

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

Sally L. Collins, BMBCh, DPhil, Gordon N. Stevenson, DPhil, Abdulla Al-Khan, MD, Nicholas P. Illsley, DPhil, Lawrence Impey, MBBS, Leigh Pappas, RDMS, RDCS, and Stacy Zamudio, PhD

**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 power Doppler ultrasound scan. The volumes were examined offline by a blinded observer. The largest area of confluent three-dimensional power Doppler signal (Area of Confluence [ $A_{con}$ ],  $cm^2$ ) at the uteroplacental interface was measured

and compared in women subsequently diagnosed with abnormally invasive placenta and women in a control group who did not have abnormally invasive placenta. Receiver operating characteristic 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]  $cm^2$ ) compared with women in the control group (4.5  $cm^2$  [2.9–6.6],  $P < .001$ ) and even greater in the 36 requiring hysterectomy (46.6  $cm^2$  [37.2–72.6],  $P < .001$ ).  $A_{con}$  rose with histopathologic diagnosis: focal accreta (32.2  $cm^2$  [17.2–57.3]), accreta (59.6  $cm^2$  [40.1–89.9]), and percreta (46.6  $cm^2$  [37.5–71.5]);  $P < .001$  analysis of variance for linear trend). Receiver operating characteristic analysis for prediction of abnormally invasive placenta revealed that with an  $A_{con}$  of 12.4  $cm^2$  or greater, 100% sensitivity (95% confidence interval [CI] 91.6–100) could be obtained with 92% specificity (95% CI 79.6–97.6); area under the curve is 0.99 (95% CI 0.94–1.0). 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  $cm^2$  or greater with 87% specificity (95% CI 74.7–94.5; area under the curve 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.

(*Obstet Gynecol* 2015;126:645–53)

DOI: 10.1097/AOG.0000000000000962

LEVEL OF EVIDENCE: II

From the Nuffield Department of Obstetrics & Gynaecology, University of Oxford, and the Fetal Medicine Unit, John Radcliffe Hospital, Oxford, and the Evelyn Perinatal Imaging Centre, Rosie Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; and the Center for Abnormal Placentation, Division of Maternal Fetal Medicine and Surgery, Department of Obstetrics and Gynecology, Hackensack University Medical Center, Hackensack, New Jersey.

Funded through the generosity of the Fetal Medicine Unit Charitable Fund in Oxford and Hackensack University Medical Center.

Data from this article were presented at the Society for Reproductive Investigation 62nd Annual Scientific Meeting, March 25–28, 2015, San Francisco, California, and the British Fetal and Maternal Medicine Society Meeting, April 23–24, 2015, London, United Kingdom.

The authors thank the staff of the Fetal Medicine Unit at the Women's Centre, John Radcliffe Hospital, for all their help with recruiting and supporting the women involved in the United Kingdom. The authors also acknowledge the following staff at Hackensack University Medical Center: Themba L. Nyirenda for excellent statistical advice; Ms. Sonia Da Silva Arnold, MS, Ms. Alison Forte, and Ms. Magda Pawlik, APN, for assisting with obtaining informed consent, abstracting of electronic medical record and coordination of patient care; Dr. Jesus Alvarez-Perez, Dr. Manuel Alvarez, and Dr. Yaakov Abdelhak, Maternal-Fetal Medicine, the Center for Abnormal Placentation for their excellent surgical care; and Dr. Elizabeth Kopp, Dr. Judy Gerardis, Dr. Maria Keanchong, Dr. Vinay Shah, Dr. Andrew Rubenstein, and many of our 100+ community-based obstetrician colleagues who supported this study and referred patients with placenta previa or suspected of abnormally invasive placenta from their practices for testing using Acon.

Corresponding author: Sally L. Collins, BMBCh, DPhil, The Fetal Medicine Unit, The Women's Centre, The John Radcliffe Hospital, Headley Way, Headlington, Oxford OX3 9DU, UK; e-mail: sally.collins@obs-gyn.ox.ac.uk.

## Financial Disclosure

The authors did not report any potential conflicts of interest.

© 2015 by The American College of Obstetricians and Gynecologists. Published by Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 0029-7844/15



**A**bnormally invasive placentation, or placenta accreta, is a life-threatening obstetric condition in which failure of placental separation at delivery can lead to catastrophic maternal hemorrhage. Prior cesarean delivery and placenta previa are the main risk factors.<sup>1</sup> 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.<sup>2,3</sup> Antenatal diagnosis rests on “typical” ultrasonographic findings.<sup>4</sup> Magnetic resonance imaging has yet to clearly demonstrate an improvement in pregnancy outcomes.<sup>5</sup> 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 power Doppler imaging offered a new marker of “numerous coherent vessels.”<sup>6</sup> However, it too remains subjective and experience-dependent.

Although 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 used when an abnormally invasive placenta is anticipated.<sup>7</sup> Prophylactic occlusive balloons in the pelvic vasculature risk significant complications.<sup>8–10</sup> 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 of gestation, resulting in iatrogenic neonatal morbidity.<sup>3,5,11,12</sup>

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

## MATERIALS AND METHODS

Women were recruited from two referral centers: the Fetal Medicine Unit, John Radcliffe Hospital (Oxford, United Kingdom) and the Center for Abnormal Placentation at Hackensack University Medical Center (New Jersey). Patients were referred by their primary health care 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 younger than 16 years (United Kingdom) or

younger than 18 years (United States) 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 were assessed at delivery according to our clinical grading system (Table 1) by an attending obstetrician who had seen more than 10 cases of abnormally invasive placenta and from histopathology results in which 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, trans-abdominal three-dimensional power Doppler ultrasound volumes of the placental bed were obtained according to a predefined protocol with the participant in a semirecumbent position and a full bladder using a RAB4-8-D 3D/4D curved array abdominal transducer (4–8.5 MHz) on a Voluson E8. Predetermined machine settings were used (for details of all settings, see Collins et al<sup>13</sup>). To allow for differences in attenuation of the power Doppler signal resulting from variation in placental site and maternal adiposity, the subnoise gain setting was selected according to a previously validated technique.<sup>14,15</sup> 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° volume was collected in the sagittal plane, midline under the uterovesical 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 were then stored anonymously using Sonoview and analyzed after delivery using the software package 4D View.

All the static volumes were opened in 4D View and examined by one operator (S.L.C.). All images were coded (deidentified) and the analysis was conducted blinded to pregnancy outcome and previous imaging findings. The three-dimensional volumes containing the uteroplacental interface were transformed until only the power Doppler signal around the uteroplacental interface remained. This was performed according to the process shown in Figure 1. A three-dimensional process is difficult to represent in two dimensions; therefore, the images in Figure 1 have been adjusted to make the concept clearer. The settings



**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 or 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 or 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 or 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 nontraumatic reflection of the urinary bladder at hysterectomy
5	At cesarean delivery or 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 nontraumatic reflection of the urinary bladder at hysterectomy)
6	At cesarean delivery or 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, with or without invasion into the urinary bladder

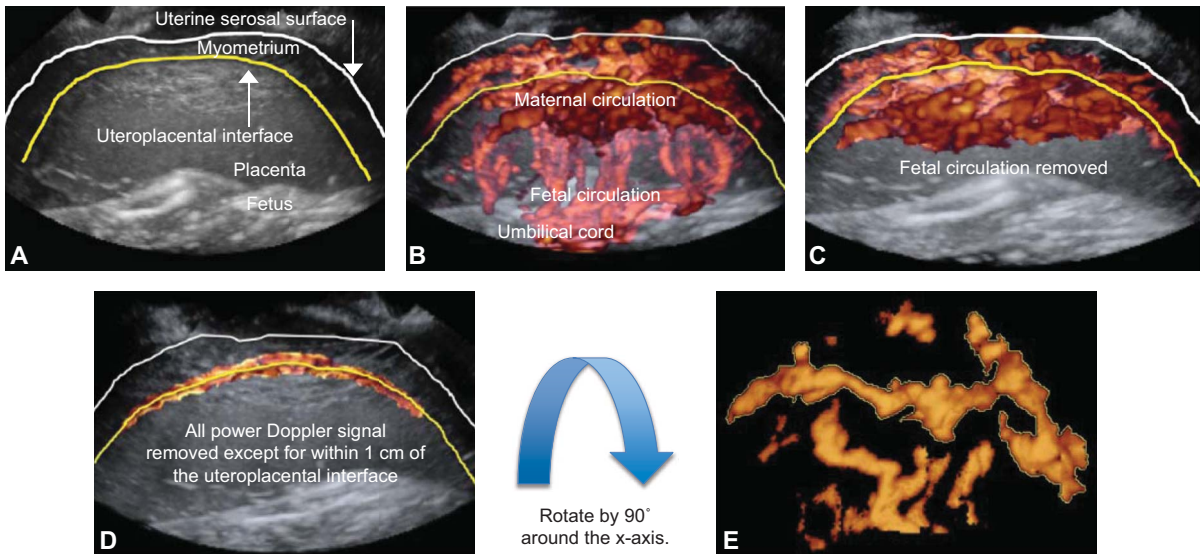
For the purposes of this scale, “uterus” includes the uterine body and uterine cervix.

were identical for all the patients including power Doppler threshold and image magnification. The three-dimensional power Doppler signal was overlaid over the three-dimensional B mode volume (Fig. 1A and B). The volume was manipulated in three dimensions using the 4D View software and the power Doppler signal was sequentially reduced using the software’s “magi-cut,” color-only function. Initially the power Doppler signal representing the fetal circulation was removed (Fig. 1C), then the remaining power Doppler signal was removed until a 1-cm deep volume was left: 0.5 cm either side of the uteroplacental interface (Fig. 1D). The volume was then reorientated until the plane of the uteroplacental interface containing the power Doppler signal of interest was perpendicular to the eyeline of the observer (Fig. 1E). The vascularity at the uteroplacental interface is thus viewed as if the observer was looking down through the flat placental bed from the myometrium toward the fetus. If the starting volume is initially in midsagittal view, this is achieved by rotating by 90° around the y-axis. The B mode was removed from view to improve visualization of the power Doppler signal. The largest area of confluent power Doppler signal (Area of Confluence [ $A_{con}$ ], cm<sup>2</sup>) 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 interobserver study, five were randomly taken from the confirmed abnormally invasive placenta group and five from the not abnormally invasive placenta group.  $A_{con}$  was estimated by two observers (S.L.C. and G.N.S.) on three different occasions blinded to their previous estimates and each other’s results. The two-way mixed intraclass correlation coefficients were calculated to assess intra- and interobserver variability.

Analyses of maternal and neonatal demographic characteristics were performed by Student’s *t* test or  $\chi^2$  as appropriate.  $A_{con}$  was not normally distributed (Kolmogorov-Smirnov  $P < .001$ ), being right-skewed in both women in the case group and those in the control group. Therefore, comparison of  $A_{con}$  between groups was conducted by nonparametric Mann-Whitney *U* and presented as box plots encompassing the 25th to 75th centiles and whiskers indicating fifth to 95th centiles.  $A_{con}$  data analyzed by diagnostic categories, whether histopathologic or by clinical grade, were log-transformed and an analysis of variance 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 curves were plotted for the





**Fig. 1.** Two-dimensional representation of the three-dimensional method used to generate area of confluence. **A.** The volume in B mode. *Lines* have been drawn in on the two-dimensional image to demonstrate the uteroplacental interface and the serosal surface of the uterus. **B.** The B mode volume with the three-dimensional power Doppler signal overlaid. **C.** The power Doppler signal after the fetal circulation has been removed. **D.** All power Doppler signal removed except within 1 cm of the uteroplacental interface. **E.** The power Doppler signal with the flattest plane of the uteroplacental interface at 90° to the eyeline of the observer, the B mode signal removed, and the largest area of power Doppler confluence estimated (*yellow outline*).

Collins. *Diagnosing Abnormally Invasive Placenta. Obstet Gynecol 2015.*

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 was calculated with the exact binomial method used to calculate the 95% confidence intervals (CIs). 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 19.0, and results were graphed using Graph Pad Prism. Results were considered to be significant when  $P<.05$ .

## RESULTS

Ninety-three women were recruited over 2 years (April 2012 to March 2014); two were lost to follow-up, one was excluded for an incomplete scan of the uteroplacental interface, and one was excluded because the woman was unable to fill her bladder sufficiently to adequately visualize the uterovesical 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 (five focal accreta, nine 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 ultrasonography for the women diagnosed with abnormally invasive placenta (median 32 1/7 weeks of gestation, range 17 1/7–33 6/7 weeks of gestation) and those without abnormally invasive placenta (32 4/7 weeks of gestation, range 15 2/7–39 2/7 weeks of gestation).

There were no differences in the body mass index, ethnicity, or parity of women with abnormally invasive placenta compared with those without abnormally invasive placenta (Table 2). The group diagnosed with abnormally invasive placenta had more total previa ( $P<.001$ ), underwent more hysterectomies ( $P<.001$ ), and were delivered earlier ( $P<.01$ ).



**Table 2. Maternal Characteristics and Abnormally Invasive Placenta Risk Factors**

Maternal Demographics	Not Abnormally Invasive Placenta (n=47)	Abnormally Invasive Placenta (n=42)	P
Prepregnancy BMI (kg/m <sup>2</sup> )	26.7±5.4 (18.1–43.0)	26.1±5.3 (17.9–43.4)	.66
Ethnicity			
White (non-Hispanic)	24 (50)	22 (53)	.80
Hispanic	9 (19)	11 (26)	1.00
Black	4 (9)	4 (9)	.70
Asian	3 (7)	4 (9)	.20
Other (including mixed race)	7 (15)	1 (2)	.06
Parity			
0	5 (11)	2 (5)	.40
1	22 (47)	15 (36)	.40
2	12 (26)	10 (24)	.60
3 or greater	8 (17)	15 (36)	.05
Gestational age (wk)			
At delivery	37 1/7 (28 2/7–42)	34 3/7 (21 5/7–26 4/7)	<.01
At ultrasound scan	32 1/7 (17 1/7–33 6/7)	32 4/7 (15 2/7–39 2/7)	.80
Hysterectomy performed	3 (6)	36 (86)	<.001
Admission to ICU	0	3 (7)	.10
Abnormally invasive placenta risk factors			
Prior cesarean delivery (0–8)			
0	10 (21)	2 (5)	.03
1	22 (47)	21 (50)	.80
2	9 (19)	9 (21)	1.00
3 or more	6 (13)	10 (24)	.30
Placenta previa			
Major placenta previa (placenta over os)	17 (36)	32 (76)	<.001
Marginal placenta previa (2 cm or less from os)	7 (15)	7 (17)	1.00
Cesarean delivery scar and major placenta previa	11 (23)	30 (71)	<.001
Previous uterine surgery			
Evacuation of retained products of conception	9 (19)	13 (31)	.23
Myomectomy	3 (6)	2 (5)	1.0
Transcervical resection of fibroids	1 (2)	1 (2)	1.0
Endometrial ablation	0	1 (2)	.10
Assisted reproductive technology	1 (2)	3 (7)	.30

BMI, body mass index; ICU, intensive care unit.

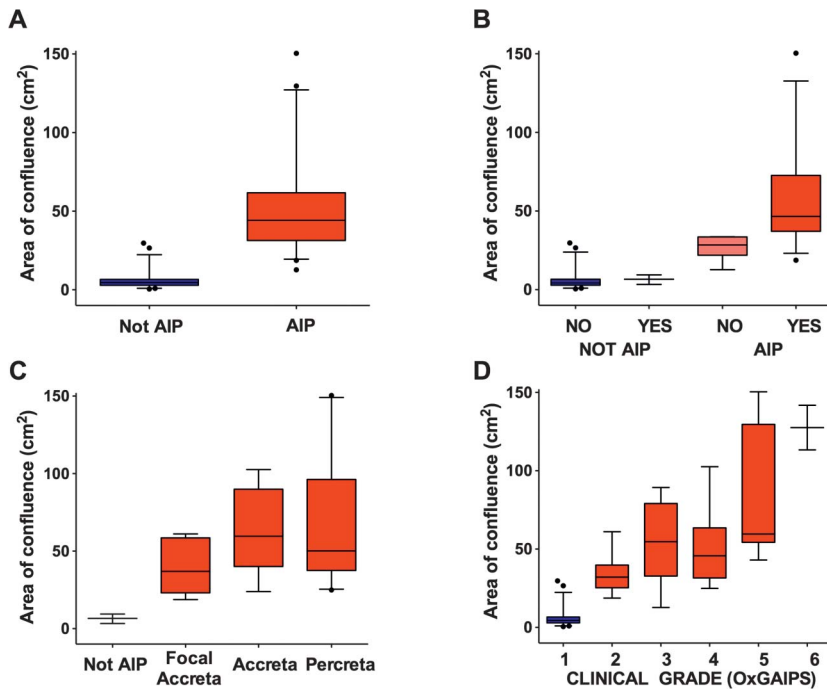
Data are mean±standard deviation (range), n (%), or median (range) unless otherwise specified.

The intraclass correlation coefficient for the values of  $A_{con}$  estimated by the two different observers (interobserver) was 0.92 (95% CI 0.85–0.97). The intraclass correlation coefficients for three repeated estimates by each observer (intraobserver) were 0.94 (G.N.S.: 0.89–0.99) and 0.95 (S.L.C.: 0.90–1.0).

$A_{con}$  values were greater for the group clinically diagnosed with abnormally invasive placenta ( $n=42$ , median 44.2, 25th–75th centile 31.4–61.7) than those without abnormally invasive placenta (4.5 [2.9–6.6], Mann-Whitney  $U$ ,  $P<.001$ ; Fig. 2A).  $A_{con}$  values were even greater in the subset of the abnormally invasive placenta group whose pathology was severe enough to require hysterectomy (46.6 [37.2–72.6]) compared with those clinically

diagnosed with abnormally invasive placenta but managed by placental removal without hysterectomy (28.4 [21.9–33.6],  $P<.005$ ; Fig. 2B).  $A_{con}$  rose with more severe histopathologic diagnosis focal accreta (32.2 cm<sup>2</sup> [17.2–57.3]), accreta (59.6 cm<sup>2</sup> [40.1–89.9]), and percreta ( $n=22$ , 46.6 cm<sup>2</sup> [37.5–71.5],  $P<.001$ , analysis of variance test for linear trend between means). When the histopathologic diagnosis was compared between the 36 with abnormally invasive placenta and the three without abnormally invasive placenta who underwent hysterectomy,  $A_{con}$  was greater for any form of accreta ( $P<.001$ , Kruskal-Wallis with Dunn's multiple comparison; Fig. 2C). Likewise, when  $A_{con}$  was plotted against the clinical grade assigned to each case, all





**Fig. 2.** The median and 95% confidence intervals of the area of confluence ( $\text{cm}^2$ ) for the following comparisons. **A.** The clinical diagnosis of not abnormally invasive placenta (AIP) ( $n=47$ , range  $0.5\text{--}29.7\text{ cm}^2$ ) compared with AIP ( $n=42$ , range  $12.7\text{--}150.4\text{ cm}^2$ ,  $P<.001$ ). **B.** Left two box plots illustrate patients without AIP who did not have a hysterectomy (no,  $n=44$ , range  $0.5\text{--}29.7\text{ cm}^2$ ) or who did have a hysterectomy (yes,  $n=3$ , range:  $2.2\text{--}9.4\text{ cm}^2$ ,  $P=\text{non-significant}$ ). Right two box plots illustrate patients with AIP who did not have a hysterectomy (no,  $n=6$ , range  $12.7\text{--}33.6\text{ cm}^2$ ) or who did have a hysterectomy (yes,  $n=36$ , range  $18.7\text{--}150.4\text{ cm}^2$ ,  $P<.005$ ). **C.** Patients histopathologically confirmed as not AIP ( $n=3$ ), focal accreta ( $n=5$ , range  $18.7\text{--}61.1\text{ cm}^2$ ), accreta ( $n=9$ , range  $23.9\text{--}102.6\text{ cm}^2$ ), or percreta ( $n=22$ , range  $24.9\text{--}150.4\text{ cm}^2$ ,  $P<.001$ ). **D.** Clinical grade was greater for all grades relative to control ( $P<.001$ ). Grade 2 ( $n=12$ , median  $32.2\text{ cm}^2$ , range  $18.7\text{--}61.1$ ); grade 3 ( $n=6$ , median  $54.7\text{ cm}^2$ , range  $43.0\text{--}150.4$ ); and grade 6 ( $n=2$ , median  $126.6\text{ cm}^2$ , range  $113.3\text{--}141.8$ ). \*See Table 1 for definition of clinical grades.

Collins. Diagnosing Abnormally Invasive Placenta. *Obstet Gynecol* 2015.

grades had an elevated  $A_{\text{con}}$  relative to control ( $P<.001$ , analysis of variance test for linear trend between means; Fig. 2D). There was no correlation between  $A_{\text{con}}$  and gestational age at the time of the ultrasound scan ( $r^2$  for abnormally invasive placenta =  $0.12$ ; for not abnormally invasive placenta  $r^2 = 0.08$ ).

All 42 abnormally invasive placenta cases had  $A_{\text{con}}$  values of  $12.4\text{ cm}^2$  or greater, whereas four of 47 women in the control group had values greater than  $12.4\text{ cm}^2$  (false-positives, range  $12.8\text{--}29.7$ ). The receiver operating characteristic curve for prediction of a clinical diagnosis of abnormally invasive placenta (all grades) shows an area under the curve of  $0.99$  ( $0.94\text{--}1.0$ ; Fig. 3A; Table 3). With an  $A_{\text{con}}$  of  $12.4\text{ cm}^2$  or greater, 100% sensitivity could be achieved for the prediction of all clinically diagnosed abnormally invasive placenta with a 92% specificity and a positive predictive value of 92% (8% false-positive rate). Of greater clinical relevance, the area under the curve for abnormally invasive placenta requiring hysterectomy compared with all other cases (including clinically diagnosed abnormally invasive placenta managed conservatively) was  $0.98$  ( $0.93\text{--}1.0$ ). Therefore, an  $A_{\text{con}}$  of  $17.4\text{ cm}^2$  or greater yielded 100% sensitivity with 87% specificity and a 13% false-positive rate.

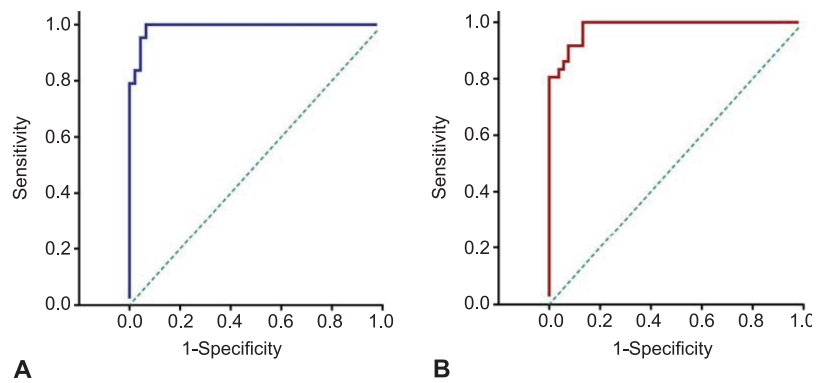
## DISCUSSION

Abnormally invasive placenta is a dangerous pathology; it is difficult to manage clinically and is increasing worldwide.<sup>16</sup> Our results suggest that a quantitative measure, designated here as largest Area of Confluence ( $A_{\text{con}}$ ), can differentiate between the presence and absence of abnormally invasive placenta, and is associated with the histopathologic 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 false-positive rate, because 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 used as a screening tool on a low-risk population as a result of the risk of the false-positive paradox (the false-positive rate being greater than the true-positive rate as a result of the rarity of the condition).<sup>17</sup>

The observed increase in  $A_{\text{con}}$  with increasing severity, both clinical and histopathologic, suggests



**Fig. 3.** Receiver operator curves for the prediction of abnormally invasive placenta using area of confluence. **A.** Receiver operating characteristic curve for any clinically diagnosed abnormally invasive placenta (all grades) relative to controls. Area under the curve is 0.99,  $P < .001$ . **B.** Receiver operator characteristic curve for any histopathologically confirmed abnormally invasive placenta significant enough to warrant hysterectomy relative to controls (not abnormally invasive placenta and clinically diagnosed abnormally invasive placenta managed with manual removal of placenta). Area under the curve is 0.98,  $P < .001$ .



Collins. *Diagnosing Abnormally Invasive Placenta*. *Obstet Gynecol* 2015.

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 histopathologic 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 histopathologic data with which to confirm a subjective diagnosis, despite large numbers of patients.<sup>18</sup> 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 is required to further evaluate the test and to determine gestation-appropriate values.

Hundred percentage 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 in which antenatal diagnosis has been shown to significantly decrease maternal morbidity.<sup>2,3</sup>

The technique itself also has weaknesses and unknown factors. The manual process currently used to obtain  $A_{con}$  using 4D View requires considerable practice and must be undertaken by operators both experienced in placental imaging and manipulating three-dimensional power Doppler 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.<sup>19–21</sup> We have already developed a semiautomated technique to analyze the placenta, uteroplacental interface, and its vasculature in the first trimester.<sup>21,22</sup> These techniques could be applied to facilitate semiautomated estimation of  $A_{con}$  thereby simplifying the process and decreasing operator dependence.

**Table 3.** Receiver Operating Characteristic Curves for Prediction of Any Abnormally Invasive Placenta and Abnormally Invasive Placenta Requiring Cesarean Hysterectomy

Abnormally Invasive Placenta	Area of Confluence			
	Threshold Value (cm <sup>2</sup> )	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
Any	12.4	100% (91.6–100)	91.5% (79.6–97.6)	0.99 (0.94–1.00)
Requiring cesarean hysterectomy	17.4	100% (90.3–100)	86.8% (74.7–94.5)	0.98 (0.93–1.00)

CI, confidence interval; AUC, area under the curve.



Little is known of the process underlying the development of the area of confluence. One theory is that it represents enlarged arteriovenous anastomoses located in the subplacental myometrium,<sup>23</sup> 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 remodeling deep in the myometrium.<sup>24</sup> 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 American College of Obstetricians and Gynecologists' recommendations suggest delivery at 34 weeks of gestation.<sup>12</sup> Although our data do not support a strong correlation between the size of  $A_{con}$  and gestational age, the majority of our data was collected in the late second and early third trimester. With a larger sample size, CIs for  $A_{con}$  can be determined across gestation and in all grades of abnormally invasive placenta, thereby enabling establishment of clinically useful cutoff 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 in which prenatal diagnosis has been shown to reduce the high maternal mortality and morbidity.<sup>25</sup> 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.

## REFERENCES

- Rosenberg T, Pariente G, Sergienko R, Wiznitzer A, Sheiner E. Critical analysis of risk factors and outcome of placenta previa. *Arch Gynecol Obstet* 2011;284:47–51.
- Eller AG, Bennett MA, Sharshiner M, Masheter C, Soisson AP, Dodson M, et al. Maternal morbidity in cases of placenta accreta managed by a multidisciplinary care team compared with standard obstetric care. *Obstet Gynecol* 2011; 117:331–7.
- Al-Khan A, Gupta V, Illsley NP, Mannion C, Koenig C, Bogomol A, et al. Maternal and fetal outcomes in placenta accreta after institution of team-managed care. *Reprod Sci* 2014;21:761–71.
- Wong HS, Cheung YK, Zuccollo J, Tait J, Pringle KC. Evaluation of sonographic diagnostic criteria for placenta accreta. *J Clin Ultrasound* 2008;36:551–9.
- Publications Committee, Society for Maternal-Fetal Medicine; Belfort MA. Placenta accreta. *Am J Obstet Gynecol* 2010;203: 430–9.
- Shih JC, Palacios Jaraquemada JM, Su YN, Shyu MK, Lin CH, Lin SY, et al. Role of three-dimensional power Doppler in the antenatal diagnosis of placenta accreta: comparison with gray-scale and color Doppler techniques. *Ultrasound Obstet Gynecol* 2009;33:193–203.
- Dildy GA III. Postpartum hemorrhage: new management options. *Clin Obstet Gynecol* 2002;45:330–44.
- Dilauro MD, Dason S, Athreya S. Prophylactic balloon occlusion of internal iliac arteries in women with placenta accreta: literature review and analysis. *Clin Radiol* 2012;67: 515–20.
- Teare J, Evans E, Belli A, Wendler R. Sciatic nerve ischaemia after iliac artery occlusion balloon catheter placement for placenta percreta. *Int J Obstet Anesth* 2014;23:178–81.
- Gagnon J, Boucher L, Kaufman I, Brown R, Moore A. Iliac artery rupture related to balloon insertion for placenta accreta causing maternal hemorrhage and neonatal compromise. *Can J Anaesth* 2013;60:1212–7.
- De Luca R, Boulvain M, Irion O, Berner M, Pfister RE. Incidence of early neonatal mortality and morbidity after late-preterm and term cesarean delivery. *Pediatrics* 2009;123:e1064–71.
- Placenta accreta. Committee Opinion No. 529. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2012; 120:207–11.
- Collins SL, Stevenson GN, Noble JA, Impey L. Developmental changes in spiral artery blood flow in the human placenta observed with colour Doppler ultrasonography. *Placenta* 2012;33:782–7.
- Collins SL, Stevenson GN, Noble JA, Impey L, Welsh AW. Influence of power Doppler gain setting on Virtual Organ Computer-aided Analysis indices in vivo: can use of the individual sub-noise gain level optimize information? *Ultrasound Obstet Gynecol* 2012;40:75–80.
- Sanderson J, Wu L, Mahajan A, Meriki N, Henry A, Welsh AW. Selection of the sub-noise gain level for acquisition of VOCAL data sets: a reliability study. *Ultrasound Med Biol* 2014;40:562–7.
- Khong TY. The pathology of placenta accreta, a worldwide epidemic. *J Clin Pathol* 2008;61:1243–6.
- Vacher HL. Quantitative literacy–drug testing, cancer screening, and the identification of igneous rocks. *J Geosci Edu* 2003; 51:2.
- Palacios Jaraquemada JM, Bruno CH. Magnetic resonance imaging in 300 cases of placenta accreta: surgical correlation of new findings. *Acta Obstet Gynecol Scand* 2005;84: 716–24.
- Stevenson GN, Collins SL, Impey L, Noble A. OP10.09: a novel semi-automated (SA) technique for 3D ultrasound measurement of placental volume. *Ultrasound Obstet Gynecol* 2010;36:82.
- Stevenson GN, Collins SL, Impey L, Noble JA. Surface parameterisation of the utero-placental interface using 3D power Doppler ultrasound. In: *Biomedical imaging: from nano to macro*, 2011 IEEE International Symposium on Biomedical Engineering; 2011 Mar 30–Apr 2; Chicago, IL. New York (NY): IEEE; 2011. p. 891–4.
- Stevenson GN, Collins SL, Welsh AW, Impey LW, Noble JA. A technique for the estimation of fractional moving blood volume by using three-dimensional power Doppler US. *Radiology* 2015;274:230–7.





22. Collins SL, Stevenson GN, Noble JA, Impey L. Elsevier Trophoblast Research Award Lecture: Searching for an early pregnancy 3-D morphometric ultrasound marker to predict fetal growth restriction. *Placenta* 2013;34(suppl):S85-9.
23. Schaaps JP, Tsatsaris V, Goffin F, Brichant JF, Delbecq K, Tebache M, et al. Shunting the intervillous space: new concepts in human uteroplacental vascularization. *Am J Obstet Gynecol* 2005;192:323-32.
24. Tantbirojn P, Crum CP, Parast MM. Pathophysiology of placenta creta: the role of decidua and extravillous trophoblast. *Placenta* 2008;29:639-45.
25. Solheim KN, Esakoff TF, Little SE, Cheng YW, Sparks TN, Caughey AB. The effect of cesarean delivery rates on the future incidence of placenta previa, placenta accreta, and maternal mortality. *J Matern Fetal Neonatal Med* 2011;24:1341-6.

## Earn CME Credits for Your Contribution as a Reviewer to *Obstetrics & Gynecology*

In recognition of their time, effort, and expertise, reviewers of manuscripts for *Obstetrics & Gynecology* are eligible to receive continuing medical education credits.

### ACCME Accreditation

The American College of Obstetricians and Gynecologists is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

### AMA PRA Category 1 Credit(s)<sup>TM</sup>

The American College of Obstetricians and Gynecologists designates this manuscript review activity for a maximum of 3 *AMA PRA Category 1 Credits*<sup>TM</sup>. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

### College Cognate Credit(s)

The American College of Obstetricians and Gynecologists designates this manuscript review activity for a maximum of 3 Category 1 College Cognate Credits. The College has a reciprocity agreement with the AMA that allows *AMA PRA Category 1 Credits*<sup>TM</sup> to be equivalent to College Cognate Credits.

College Fellows will be awarded credit for a maximum of five reviews yearly. Those who are not College Fellows will receive e-mail documentation approximately 1 month after completion of the review, which can be submitted to an accrediting body for credits.

rev 11/2014

