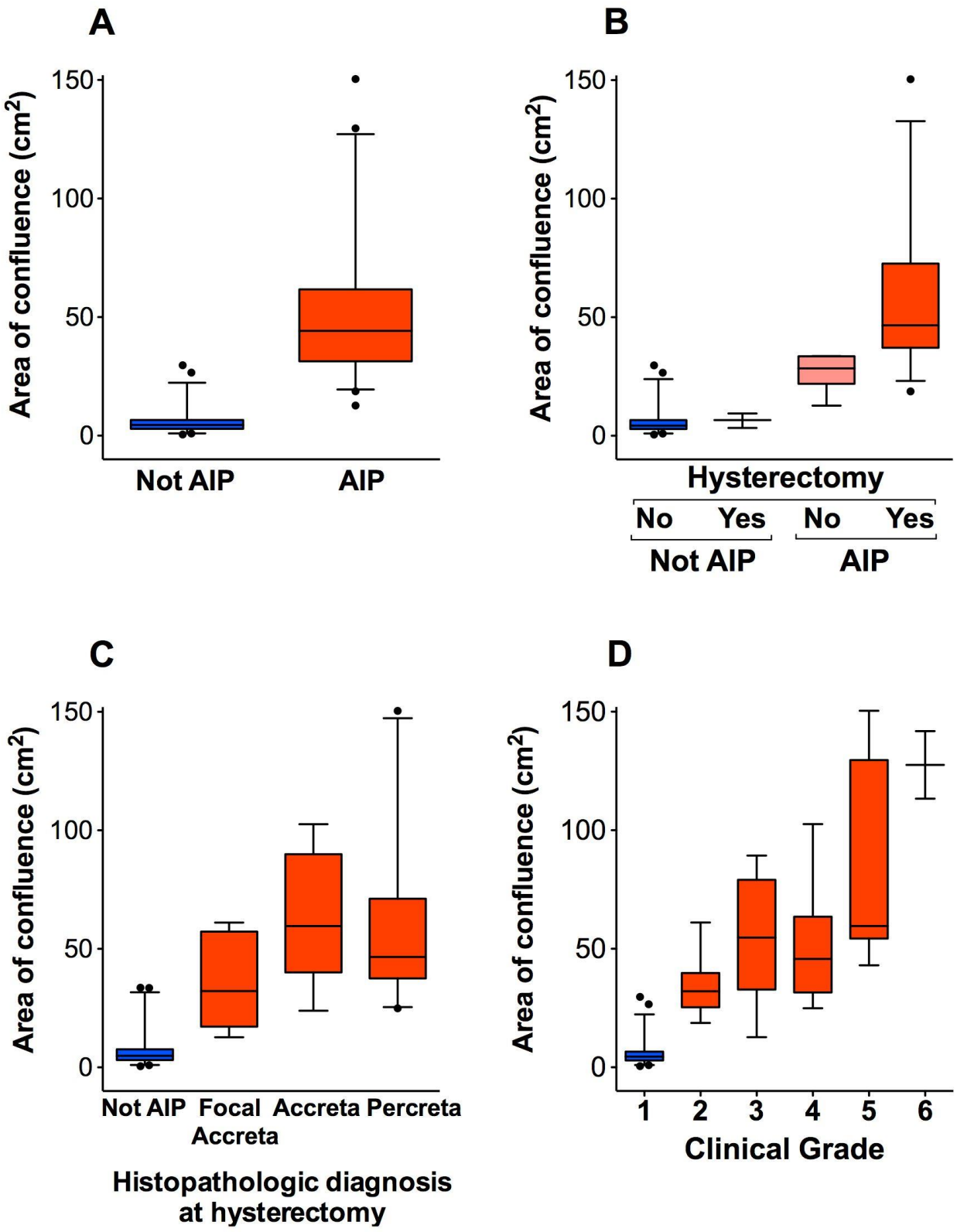
347 **Figure 2:**



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350 **Figure 3:**
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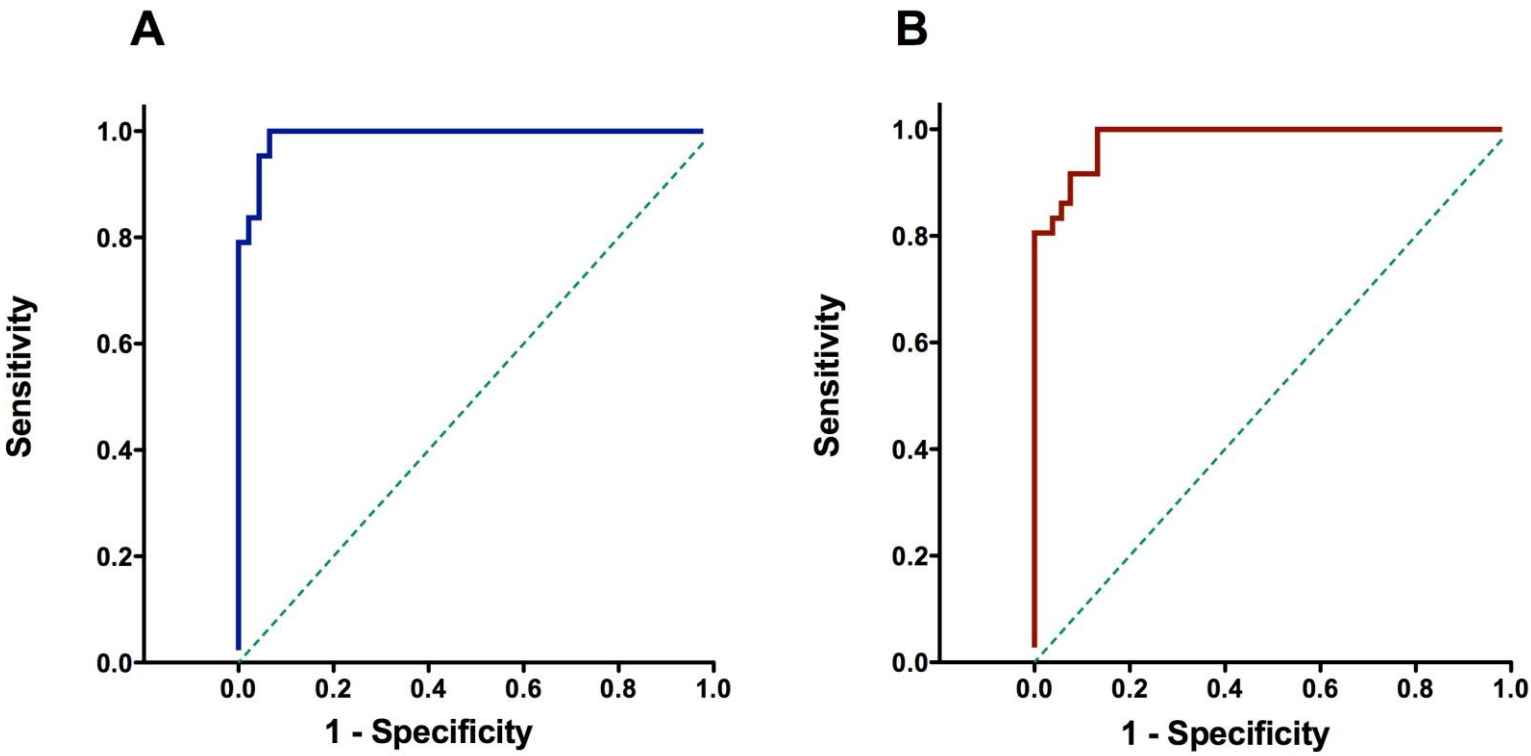

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