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Validation of a sonographic checklist for the detection of histologic placenta accreta spectrum

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Abstract:	Background: To standardize research terminology and reduce unanticipated placenta accreta spectrum (PAS), the European Working Group for Abnormally Invasive Placenta (EW-AIP) developed a consensus checklist for reporting PAS suspected on antenatal ultrasound. The diagnostic accuracy of the EW-AIP checklist has not been assessed. Objective: To test the performance of the EW-AIP sonographic checklist in predicting histologic PAS. Study Design: This is a multi-site, blinded, retrospective review of transabdominal ultrasound studies performed between 26-32 weeks gestation for subjects with histologic PAS between 2016-2020. We planned a 1:1 control cohort of subjects without histologic PAS. To reduce reader bias, we matched the control cohort for known risk factors including previa, number of prior cesarean deliveries, prior dilation and curettage (D&C), in vitro fertilization (IVF), and clinical factors affecting image quality including multiple gestation, body mass index (BMI) and gestational age at the ultrasound. Nine sonologists from 5 referral centers, blinded to the histologic outcomes, interpreted the randomized ultrasound studies using the EW-AIP checklist. The primary outcome was the sensitivity and specificity of the checklist to predict PAS. Two separate sensitivity analyses were performed: 1) we excluded subjects with mild

	disease (i.e. only assessed subjects with histologic increta and percreta); 2) we excluded interpretations from the 2 most junior sonologists. Results: 78 subjects were included (39 PAS, 39 matched control). Clinical risk factors and image quality markers were statistically similar between cohorts. The checklist sensitivity (95% Confidence Interval, CI) was 76.6% (63.4%-90.6%) and specificity (95% CI) was 92.0% (63.4%-99.9%), with a positive and negative likelihood ratio of 9.6 and 0.3, respectively. When we excluded subjects with mild PAS disease, the sensitivity (95% CI) increased to 84.7% (73.6%-96.4%) and specificity was unchanged at 92.0% (83.2%-99.9%). Sensitivity and specificity were unchanged when the interpretations from the 2 most junior sonologists were excluded. Conclusion: The 2016 EW-AIP checklist for interpreting PAS has a reasonable performance in detecting and excluding histologic placenta accreta spectrum.

TITLE PAGE

Validation of a sonographic checklist for the detection of histologic placenta accreta spectrum

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Manuscript title: Validation of a sonographic checklist for the detection of histologic placenta accreta spectrum.

Condensation: A sonographic checklist for reporting suspected placenta accreta spectrum has a positive likelihood ratio of 9.6 to detect (and 0.3 negative likelihood ratio to exclude) histologic disease.

Short title: Sonographic checklist to predict placenta accreta spectrum

AJOG at a Glance:

A. Why was this study conducted?

An expert consensus checklist was developed in 2016 to standardize sonographic reporting of suspected placenta accreta spectrum and reduce the risk of unanticipated disease. However, the diagnostic performance of the checklist is not known.

B. What are the key findings?

The checklist has a positive and negative likelihood ratio of 9.6 and 0.3, respectively, and its sensitivity and specificity improves with more severe histologic disease.

C. What does this study add to what is already known?

This study provides diagnostic accuracy to support a standardized sonographic checklist for use in clinical interpretation, research, and training for placenta accreta spectrum.

Conflict of Interest: The authors report no conflicts of interest.

Keywords: Abnormal placentation, abnormally adherent placenta, antenatal diagnosis, checklist, delivery planning, morbidly adherent placenta, multidisciplinary team, placental imaging, sonographic imaging, ultrasound

Abstract

Background: To standardize research terminology and reduce unanticipated placenta accreta spectrum (PAS), the European Working Group for Abnormally Invasive Placenta (EW-AIP) developed a consensus checklist for reporting PAS suspected on antenatal ultrasound. The diagnostic accuracy of the EW-AIP checklist has not been assessed.

Objective: To test the performance of the EW-AIP sonographic checklist in predicting histologic PAS.

Study Design: This is a multi-site, blinded, retrospective review of transabdominal ultrasound studies performed between 26-32 weeks gestation for subjects with histologic PAS between 2016-2020. We matched a 1:1 control cohort of subjects without histologic PAS. To reduce reader bias, we matched the control cohort for known risk factors including previa, number of prior cesarean deliveries, prior dilation and curettage (D&C), in vitro fertilization (IVF), and clinical factors affecting image quality including multiple gestation, body mass index (BMI) and gestational age at the ultrasound. Nine sonologists from 5 referral centers, blinded to the histologic outcomes, interpreted the randomized ultrasound studies using the EW-AIP checklist. The primary outcome was the sensitivity and specificity of the checklist to predict PAS. Two separate sensitivity analyses were performed: 1) we excluded subjects with mild disease (i.e. only assessed subjects with histologic increta and percreta); 2) we excluded interpretations from the 2 most junior sonologists.

Results: 78 subjects were included (39 PAS, 39 matched control). Clinical risk factors and image quality markers were statistically similar between cohorts. The checklist sensitivity (95% Confidence Interval, CI) was 76.6% (63.4%-90.6%) and specificity (95% CI) was 92.0% (63.4%-99.9%), with a positive and negative likelihood ratio of 9.6 and 0.3, respectively. When

we excluded subjects with mild PAS disease, the sensitivity (95% CI) increased to 84.7% (73.6%-96.4%) and specificity was unchanged at 92.0% (83.2%-99.9%). Sensitivity and specificity were unchanged when the interpretations from the 2 most junior sonologists were excluded.

Conclusion: The 2016 EW-AIP checklist for interpreting PAS has a reasonable performance in detecting and excluding histologic placenta accreta spectrum.

Introduction

The incidence of placenta accreta spectrum (PAS) is rising, and it is now the leading indication for puerperal hysterectomy[1]. Management typically includes a scheduled, late preterm delivery by a multidisciplinary team[2]. Unanticipated PAS deliveries put pregnant patients at highest risk for blood transfusion, ICU admission, and death[3]. Thus, antenatal diagnosis is prerequisite for surgical planning to reduce maternal morbidity and mortality. Despite this necessity, a recent Maternal-Fetal Medicine Unit Network study found that PAS was suspected in only 53% of subjects prior to delivery[4].

The mainstay for antenatal PAS diagnosis is ultrasound. However, ultrasound is operator dependent, and limited by a prior lack of standardized definitions of PAS ultrasound markers. Additionally, a patient's *a priori* risk for PAS, based on historical characteristics, influences interpretation of ultrasound studies. Therefore, objective assessment of PAS imaging characteristics is challenging for prospective research[5].

Given the need to standardize PAS ultrasound markers, in 2016 the European Working Group on Abnormally Invasive Placenta (EW-AIP) produced a consensus checklist for ultrasound assessment of placentation[6]. The checklist was developed by an online questionnaire of 50 international experts, and a list of 11 sonographic markers was derived from expert opinion. Two years later, both the International Federation of Gynecology and Obstetrics (FIGO) and the Society for Maternal Fetal Medicine (SMFM) endorsed the sonographic characteristics within the checklist[7,8]. While the EW-AIP checklist is derived from and endorsed by several professional societies, the clinical performance of the checklist itself has not been assessed.

Our objective was to assess the diagnostic accuracy of the Maternal-Fetal Medicine (MFM) sonologist's overall impression of PAS using the EW-AIP checklist, and to further evaluate the interrater reliability and diagnostic performance for each of the characteristics.

Materials and Methods

We conducted a multi-site, blinded, retrospective review of 26-32 week (inclusive) ultrasound studies including subjects prospectively enrolled at a single United States referral center with suspected PAS and confirmed on hysterectomy specimen between 2016 (when the EW-AIP checklist was published and adopted at our institution) and 2020. We retrospectively identified a 1:1 control cohort of subjects without PAS clinically or on the final pathology report (incidental diagnoses on placental specimens were not included), In an effort to control for expected bias influenced by clinical risk factors for PAS, we best-matched the control cohort using a greedy-matching algorithm for pre-defined clinical characteristics listed in the ACOG Obstetric Care Consensus[3], including placenta previa, number of prior cesarean deliveries, prior dilation and curettage (D&C), and in vitro fertilization (IVF). Additionally, we matched clinical characteristics influencing image quality including body mass index (BMI) at first prenatal visit, multiple gestation, and gestational age at the time of the ultrasound. Thus, the control cohort was created by including subjects with imaging conducted at the same diagnostic center and cesarean delivery conducted at the same labor and delivery during the same timeframe, then excluded those with PAS on final pathology or on review of operative note. The last step was matching the pre-defined clinical characteristics as the disease cohort.

Ultrasounds studies from 26-32 weeks gestation were chosen for review, as this timing was the institutional standard for follow up for suspected abnormal placentation diagnosed during routine anatomy scan. Regardless of the disease severity, subjects with anticipated PAS were cared for by a multidisciplinary care team and, with intraoperative confirmation and the patient's consent, adherent placenta was managed with cesarean hysterectomy. Of note, while not all subjects with PAS may have been managed with hysterectomy at our institution, a

hysterectomy was required as part of the present study design as histology was the primary outcome to test the sonographic checklist.

After the PAS and control cohorts were created, the lead author (who did not participate in interpreting the ultrasound studies) selected transabdominal images of the placenta, cervix, and placental cord insertion obtained during a detailed second trimester ultrasound (CPT 76811) or follow up ultrasound (CPT 76816). Selected images included both still and cine clips, and greyscale and color Doppler images – no dedicated image of the placenta, cervix, or cord insertion was excluded, as the EW-AIP checklist did not have a prescribed number of images. The ultrasound images were de-identified, randomized, and then interpreted by 9 Maternal-Fetal Medicine (MFM) sonologists blinded to final histology. The blinded sonologists were aware that the ultrasound series included matched controls, but were not aware of the specific ratio for matching. The 9 sonologists were from 5 United States referral centers (7 MFM faculty and 2 MFM fellows), recruited by email after an annual professional conference, and prior familiarity with the EW-AIP checklist was not required.[9] For each ultrasound, the sonologists were provided the gestational age and the matched clinical characteristics from the Obstetric Care Consensus[3], such as number of prior cesarean deliveries or prior D&Cs. To simulate a workflow at an antenatal diagnostic center, 5 minutes were suggested to review each ultrasound and the sonologists were permitted to move between images and cine clips as necessary. Consistent with the EW-AIP checklist, the nine sonologists could choose “present”, “absent”, or “unsure” for each sonographic sign, and then prompted to predict whether there was a low or high probability of PAS on pathology. To preserve integrity of statistical analysis, each sonologist was required to review 100% of the ultrasounds studies, or their responses were discarded.

Baseline demographics of the PAS and control cohorts were assessed using Chi-Square or ANOVA F-Test, depending on whether the demographic was binary or continuous, respectively. For the primary outcome, to measure the strength of agreement between sonologists' interpretation and histologic diagnosis, a dichotomous sensitivity and specificity table was created using the sonologists' aggregate overall impression. Two separate sensitivity analyses were performed: 1) we excluded subjects with mild disease (i.e. excluding subjects with histologic accreta and only including subjects with histologic increta and percreta on hysterectomy specimen); 2) we excluded interpretations from the 2 MFM fellows who were most junior in experience with ultrasound interpretation. We performed these analyses to assess how disease severity and sonologist experience affected the performance of the checklist.

For secondary outcomes, we analyzed the interrater reliability of the sonologists' responses, using Kappa statistics to compute an interrater correlation coefficient (ICC) to assess the agreement for each characteristic between the 9 sonologists. Additionally, to compute the aggregate sonologists' responses for individual characteristics to the true histologic diagnosis of PAS, we used Cohen's Kappa, which provided a numerical summary between -1 and 1, where 0 indicates no agreement beyond what is expected by chance, 1 indicates perfect agreement, and -1 indicates perfect disagreement.

The images were anonymized and exported from the clinical picture archiving and communications system (Viewpoint 6.11, General Electric) onto an encrypted, cloud-based content management platform (Box Service, 2022). The checklist for each subject was completed on REDCap 12.0.2. Statistical software used was SAS 9.4 (SAS Institute, Cary, NC). The study was approved by the institutional review board at each of the five participating institutions and a data transfer agreement was executed to facilitate transfer of the de-identified images. The de-

identified images and code used for analysis are available upon request for either research or education purposes.

Results

Subject recruitment is demonstrated in Figure 1. In total, there were 39 subjects with PAS that met inclusion criteria including: a) performance of an ultrasound between 26-32 weeks gestation, b) hysterectomy performed between 2016-2020 with histology confirming PAS. After pooling the PAS cohort's pre-defined risk factors, the 1:1 control cohort was identified by querying 3,348 subjects who had a cesarean delivery at the same center during the same time period, but without PAS suspected clinically or on final pathology. Baseline demographics between the PAS and control cohorts were statistically similar, including presence of placenta previa on ultrasound (64.1% vs 59.0%, p=0.64), median (25^{th}, 75^{th} percentile) number of prior cesarean deliveries (2 [1, 3], for both cohorts, p>0.99), prior D&Cs (23.1% vs 25.6%, p=0.79) and IVF conception (2.6% for both cohorts, p>0.99). Furthermore, factors influencing image quality were statistically similar including BMI, multiple gestation, and gestational age of ultrasound (Table 1). Of note, although study sonologists were unaware of this fact, there were more images for PAS subjects than control subjects (median 23.0 [13.0, 33.0] versus 16.0 [9.0, 20.0], respectively, p=0.002).

Each of the 9 sonologists completed the checklist for all subjects. The median (25^{th}, 75^{th} percentile) years of MFM experience was 5.0 (2.8, 8.0), with a range of 1-22. Seven sonologists were practicing MFM faculty (6 board-certified, 1 board-eligible), and 2 were active MFM fellows.

Primary outcomes are listed in Table 2. The sensitivity (95% Confidence Interval, CI) of the EW-AIP checklist detecting histologic PAS was 76.6% (63.4%-90.6%) and specificity (95% CI) was 92.0% (63.4%-99.9%), yielding a positive likelihood ratio to detect PAS of 9.6, and a negative likelihood ratio to exclude PAS of 0.3. When excluding mild cases (or histologic

accreta (n=10), and assessing only histologic increta and percreta) the sensitivity (95% CI) increased to 84.7% (73.6%-96.4%) and specificity remained the same with a narrowed CI, 92.0% (83.2%-99.9%). When excluding the responses of the two MFM fellows, the sensitivity and specificity were negligibly affected, 78.0% (64.8%-91.2%) and 93.0% (85.0%-99.9%), respectively.

For secondary outcomes, the interrater classification coefficient (which reflects the degree of correlation and agreement between measurements among 9 sonologists) is shown in Table 3. The two characteristics with the most agreement between sonologists was abnormal placental lacunae (0.4) and uterovesical hypervascularity (0.41), indicating good reliability between reviewers. Bladder wall interruption (0.19) and focal exophytic mass (0.05) were noted least consistently, indicating poor reliability. In the sensitivity analysis, sonologist agreement for each of the 11 characteristics increased with more severe histologic disease. Additionally, when excluding the responses of the most junior sonologists, there was an increase in agreement for each of the 11 characteristics, even if this did not change their overall diagnostic impression.

Table 4 lists the performance of individual characteristic against histologic PAS, or in other words, the predictive value of histologic PAS if the individual characteristic was identified. Each of the characteristics had a positive association with histological PAS, with the highest agreement being myometrial thinning (0.56), loss of clear zone (0.55), and placental bulge (0.48). The least correlated with severe disease was the parametrial involvement, with a kappa of 0.05. Similarly, the agreement between sonographic characteristic and true PAS diagnosis improved with more severe disease, as well as excluding the responses from the two junior sonologists.

Discussion

Principal Findings

Using a consensus expert opinion initially proposed in 2016 by EW-AIP and endorsed in 2018 by FIGO and SMFM, we assessed the clinical performance of an ultrasound checklist for the histologic diagnosis of PAS. The sensitivity (95% CI) was 76.6% (63.4%-90.6%) and specificity (95% CI) was 92.0% (63.4%-99.9%) in predicting PAS, yielding a positive likelihood ratio to detect PAS of 9.6, and a negative likelihood ratio to exclude PAS of 0.3. The performance of the checklist to predict histologic PAS improved with more severe disease (increta and percreta) and maintained a strong performance when employed by less experienced sonologists (MFM fellows).

Results in the context of what is known

As our understanding of the pathophysiology of PAS evolves from a model centering on *placental-invasion* to a model of *uterine-dehiscence*[10], reporting radiologic, clinical, or pathologic PAS has moved away from categorical "accreta", "increta" and "percreta" terminology to a more descriptive approach. For example, in 2018 FIGO sought to standardize intraoperative findings with a clinical criteria that describes pelvic involvement of placentation[11] rather than using categorical terms. Additionally, a consensus panel of clinical pathologists have replaced the categorical terminology to a 10 characteristic, descriptive grading system[12]. Similarly, driven by the need to standardize sonographic PAS markers, multiple professional societies have called for a systematic approach to the evaluation of the uterus and placenta. EW-AIP put forth a proposed checklist in 2016, reviewing 23 manuscripts and drafting a list of 11 PAS ultrasound markers (6 markers are greyscale, 4 are 2D color Doppler, and 1 is

3D power Doppler)[6]. The present study now provides clinical performance outcomes for the expert-consensus checklist put forward by EW-AIP.

Research implications

Studies assessing predictive value of ultrasound markers for PAS are limited by small sample sizes, retrospective designs without a control cohort, and heterogenous definitions of PAS. For example, the sensitivity and specificity of hypervascular uterovesical interface ranges widely from 11-100% and 36-100% respectively[13,14]. Given the broad range of predictive values for each characteristic within the checklist, the EW-AIP consensus stresses that all markers should be systematically assessed and unambiguously reported until further research clarifies their individual utility. Therefore, the primary outcome of this study was to report the performance of the "bundle" of sonographic markers in a checklist format that may be readily adopted by antenatal diagnostic centers.

An interesting finding was that responses from the MFM fellows did not significantly impact overall predictive performance, suggesting that this checklist may have an early learning curve if adopted as a part of MFM training. While the independent items within the checklist had more variability, the overall impression was similar to experienced clinicians. Components of the checklist may be helpful for training in familiarity and recognition, but the overall impression is the most clinically relevant. Checklists have emerged for the management of complex conditions to standardize evidence- or consensus-based processes and promote high quality and consistent care. Accordingly, SMFM has created a checklist for surgical planning for anticipated and unexpected PAS[15]. Establishing a clinically validated checklist for the systematic evaluation of placenta and uterus is imperative for education, training, and research.

Strengths and limitations

There are two key, related limitations to this study. Although the study involved blinded interpretations by sonologists from multiple institutions, it is retrospective in design. Therefore, images were not systematically procured in a checklist manner to capture or exclude components of the checklist itself. We suspect that this limitation is pertinent to the secondary outcomes, assessing the individual characteristics of the checklist. We therefore recommend caution in interpreting Table 4 as these may underreport the performance against the true PAS diagnosis. Second, there were more images within the PAS cohort than the control cohort, likely reflecting the sonographers internal assessment as they were obtaining images for interpretation or requested additional focus. While the sonologists in this study were blinded to the clinical outcome, a potential bias is introduced. The lead author intentionally did not control this known discrepancy in advance to avoid introducing a selection bias by "cherry picking" included images for blinded review (aside from removing non-placental images).

There are four strengths to the study. First, the use of a control cohort matched comprehensively for PAS risk factors is an effort to neutralize the impact of knowing the patient's clinical history before reading the images. Mimicking real world ultrasound reading, sonologists had the basic clinical information prior to reading the scan, such as number of prior cesarean or IVF conception, and the clinical characteristics were comparable between the PAS and control cohorts. Second, both the PAS and control cohort were selected from the same referral center, therefore standardizing variables such as sonographer education, image procurement, and ultrasound machines used. Additionally, to reduce the risk of recall bias, images were blinded and reviewed by sonologists from four external institutions that did not participate in the subjects' clinical care and therefore had never seen the images previously. Lastly, the planned sensitivity analysis assessed the impact of disease severity as

well as sonologist training in order to assess potential uptake of the checklist as a part of clinical care or education.

Conclusion

Our multi-site study has assessed the diagnostic accuracy of an ultrasound checklist for the detection of placenta accreta spectrum, with a high likelihood ratio. The routine incorporation of this checklist may contribute to decreased unanticipated PAS cases and timely referral to PAS centers, as well as standardize research terminology.

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Table 1: Baseline demographics between PAS and 1:1 matched control cohort

	PAS on hysterectomy specimen (n=39)	**Control cohort without PAS (n=39)**	***p* value**
Placenta previa	25 (64.1%)	23 (59.0%)	0.64[1]
Number of prior cesarean	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	>0.99[2]
IVF	1 (2.6%)	1 (2.6%)	>0.99[1]
Prior D&C	9 (23.1%)	10 (25.6%)	0.79[1]
BMI (kg/m^2)	29.3 (24.5, 36.1)	28.5 (22.6, 37.6)	0.82[2]
Multiple gestation	1 (2.6%)	1 (2.6%)	>0.99[1]
US gestational age (weeks)	28.0 (26.0, 29.0)	29.0 (26.0, 29.0)	0.93[2]
Number of images per US	23.0 (13.0, 33.0)	13.0 (9.0, 20.0)	0.002[2]
Indication for US in control cohort			
Placental reassessment		30 (76.9%)	
Fetal Indication		6 (15.4%)	
Anatomy		3 (7.7%)	
Final pathology			<0.001[1]
No PAS	0 (0.0%)	39.0 (100.0%)	
Accreta	10 (26.3%)	0 (0.0%)	
Increta or percreta	29 (76.3%)	0 (0.0%)	

Binary variables are represented number (%)
Continuous variables are median (25^{th} percentile, 75^{th} percentile)

IVF: *in vitro* fertilization; US: ultrasound; BMI: body mass index; PAS: placenta accreta spectrum

[1]Chi-square; [2]ANOVA F-Test

Table 2: Primary outcome – performance of EW-AIP checklist on detection of PAS

	All cases (n=78)	**Excluding histologic accreta (n=68)**	**Excluding 2 MFM fellows (n=78)**
Sensitivity	76.7% (63.4%-90.6%)	84.7% (73.6%-96.4%	78.0% (64.8%-91.2%)
Specificity	92.0% (63.4%-99.9%)	92.0% (83.2%-99.9%)	93.0% (85.0%-99.9%)
Positive Likelihood Ratio	9.6	10.6	11.8
Negative Likelihood Ratio	0.3	0.2	0.2
Sensitivity and specific above measured with 95% confidence interval			

Table 3: Secondary outcome – interobserver variability of individual characteristics

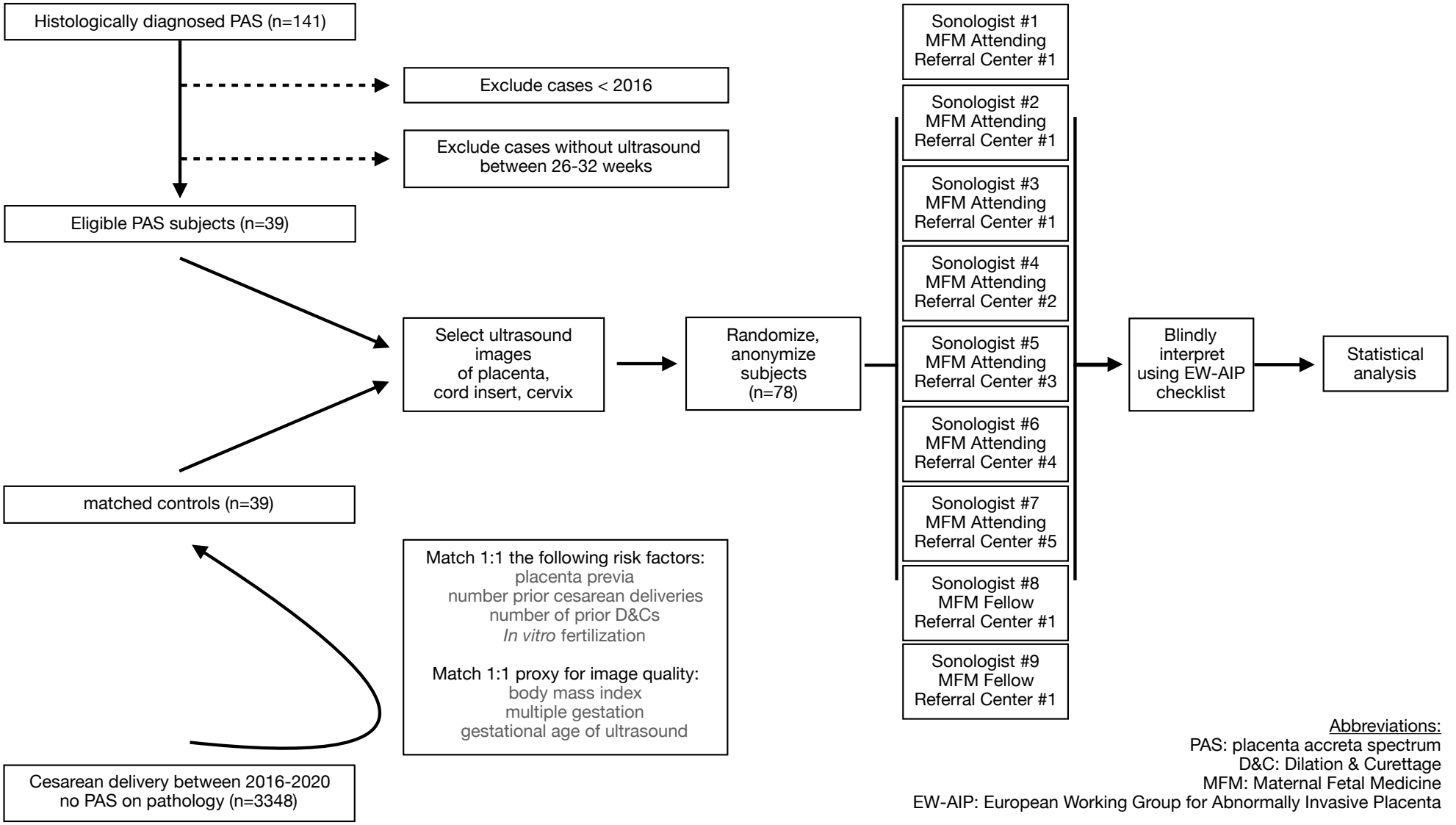
	All cases (n=78)	**Excluding histologic accreta (n=68)**	**Excluding 2 MFM fellows (n=78)**
Loss of clear zone	0.25	0.49	0.50
Myometrial thinning	0.29	0.53	0.58
Abnormal placental lacunae	0.40	0.54	0.57
Bladder wall interruption	0.19	0.34	0.35
Placental bulge	0.22	0.48	0.50
Focal exophytic mass	0.05*	0.12*	0.10
Uterovesical hypervascularity	0.41	0.62	0.61
Subplacental hypervascularity	0.33	0.62	0.48
Bridging vessels	0.23	0.44	0.44
Placental lacunae feeder vessels	0.30	0.43	0.40
Parametrial involvement	0.23	0.02*	0.03*
*Mixed-effects model did not converge.			
Inter-characteristic correlation (ICC) with no restrictions is 0.71 which indicates a reasonable sonologist-to-sonologist reliability. Estimates closer to this number indicate more reliable performance measures.			

Table 4: Secondary outcome – performance of individual characteristics

	All cases (n=78)	**Excluding histologic accreta (n=68)**	**Excluding 2 MFM fellows (n=78)**
Loss of clear zone	0.55	0.63	0.59
Myometrial thinning	0.56	0.64	0.61
Abnormal placental lacunae	0.44	0.52	0.45
Bladder wall interruption	0.34	0.45	0.36
Placental bulge	0.48	0.59	0.54
Focal exophytic mass	0.11	0.17	0.13
Uterovesical hypervascularity	0.44	0.49	0.45
Subplacental hypervascularity	0.33	0.38	0.34
Bridging vessels	0.35	0.41	0.35
Placental lacunae feeder vessels	0.23	0.32	0.30
Parametrial involvement	0.049	0.045	0.12

To check agreement between sonologists' individual (binary) responses (e.g., loss of clear zone) and the true case/control status we used Cohen's kappa. This provided us with a numerical summary between -1 and 1 for each sonologist, where 0 indicates no agreement beyond what is expected by chance, 1 indicates perfect agreement, and -1 indicates perfect disagreement.

Figure 1: Subject recruitment, disease and for matched control



Abbreviations:
PAS: placenta accreta spectrum
D&C: Dilation & Curettage
MFM: Maternal Fetal Medicine
EW-AIP: European Working Group for Abnormally Invasive Placenta

AJOG MFM
American Journal of Obstetrics & Gynecology
Maternal Fetal Medicine

STATEMENT OF AUTHORSHIP

Each author is required to submit a signed Statement of Authorship upon submission. This applies to all submission types including Editorials, Letters to the Editor, etc.

Date: 3/22/2022 **Manuscript # (if available):** _____

Manuscript title: Validation of a sonographic checklist on the detection of histologic placenta accreta spectrum

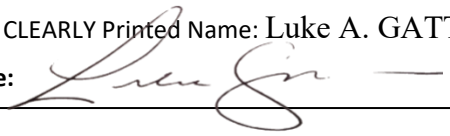
Corresponding author: Luke Gatta, MD

Authors may either sign the same form or submit individually

I am an author on this submission, have adhered to all editorial policies for submission as described in the Information for Authors, attest to having met all authorship criteria, and all potential conflicts of interest / financial disclosures appears on the title page of the submission.

Signatures are required - typed signatures are unacceptable.

Typed or CLEARLY Printed Name: Luke A. GATTA, MD

Signature: 

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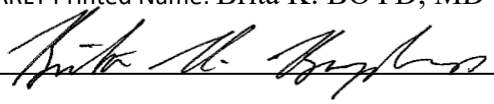
Signature: 

Typed or CLEARLY Printed Name: Sally COLLINS, BMBCh, DPhil

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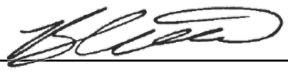
Signature: 

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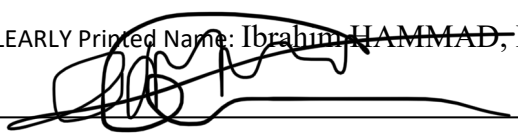
Signature: 

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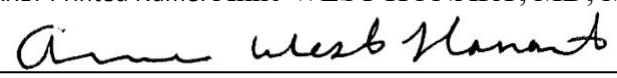
Signature: 

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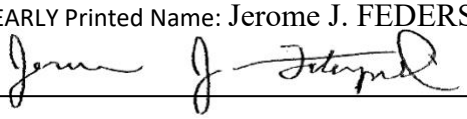
Signature: 

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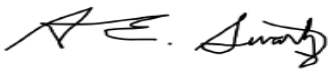
Signature: 

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Duke Obstetrics & Gynecology
Duke University School of Medicine

1 April 2023

Vincenzo Berghella, MD
Editor-in-Chief
American Journal of Obstetrics and Gynecology – Maternal-Fetal Medicine
Online Submission

Dear Dr. Berghella and Deputy Editors,

On behalf of our co-authors, we respectfully submit our manuscript entitled "Validation of a sonographic checklist on the detection of histologic placenta accreta spectrum" for consideration for publication in *AJOG-MFM*.

The authors attest that this an original submission, it has not been previously published, nor submitted elsewhere, and that all authors have read and approve of the submission. Data from this manuscript has not previously been published nor is currently under preparation for other manuscripts that would come in conflict with the submitted data.

Data from this manuscript were presented at as an oral communication at the International Society for Ultrasound in Obstetrics & Gynecology (ISUOG) World Congress 2022 on September 16th, 2022, in London, United Kingdom.

This study was approved 9/2020 under Duke University School of Medicine IRB Pro00025434 and Duke IRB Pro00100007, with data transfer agreements signed and on file for each of the five participating institutions.

This study was funded by the Charles B. Hammond, MD fund, an internal fund directed for Ob/Gyn trainees at Duke University.

Thank you for your review and consideration of our manuscript for your journal.

Sincerely,

Luke Alexander Gatta, MD
Fellow, Class of 2023
Division of Maternal Fetal Medicine

Jennifer B. Gilner, MD, PhD
Assistant Professor
Division of Maternal Fetal Medicine

Manuscript title: Validation of a sonographic checklist for the detection of histologic placenta accreta spectrum.

Condensation: A sonographic checklist for reporting suspected placenta accreta spectrum has a positive likelihood ratio of 9.6 to detect (and 0.3 negative likelihood ratio to exclude) histologic disease.

Short title: Sonographic checklist to predict placenta accreta spectrum

AJOG at a Glance:

A. Why was this study conducted?

An expert consensus checklist was developed in 2016 to standardize sonographic reporting of suspected placenta accreta spectrum and reduce the risk of unanticipated disease. However, the diagnostic performance of the checklist is not known.

B. What are the key findings?

The checklist has a positive and negative likelihood ratio of 9.6 and 0.3, respectively, and its sensitivity and specificity improves with more severe histologic disease.

C. What does this study add to what is already known?

This study provides diagnostic accuracy to support a standardized sonographic checklist for use in clinical interpretation, research, and training for placenta accreta spectrum.

Conflict of Interest: The authors report no conflicts of interest.

Keywords: Abnormal placentation, abnormally adherent placenta, antenatal diagnosis, checklist, delivery planning, morbidly adherent placenta, multidisciplinary team, placental imaging, sonographic imaging, ultrasound

Abstract

Background: To standardize research terminology and reduce unanticipated placenta accreta spectrum (PAS), the European Working Group for Abnormally Invasive Placenta (EW-AIP) developed a consensus checklist for reporting PAS suspected on antenatal ultrasound. The diagnostic accuracy of the EW-AIP checklist has not been assessed.

Objective: To test the performance of the EW-AIP sonographic checklist in predicting histologic PAS.

Study Design: This is a multi-site, blinded, retrospective review of transabdominal ultrasound studies performed between 26-32 weeks gestation for subjects with histologic PAS between 2016-2020. We planned a 1:1 control cohort of subjects without histologic PAS. To reduce reader bias, we matched the control cohort for known risk factors including previa, number of prior cesarean deliveries, prior dilation and curettage (D&C), in vitro fertilization (IVF), and clinical factors affecting image quality including multiple gestation, body mass index (BMI) and gestational age at the ultrasound. Nine sonologists from 5 referral centers, blinded to the histologic outcomes, interpreted the randomized ultrasound studies using the EW-AIP checklist. The primary outcome was the sensitivity and specificity of the checklist to predict PAS. Two separate sensitivity analyses were performed: 1) we excluded subjects with mild disease (i.e. only assessed subjects with histologic increta and percreta); 2) we excluded interpretations from the 2 most junior sonologists.

Results: 78 subjects were included (39 PAS, 39 matched control). Clinical risk factors and image quality markers were statistically similar between cohorts. The checklist sensitivity (95% Confidence Interval, CI) was 76.6% (63.4%-90.6%) and specificity (95% CI) was 92.0% (63.4%-99.9%), with a positive and negative likelihood ratio of 9.6 and 0.3, respectively. When

we excluded subjects with mild PAS disease, the sensitivity (95% CI) increased to 84.7% (73.6%-96.4%) and specificity was unchanged at 92.0% (83.2%-99.9%). Sensitivity and specificity were unchanged when the interpretations from the 2 most junior sonologists were excluded.

Conclusion: The 2016 EW-AIP checklist for interpreting PAS has a reasonable performance in detecting and excluding histologic placenta accreta spectrum.

Introduction

The incidence of placenta accreta spectrum (PAS) is rising, and it is now the leading indication for puerperal hysterectomy[1]. Management typically includes a scheduled, late preterm delivery by a multidisciplinary team[2]. Unanticipated PAS deliveries put pregnant patients at highest risk for blood transfusion, ICU admission, and death[3]. Thus, antenatal diagnosis is prerequisite for surgical planning to reduce maternal morbidity and mortality. Despite this necessity, a recent Maternal-Fetal Medicine Unit Network study found that PAS was suspected in only 53% of subjects prior to delivery[4].

The mainstay for antenatal PAS diagnosis is ultrasound. However, ultrasound is operator dependent, and limited by a prior lack of standardized definitions of PAS ultrasound markers. Additionally, a patient's *a priori* risk for PAS, based on historical characteristics, influences interpretation of ultrasound studies. Therefore, objective assessment of PAS imaging characteristics is challenging for prospective research[5].

Given the need to standardize PAS ultrasound markers, in 2016 the European Working Group on Abnormally Invasive Placenta (EW-AIP) produced a consensus checklist for ultrasound assessment of placentation[6]. The checklist was developed by an online questionnaire of 50 international experts, and a list of 11 sonographic markers was derived from expert opinion. Two years later, both the International Federation of Gynecology and Obstetrics (FIGO) and the Society for Maternal Fetal Medicine (SMFM) endorsed the sonographic characteristics within the checklist[7,8]. While the EW-AIP checklist is derived from and endorsed by several professional societies, the clinical performance of the checklist itself has not been assessed.

Our objective was to assess the diagnostic accuracy of the Maternal-Fetal Medicine (MFM) sonologist's overall impression of PAS using the EW-AIP checklist, and to further evaluate the interrater reliability and diagnostic performance for each of the characteristics.

Materials and Methods

We conducted a multi-site, blinded, retrospective review of 26-32 week (inclusive) ultrasound studies for subjects from a single United States referral center with PAS confirmed on hysterectomy specimen between 2016 (when the EW-AIP checklist was published and adopted at our institution) and 2020. We identified a 1:1 control cohort of subjects without PAS clinically or on final pathology, imaged antenatally at the same diagnostic center and undergoing cesarean delivery at the same hospital as the PAS subjects. In an effort to control for expected bias influenced by clinical risk factors for PAS, we matched the control cohort using a greedy-matching algorithm for pre-defined clinical characteristics listed in the ACOG Obstetric Care Consensus[3], including placenta previa, number of prior cesarean deliveries, prior dilation and curettage (D&C), and in vitro fertilization (IVF). Additionally, we matched clinical characteristics influencing image quality including body mass index (BMI), multiple gestation, and gestational age at the time of the ultrasound.

Ultrasounds studies from 26-32 weeks gestation were chosen for review, as this timing was the institutional standard for follow up for suspected abnormal placentation diagnosed during routine anatomy scan. Of note, while not all subjects with anticipated PAS were managed with hysterectomy at our institution, a hysterectomy was required as part of the present study design as histology was the primary outcome to test the sonographic checklist.

After the PAS and control cohorts were created, the lead author (who did not participate in interpreting the ultrasound studies) selected ultrasound images and cine clips of the placenta, cervix, and placental cord insertion. The ultrasounds were de-identified, randomized, and then interpreted by 9 Maternal-Fetal Medicine (MFM) sonologists blinded to final histology. The blinded sonologists were aware that the ultrasound series included matched controls, but were

not aware of the specific ratio for matching. The 9 sonologists were from 5 United States referral centers (7 MFM faculty and 2 MFM fellows), recruited by email after an annual professional conference[9] For each ultrasound, the sonologists were provided the gestational age and the matched clinical characteristics from the Obstetric Care Consensus[3], such as number of prior cesarean deliveries or prior D&Cs. To simulate a workflow at an antenatal diagnostic center, 5 minutes were suggested to review each ultrasound and the sonologists were permitted to move between images and cine clips as necessary. Consistent with the EW-AIP checklist, the nine sonologists could choose "present", "absent", or "unsure" for each sonographic sign, and then prompted to predict whether there was a low or high probability of PAS on pathology. To preserve integrity of statistical analysis, each sonologist was required to review 100% of the ultrasounds studies, or their responses were discarded.

Baseline demographics of the PAS and control cohorts were assessed using Chi-Square or ANOVA F-Test, depending on whether the demographic was binary or continuous, respectively. For the primary outcome, to measure the strength of agreement between sonologists' interpretation and histologic diagnosis, a dichotomous sensitivity and specificity table was created using the sonologists' aggregate overall impression. Two separate sensitivity analyses were performed: 1) we excluded subjects with mild disease (i.e. excluding subjects with histologic accreta and only including subjects with histologic increta and percreta on hysterectomy specimen); 2) we excluded interpretations from the 2 MFM fellows who were most junior in experience with ultrasound interpretation. We performed these analyses to assess how disease severity and sonologist experience affected the performance of the checklist.

For secondary outcomes, we analyzed the interrater reliability of the sonologists' responses, using Kappa statistics to compute an interrater correlation coefficient (ICC) to assess

the agreement for each characteristic between the 9 sonologists. Additionally, to compute the aggregate sonologists' responses for individual characteristics to the true histologic diagnosis of PAS, we used Cohen's Kappa, which provided a numerical summary between -1 and 1, where 0 indicates no agreement beyond what is expected by chance, 1 indicates perfect agreement, and -1 indicates perfect disagreement.

The images were anonymized and exported from the clinical picture archiving and communications system (Viewpoint 6.11, General Electric) onto an encrypted, cloud-based content management platform (Box Service, 2022). The checklist for each subject was completed on REDCap 12.0.2. Statistical software used was SAS 9.4 (SAS Institute, Cary, NC). The study was approved by the institutional review board at each of the five participating institutions and a data transfer agreement was executed to facilitate transfer of the de-identified images. The de-identified images and code used for analysis are available upon request for either research or education purposes.

Results

Subject recruitment is demonstrated in Figure 1. In total, there were 39 subjects with PAS that met inclusion criteria including: a) performance of an ultrasound between 26-32 weeks gestation, b) hysterectomy performed between 2016-2020 with histology confirming PAS. After pooling the PAS cohort's pre-defined risk factors, the 1:1 control cohort was identified by querying 3,348 subjects who had a cesarean delivery at the same center during the same time period, but without PAS suspected clinically or on final pathology. Baseline demographics between the PAS and control cohorts were statistically similar, including presence of placenta previa on ultrasound (64.1% vs 59.0%, p=0.64), median (25^{th}, 75^{th} percentile) number of prior cesarean deliveries (2 [1, 3], for both cohorts, p>0.99), prior D&Cs (23.1% vs 25.6%, p=0.79) and IVF conception (2.6% for both cohorts, p>0.99). Furthermore, factors influencing image quality were statistically similar including BMI, multiple gestation, and gestational age of ultrasound (Table 1). Of note, although study sonologists were unaware of this fact, there were more images for PAS subjects than control subjects (median 23.0 [13.0, 33.0] versus 16.0 [9.0, 20.0], respectively, p=0.002).

Each of the 9 sonologists completed the checklist for all subjects. The median (25^{th}, 75^{th} percentile) years of MFM experience was 5.0 (2.8, 8.0), with a range of 1-22. Seven sonologists were practicing MFM faculty (6 board-certified, 1 board-eligible), and 2 were active MFM fellows.

Primary outcomes are listed in Table 2. The sensitivity (95% Confidence Interval, CI) of the EW-AIP checklist detecting histologic PAS was 76.6% (63.4%-90.6%) and specificity (95% CI) was 92.0% (63.4%-99.9%), yielding a positive likelihood ratio to detect PAS of 9.6, and a negative likelihood ratio to exclude PAS of 0.3. When excluding mild cases, or histologic

accreta (n=10), and assessing only histologic increta and percreta, the sensitivity (95% CI) increased to 84.7% (73.6%-96.4%) and specificity remained the same with a narrowed CI, 92.0% (83.2%-99.9%). When excluding the responses of the two MFM fellows, the sensitivity and specificity were negligibly affected, 78.0% (64.8%-91.2%) and 93.0% (85.0%-99.9%), respectively.

For secondary outcomes, the interrater classification coefficient (which reflects the degree of correlation and agreement between measurements among 9 sonologists) is shown in Table 3. The two characteristics with the most agreement between sonologists was abnormal placental lacunae (0.4) and uterovesical hypervascularity (0.41), indicating good reliability between reviewers. Bladder wall interruption (0.19) and focal exophytic mass (0.05) were noted least consistently, indicating poor reliability. In the sensitivity analysis, sonologist agreement for each of the 11 characteristics increased with more severe histologic disease. Additionally, when excluding the responses of the most junior sonologists, there was an increase in agreement for each of the 11 characteristics, even if this did not change their overall diagnostic impression.

Table 4 lists the performance of individual characteristic against histologic PAS, or in other words, the predictive value of histologic PAS if the individual characteristic was identified. Each of the characteristics had a positive association with histological PAS, with the highest agreement being myometrial thinning (0.56), loss of clear zone (0.55), and bladder wall interruption (0.34). The least correlated with severe disease was the parametrial involvement, with a kappa of 0.05. Similarly, the agreement between sonographic characteristic and true PAS diagnosis improved with more severe disease, as well as excluding the responses from the two junior sonologists.

Discussion

Principal Findings

Using a consensus expert opinion initially proposed in 2016 by EW-AIP and endorsed in 2018 by FIGO and SMFM, we assessed the clinical performance of an ultrasound checklist for the histologic diagnosis of PAS. The sensitivity (95% CI) was 76.6% (63.4%-90.6%) and specificity (95% CI) was 92.0% (63.4%-99.9%) in predicting PAS, yielding a positive likelihood ratio to detect PAS of 9.6, and a negative likelihood ratio to exclude PAS of 0.3. The performance of the checklist to predict histologic PAS improved with more severe disease (increta and percreta) and maintained a strong performance when employed by less experienced sonologists (MFM fellows).

Results in the context of what is known

As our understanding of the pathophysiology of PAS evolves from a model centering on *placental-invasion* to a model of *uterine-dehiscence*[10], reporting radiologic, clinical, or pathologic PAS has moved away from categorical "accreta", "increta" and "percreta" terminology to a more descriptive approach. For example, in 2018 FIGO sought to standardize intraoperative findings with a clinical criteria that describes pelvic involvement of placentation[11] rather than using categorical terms. Additionally, a consensus panel of clinical pathologists have replaced the categorical terminology to a 10 characteristic, descriptive grading system[12]. Similarly, driven by the need to standardize sonographic PAS markers, multiple professional societies have called for a systematic approach to the evaluation of the uterus and placenta. EW-AIP put forth a proposed checklist in 2016, reviewing 23 manuscripts and drafting a list of 11 PAS ultrasound markers (6 markers are greyscale, 4 are 2D color Doppler, and 1 is

3D power Doppler)[6]. The present study now provides clinical performance outcomes for the expert-consensus checklist put forward by EW-AIP.

Research implications

Studies assessing predictive value of ultrasound markers for PAS are limited by small sample sizes, retrospective designs without a control cohort, and heterogenous definitions of PAS. For example, the sensitivity and specificity of hypervascular uterovesical interface ranges widely from 11-100% and 36-100% respectively[13,14]. Given the broad range of predictive values for each characteristic within the checklist, the EW-AIP consensus stresses that all markers should be systematically assessed and unambiguously reported until further research clarifies their individual utility. Therefore, the primary outcome of this study was to report the performance of the "bundle" of sonographic markers in a checklist format that may be readily adopted by antenatal diagnostic centers.

An interesting finding was that responses from the MFM fellows did not significantly impact overall predictive performance, suggesting that this checklist may have an early learning curve if adopted as a part of MFM training. Checklists have emerged for the management of complex conditions to standardize evidence- or consensus-based processes and promote high quality and consistent care. Accordingly, SMFM has created a checklist for surgical planning for anticipated and unexpected PAS[15]. Establishing a clinically validated checklist for the systematic evaluation of placenta and uterus is imperative for education, training, and research.

Strengths and limitations

There are two key, related limitations to this study. Although the study involved blinded interpretations by sonologists from multiple institutions, it is retrospective in design. Therefore, images were not systematically procured in a checklist manner to capture or exclude components

of the checklist itself. We suspect that this limitation is pertinent to the secondary outcomes, assessing the individual characteristics of the checklist. We therefore recommend caution in interpreting Table 4 as these may underreport the performance against the true PAS diagnosis. Second, there were more images within the PAS cohort than the control cohort, likely reflecting the sonographers internal assessment as they were obtaining images for interpretation or requested additional focus. While the sonologists in this study were blinded to the clinical outcome, a potential bias is introduced. The lead author intentionally did not control this known discrepancy in advance to avoid introducing a selection bias by "cherry picking" images for blinded review.

There are four strengths to the study. First, the use of a control cohort matched comprehensively for PAS risk factors is an effort to neutralize the impact of knowing the patient's clinical history before reading the images. Mimicking real world ultrasound reading, sonologists had the basic clinical information prior to reading the scan, such as number of prior cesarean or IVF conception, and the clinical characteristics were comparable between the PAS and control cohorts. Second, both the PAS and control cohort were selected from the same referral center, therefore standardizing variables such as sonographer education, image procurement, and ultrasound machines used. Additionally, to reduce the risk of recall bias, images were blinded and reviewed by sonologists from four external institutions that did not participate in the subjects' clinical care and therefore had never seen the images previously. Lastly, the planned sensitivity analysis assessed the impact of disease severity as well as sonologist training in order to assess potential uptake of the checklist as a part of clinical care or education.

Conclusion

Our multi-site study has assessed the diagnostic accuracy of an ultrasound checklist for the detection of placenta accreta spectrum, with a high likelihood ratio. The routine incorporation of this checklist may contribute to decreased unanticipated PAS cases and timely referral to PAS centers, as well as standardize research terminology.

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REVIEWER COMMENTS:

REVIEWER 1, POINT #1

A. *The authors evaluated for the first time the diagnostic performance of the EW-AIP checklist in the detection of placenta accreta and increta. It is a checklist with different items allowing to conduct the ultrasound examination in case of suspicion of an abnormal invasive placenta and to evaluate the probability of a PAS in order to improve the management of the women.*

   The authors report a good performance in the detection of placenta accreta (sensitivity 76.6% and specificity 92.0% with positive and negative likelihood ratio at 9.6 and 0.3 respectively).

   Overall, the manuscript is well written and the methodology is robust. Although the total number of examinations evaluated is moderate (39 ultrasounds with confirmed PAS and 39 controls), the number of sonographers is nine, which seems correct for the evaluation of performance and inter-sonographer variability.

   A few points to note, however concerning the methods:

   All women included in the "confirmed accreta" group had a hysterectomy (histological diagnosis). There is no information on the management of placenta accreta at the center in question (% hysterectomy and % conservative treatment). It is possible that patients who have a hysterectomy for placenta accreta (rather than conservative treatment) have more severe placenta accreta. This checklist would therefore be evaluated and effective for severe placenta accreta and therefore may be more visible on ultrasound. This is a limitation that I think it is appropriate to mention (external validity)

B. At the institution, cesarean hysterectomy was the default treatment for all anticipated disease. The purpose of the EW-AIP checklist (the primary exposure) was to detect clinically relevant disease that would be at highest risk for maternal morbidity.
   a. In response to the reviewer, **we clarified this in the text.**

C. Lines 150-66

D. "Ultrasounds studies from 26-32 weeks gestation were chosen for review, as this timing was the institutional standard for follow up for suspected abnormal placentation diagnosed during routine anatomy scan**. Regardless of the disease severity, subjects with anticipated PAS were managed by a multidisciplinary care team and, with intraoperative confirmation and the patient's consent, the disease was managed with cesarean hysterectomy. Of note, while not all subjects with PAS may have been managed with hysterectomy at our institution, a hysterectomy was required as part of the present study design as histology was the primary outcome to test the sonographic checklist."**

REVIEWER 1, POINT #2

A. *It is not specified whether all the women in the confirmed accreta group had an antenatal diagnosis of placenta accreta or whether there were incidental discoveries as well (with ultrasound performed in the center anyway), to be specified.*

B. All subjects in the disease cohort had suspected PAS.

a. Table 1 notes that 10 subjects (26.3%) had suspected accreta, and 29 (76.3%) subjects had suspected increta or percreta. No subject was incidentally diagnosed on pathology.
b. In response to the reviewer, **we clarified this in the text.**

C. Lines 134-7.

D. "We conducted a multi-site, blinded, retrospective review of 26-32 week (inclusive) ultrasound studies including subjects prospectively enrolled at a single United States referral center with **suspected PAS and confirmed on hysterectomy specimen** between 2016 (when the EW-AIP checklist was published and adopted at our institution) and 2020"

REVIEWER 1, POINT #3

A. *The main author made the selection of the images from the ultrasound examinations, the modalities of selection of these images are not very well explained and it seems to me that this can be a major bias.*

B. **We added detail regarding the selection of ultrasound images.** After the disease and control cohorts were selected by risk factors, the lead author selected placental, cervix, and cord insertion images included with either the detailed anatomy or follow up scans. To reduce the risk of bias, all placental images were included, and the author did not participate in interpretation.
    a. Of note, the EW-AIP checklist studied does not include a prescribed number of images to include, nor impart recommendations on ultrasound settings. This is an area for further research.[1]

C. Lines 167-72.

D. "After the PAS and control cohorts were created, the lead author (who did not participate in interpreting the ultrasound studies) **selected transabdominal images of the placenta, cervix, and placental cord insertion obtained during a detailed second trimester ultrasound (CPT 76811) or follow up ultrasound (CPT 76816). Selected images included both still and cine clips, and greyscale and color Doppler images – no dedicated image of the placenta, cervix, or cord insertion was excluded, as the EW-AIP checklist did not have prescribed number of images**"

REVIEWER 1, POINT #4

A. *The authors therefore use this checklist a posteriori, whereas it is a checklist intended to guide the sonographer and therefore to focus his examination on the search for these signs. Unless I am mistaken, this limit is not mentioned in the manuscript.*

B. **Yes -- this was an anticipated limitation and mentioned in the text.** The checklist is intended for interpretation, not image procurement. Future research must guide recommendations to optimize image settings, and the manuscript supports training the sonographer to consider the checklist when obtaining images.

C. Lines 332-39

[1] Alfirevic Z, Tang AW, Collins SL, Robson SC, Palacios-Jaraquemada J for the Ad Hoc International AIP Expert Group. Pro forma for ultrasound reporting in suspected abnormally invasive placenta (AIP): an international consensus. *Ultrasound Obstet Gynecol*, 2016. **47**(3): p. 276-8.

D. "Therefore, **images were not systematically procured in a checklist manner to capture or exclude components of the checklist itself. We suspect that this limitation is pertinent to the secondary outcomes, assessing the individual characteristics of the checklist**. We therefore recommend caution in interpreting Table 4 as these may underreport the performance against the true PAS diagnosis. Second, there were more images within the PAS cohort than the control cohort, likely reflecting the sonographers internal assessment as they were obtaining images for interpretation or requested additional focus."

REVIEWER 2, POINT #1

A. *The authors performed a retrospective matched case-control study to evaluate the performance characteristics of the EW-AIP checklist for predicting histologic PAS. They found the checklist performed reasonably with a 76.6% sensitivity and a 92.0% specificity. There was also moderate interobserver agreement in assessing elements of the checklist. I think the study is well-designed and reasonably written. I have the following minor suggestions:*

   In order to improve clarity, change line 50 of the abstract from "We planned a 1:1 control cohort of subjects without histologic PAS" to "We matched 1:1 to a control cohort of subjects without histologic PAS".

B. Changed as requested.

C. Line 50

D. We **matched** a 1:1 control cohort of subjects without histologic PAS.

REVIEWER 2, POINT #2

A. *Regarding table 4 (Lines 238-242), the three characteristics with the highest agreement are myometrial thinning (0.56), loss of clear zone (0.55) and placental bulge (0.48); not bladder wall interruption (0.34).*

B. Thank you! The reviewer is correct. Table 4 is correct as shown, and we edited the text to reflect the results.

C. Lines 277-9.

D. "Each of the characteristics had a positive association with histological PAS, with the highest agreement being myometrial thinning (0.56), loss of clear zone (0.55), and **placental bulge (0.48).**"

REVIEWER 3, POINT #1

A. *Thank you for the opportunity to review this paper.*

   This is a paper validating the EW-AIP checklist for ultrasound diagnosis of placenta accreta spectrum (PAS) disorders. Strengths include the large number of MFMs from multiple institutions reviewing ultrasounds. Consideration of individual scoring components is also a plus. The number of patients and controls is reasonable given the use of full clinical studies and the rarity of hysterectomy cases.

My largest concerns with the paper involve the controls. Some of the issues are non-modifiable given a retrospective study design and the labor-intensive nature of reviewing cases (that is - I do not recommend doing a second set of controls(!)). However, I think a more extensive description of this group would be useful. What is the indication for the exam (this might be included in a table)?

B. In response, we reviewed the indications for follow up ultrasounds for the control cohort, and **added this to the paper in Table 1**. Out of the 39 control subjects, 30 (76.9%) were indicated by placental reassessment, 6 (15.4%) were for fetal indications, 3 (7.7%) were for anatomy ultrasounds.

C. Added to Table 1

D.

Indication for US in control cohort			
Placental reassessment		30 (76.9%)	
Fetal Indication		6 (15.4%)	
Anatomy		3 (7.7%)	

REVIEWER 3, POINT #3

A. How was it established that controls were "without PAS suspected clinically or on final pathology"? Does "clinical suspicion of PAS" refer only to pre-delivery suspicion or does it include abnormally adherent placenta at delivery

B. The control cohort was created by querying all patients who had:
- Detailed anatomy (76811) or follow up ultrasound (76816) (same as disease)
- Between 2016-2020 at institution's Diagnostic Center (same as disease)
- Cesarean delivery at the institutions Labor & Delivery (same as disease)

And excluding those with:
- Placenta accreta on final pathology reports (unlike disease)
- Placenta accreta noted on the operative note (unlike disease)

This resulted in 3348 subjects.

We then used a greedy-matching algorithm to best match the risk factors to render a control cohort of 39 subjects, baseline demographics in Table 1.

This was added to the text for clarity.

C. Lines 134-49.

D. "We conducted a multi-site, blinded, retrospective review of 26-32 week (inclusive) ultrasound studies including subjects from a single United States referral center with suspected PAS and confirmed on hysterectomy specimen between 2016 (when the EW-AIP checklist was published

and adopted at our institution) and 2020. We identified a 1:1 control cohort of subjects without PAS clinically or on the final pathology report. In an effort to control for expected bias influenced by clinical risk factors for PAS, we best-matched the control cohort using a greedy-matching algorithm for pre-defined clinical characteristics listed in the ACOG Obstetric Care Consensus[3], including placenta previa, number of prior cesarean deliveries, prior dilation and curettage (D&C), and in vitro fertilization (IVF). Additionally, we matched clinical characteristics influencing image quality including body mass index (BMI), multiple gestation, and gestational age at the time of the ultrasound. **Thus, the control cohort was created by including subjects with imaging conducted at the same diagnostic center and cesarean delivery conducted at the same labor and delivery during the same timeframe, then excluded those with PAS on final pathology or on review of operative note. The last step was matching the pre-defined clinical characteristics as the disease cohort.**

REVIEWER 3, POINT #4

A. *Does final pathology include lower microscopic grades of accreta, such as microscopic accreta or adherent myometrial fibers at the basal plate? Were pathology reports of slides examined? If so, by whom?*

B. For pathologic definitions, we used *Hecht JL et al*[2] as a guide, which states "[Basal Plate myometrial fibers] are often detected incidentally on delivered placentas based on random sectioning (with no associated gross findings), so quantitation based on gross features is difficult". The pathologic definition is reference #12 in the manuscript.

Therefore, we did not include microscopic accreta or BPMF in the primary outcome, and included disease denoted as accreta, increta, or percreta. The intent of the checklist was to detect clinically significant PAS, rather than incidental PAS.

The pathologic reports were reviewed by the lead author. **We have added this to the manuscript for clarity.**

C. Lines137-40

D. We retrospectively identified a 1:1 control cohort of subjects without PAS clinically or on the final pathology report (**incidental diagnoses on placental specimens were not included**)

REVIEWER 3, POINT #5

A. *Given that controls were examined for reasons other than the PAS checklist, were images reviewed by the first author to ensure that the views and studies necessary to capture all the checklist items were present?*

B. See Reviewer #1, Point #4, above

REVIEWER 3, POINT #6

[2] Hecht JL. Baergen R, Ernst LM, et al. 2020. Classification and reporting guidelines for the pathology diagnosis of placenta accreta spectrum (PAS) disorders: recommendations from an expert panel. *Modern Pathology.* 2020;33(12):2382-2396. doi:10.1038/s41379-020-0569-1

A. *The difference in image numbers presents a problem. The author's provide a reasonable explanation (although see below about line 151 vs. 299), but I remain concerned that MFMs reviewing images may have taken cues from the number and type of images in guessing whether the study was for suspected accreta. It may be worth asking reviewers whether they were able to make such a guess, but I am unable to identify an appropriate design for such a post-hoc study. I assume the interval image review and submission has been lengthy, which would make responses less reliable.*

B. Yes, we agree this is an anticipated limitation and due to the retrospective design. This is clearly laid out in the limitations. As the reviewer presumes, the interval between review (September 2021) and submission is lengthy, rendering the responses unreliable. However, it is a prudent idea for prospective study design.

C. Lines 337-42.

D. "Second, there were more images within the PAS cohort than the control cohort, likely reflecting the sonographers internal assessment as they were obtaining images for interpretation or requested additional focus. While the sonologists in this study were blinded to the clinical outcome, a potential bias is introduced. The lead author intentionally did not control this known discrepancy in advance to avoid introducing a selection bias by "cherry picking" included images for blinded review (aside from removing non-placental images).

REVIEWER 3, POINT #7

A. *Line 94 - Regarding the 53% suspicion, what did suspicion entail and what was the definition of PAS (clinical? microscopic? at hysterectomy?)?*

B. In the MFMU article referenced in the manuscript[3], among the 158 subjects with PAS (diagnosed clinically by review by two blinded co-authors), 84 (53.2%) had a suspected diagnosis and 74 were unsuspected (46.8%).

C. N/a

D. N/a

REVIEWER 3, POINT #8

A. *Line 151 - It's stated that images were selected. However line 299 states the first author did not 'cherry pick' specific images or studies. Please clarify.*

B. The lead author included images of the placenta, cervix, and cord insertion for efficiency of sonologist review (i.e. excluded fetal images). Among the placental images included, none were excluded. **This was clarified in the text**.

C. Lines 340-2.

[3] Bailit, J. L. , Grobman, W. A. , Rice, M. M. , Reddy, U. M. , Wapner, R. J. , Varner, M. W. , Leveno, K. J. , Iams, J. D. , Tita, A. T. , Saade, G. , Rouse, D. J. & Blackwell, S. C. (2015). Morbidly Adherent Placenta Treatments and Outcomes. Obstetrics & Gynecology, 125 (3), 683-689. doi: 10.1097/AOG.0000000000000680.

D. The lead author intentionally did not control this known discrepancy in advance to avoid introducing a selection bias by "cherry picking" included images for blinded review (**aside from removing non-placental images).**

REVIEWER 3, POINT #9

A. Line 202 - Since the study is retrospective I assume patients were not specifically recruited for this study - please confirm (similar language in Figure 1)

B. Subjects with PAS (the disease cohort) was prospectively enrolled as part of an institutional registry. The control subjects were retrospectively identified. **This was clarified in the text.**

C. Lines 134-8

D. "We conducted a multi-site, blinded, retrospective review of 26-32 week (inclusive) ultrasound studies including subjects **prospectively enrolled** at a single United States referral center with suspected PAS and confirmed on hysterectomy specimen between 2016 (when the EW-AIP checklist was published and adopted at our institution) and 2020. **We retrospectively identified** a 1:1 control cohort of subjects…"

REVIEWER 3, POINT #10

A. Line 223-224 - Is mild defined as accreta?

B. Yes. **This is clarified in the text.**

C. Lines 259-62.

D. When excluding mild cases (or histologic accreta (n=10), and assessing only histologic increta and percreta) the sensitivity (95% CI) increased to 84.7% (73.6%-96.4%) and specificity remained the same with a narrowed CI, 92.0% (83.2%-99.9%).

REVIEWER 3, POINT #11

A. Lines 238-245 - Consider reporting sens/spec of individual components (vs. kappa). Consider reporting correlation between components.

B. We considered reporting sensitivity/specificity in the development of the study design due to increased familiarity to this statistic among the clinical community. However, we ultimately made the sensitivity / specificity of the checklist as the *primary outcome* in order to assess the validity of the checklist (i.e. does it accurately predict histologic PAS?), and *reported a kappa* as the *secondary outcome* in order to answer the question of reliability (i.e. how consistent are the reviewer responses?). The sensitivity/specificity of individual components of the checklist have been previously studied[4], and our secondary outcomes focused on their pragmatic application

[4] Skupski, D. W., Duzyj, C. M., Scholl, J., Perez-Delboy, A., Ruhstaller, K., Plante, L. A., Hart, L. A., Palomares, K. T. S., Ajemian, B., Rosen, T., Kinzler, W. L., Ananth, C., & Perinatal Research Consortium (2022). Evaluation of classic and novel ultrasound signs of placenta accreta spectrum. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*, *59*(4), 465–473. https://doi.org/10.1002/uog.24804

across institutions. Since the clinical reader may be unfamiliar with kappa, we placed this in plain language in the text and on the Table 4.

C. Table 4; Lines201-7

D. Table 4: "To check agreement between sonologists' individual (binary) responses (e.g., loss of clear zone) and the true case/control status we used Cohen's kappa. This provided us with a numerical summary between -1 and 1 for each sonologist, where 0 indicates no agreement beyond what is expected by chance, 1 indicates perfect agreement, and -1 indicates perfect disagreement."

Lines 201-7: For secondary outcomes, we analyzed the interrater reliability of the sonologists' responses, using Kappa statistics to compute an interrater correlation coefficient (ICC) to assess the agreement for each characteristic between the 9 sonologists. Additionally, to compute the aggregate sonologists' responses for individual characteristics to the true histologic diagnosis of PAS, we used Cohen's Kappa, which provided a numerical summary between -1 and 1, where 0 indicates no agreement beyond what is expected by chance, 1 indicates perfect agreement, and -1 indicates perfect disagreement.

REVIEWER 3, POINT #12

A. Lines 243-245 - It may be worth digging into fellow performance a bit more. The fellows are doing well in the overall diagnosis but not as well for individual items. This suggests some redundancy in the items (thus correlations are useful). This could suggest a lack of familiarity. If the fellows systematically undercall or overcall specific findings that may point to areas of focus in education.

B. The primary outcome was to assess diagnostic performance of the checklist; the learning curve was a secondary outcome. With 2 out of 9 sonologists fellows, it would be difficult to interpret fellow responses with a robust conclusion although this question is certainly for further research. We have added this to the discussion.

C. Lines 322-5.

D. "An interesting finding was that responses from the MFM fellows did not significantly impact overall predictive performance, suggesting that this checklist may have an early learning curve if adopted as a part of MFM training. While the independent items within the checklist had more variability, the overall impression was similar to experienced clinicians. Components of the checklist may be helpful for training for familiarity and recognition, but the overall impression is the most relevant. Checklists have emerged for the management of complex conditions to standardize evidence- or consensus-based processes and promote high quality and consistent care. Accordingly, SMFM has created a checklist for surgical planning for anticipated and unexpected PAS[15]. Establishing a clinically validated checklist for the systematic evaluation of placenta and uterus is imperative for education, training, and research."

REVIEWER 3, POINT #13

A. Table 1 - I assume BMI is at time of exam?

B. BMI was calculated at the new prenatal visit. This was added to the text for clarity.

C. Lines 144-5

D. "Additionally, we matched clinical characteristics influencing image quality including body mass index (BMI) **at first prenatal visit**, multiple gestation, and gestational age at the time of the ultrasound."

REVIEWER 4, POINT #1

A. Thank you for the opportunity to review this manuscript; understanding the accuracy of diagnostic tools for PAS is highly important in allocation of hospital resources and preparing for potentially complex cases. PAS research is challenging to conduct in an optimal, prospective manner and I appreciate both the efforts taken by the authors to contribute in this arena and their acknowledgment of their limitations.

How many of the PAS cases were initially identified or suspected on ultrasound prior to delivery? I see the MFMU rate of 53% suspected prior to delivery, but I'm curious about the rate in this cohort?

B. We queried our database of histologic-confirmed PAS cases during 2016-2020 (the same timeframe as the inclusion criteria for the present manuscript), and there were 62 cases at the same institution. 39 of these cases were suspected; thus **62.9% cases were anticipated** and confirmed on histology.

REVIEWER 4, POINT #2

A. Did you assess provider familiarity with the EW-AIP checklist? Did all providers routinely use this checklist prior to the study or was it new for certain providers?

B. Prior familiarity with the checklist was not specifically required by the sonologists, although given the checklist items were published as part of an SMFM consult series, familiarity with the components within the checklist was expected.[5]

C. Lines 177-8.

D. The 9 sonologists were from 5 United States referral centers (7 MFM faculty and 2 MFM fellows), recruited by email after an annual professional conference, and **prior familiarity with the EW-AIP checklist was not required**

REVIEWER 4, POINT #3

A. You mention that not all subjects with anticipated PAS are managed with hysterectomy at your institution, something that may affect the severity of the disease in the cohort of cases with histologic confirmation. Could you add in the criteria used to determine conservative management vs. hysterectomy at your institution to better understand the disease spectrum that would be seen on histologic specimens?

B. See Reviewer #1, Point #1, above.

[5] Shainker SA, Coleman B, Timor-Tritsch IE, Bhide A, Bromley B, Cahill AG, et al. Special Report of the Society for Maternal-Fetal Medicine Placenta Accreta Spectrum Ultrasound Marker Task Force: Consensus on definition of markers and approach to the ultrasound examination in pregnancies at risk for placenta accreta spectrum. Am J Obstet Gynecol, 2021. 224(1):B2-B14.

Manuscript title: Validation of a sonographic checklist for the detection of histologic placenta accreta spectrum.

Condensation: A sonographic checklist for reporting suspected placenta accreta spectrum has a positive likelihood ratio of 9.6 to detect (and 0.3 negative likelihood ratio to exclude) histologic disease.

Short title: Sonographic checklist to predict placenta accreta spectrum

AJOG at a Glance:

A. Why was this study conducted?

An expert consensus checklist was developed in 2016 to standardize sonographic reporting of suspected placenta accreta spectrum and reduce the risk of unanticipated disease. However, the diagnostic performance of the checklist is not known.

B. What are the key findings?

The checklist has a positive and negative likelihood ratio of 9.6 and 0.3, respectively, and its sensitivity and specificity improves with more severe histologic disease.

C. What does this study add to what is already known?

This study provides diagnostic accuracy to support a standardized sonographic checklist for use in clinical interpretation, research, and training for placenta accreta spectrum.

Conflict of Interest: The authors report no conflicts of interest.

Keywords: Abnormal placentation, abnormally adherent placenta, antenatal diagnosis, checklist, delivery planning, morbidly adherent placenta, multidisciplinary team, placental imaging, sonographic imaging, ultrasound

Abstract

Background: To standardize research terminology and reduce unanticipated placenta accreta spectrum (PAS), the European Working Group for Abnormally Invasive Placenta (EW-AIP) developed a consensus checklist for reporting PAS suspected on antenatal ultrasound. The diagnostic accuracy of the EW-AIP checklist has not been assessed.

Objective: To test the performance of the EW-AIP sonographic checklist in predicting histologic PAS.

Study Design: This is a multi-site, blinded, retrospective review of transabdominal ultrasound studies performed between 26-32 weeks gestation for subjects with histologic PAS between 2016-2020. We ~~planned~~ matched a 1:1 control cohort of subjects without histologic PAS. To reduce reader bias, we matched the control cohort for known risk factors including previa, number of prior cesarean deliveries, prior dilation and curettage (D&C), in vitro fertilization (IVF), and clinical factors affecting image quality including multiple gestation, body mass index (BMI) and gestational age at the ultrasound. Nine sonologists from 5 referral centers, blinded to the histologic outcomes, interpreted the randomized ultrasound studies using the EW-AIP checklist. The primary outcome was the sensitivity and specificity of the checklist to predict PAS. Two separate sensitivity analyses were performed: 1) we excluded subjects with mild disease (i.e. only assessed subjects with histologic increta and percreta); 2) we excluded interpretations from the 2 most junior sonologists.

Results: 78 subjects were included (39 PAS, 39 matched control). Clinical risk factors and image quality markers were statistically similar between cohorts. The checklist sensitivity (95% Confidence Interval, CI) was 76.6% (63.4%-90.6%) and specificity (95% CI) was 92.0% (63.4%-99.9%), with a positive and negative likelihood ratio of 9.6 and 0.3, respectively. When

we excluded subjects with mild PAS disease, the sensitivity (95% CI) increased to 84.7% (73.6%-96.4%) and specificity was unchanged at 92.0% (83.2%-99.9%). Sensitivity and specificity were unchanged when the interpretations from the 2 most junior sonologists were excluded.

Conclusion: The 2016 EW-AIP checklist for interpreting PAS has a reasonable performance in detecting and excluding histologic placenta accreta spectrum.

Introduction

The incidence of placenta accreta spectrum (PAS) is rising, and it is now the leading indication for puerperal hysterectomy[1]. Management typically includes a scheduled, late preterm delivery by a multidisciplinary team[2]. Unanticipated PAS deliveries put pregnant patients at highest risk for blood transfusion, ICU admission, and death[3]. Thus, antenatal diagnosis is prerequisite for surgical planning to reduce maternal morbidity and mortality. Despite this necessity, a recent Maternal-Fetal Medicine Unit Network study found that PAS was suspected in only 53% of subjects prior to delivery[4].

The mainstay for antenatal PAS diagnosis is ultrasound. However, ultrasound is operator dependent, and limited by a prior lack of standardized definitions of PAS ultrasound markers. Additionally, a patient's *a priori* risk for PAS, based on historical characteristics, influences interpretation of ultrasound studies. Therefore, objective assessment of PAS imaging characteristics is challenging for prospective research[5].

Given the need to standardize PAS ultrasound markers, in 2016 the European Working Group on Abnormally Invasive Placenta (EW-AIP) produced a consensus checklist for ultrasound assessment of placentation[6]. The checklist was developed by an online questionnaire of 50 international experts, and a list of 11 sonographic markers was derived from expert opinion. Two years later, both the International Federation of Gynecology and Obstetrics (FIGO) and the Society for Maternal Fetal Medicine (SMFM) endorsed the sonographic characteristics within the checklist[7,8]. While the EW-AIP checklist is derived from and endorsed by several professional societies, the clinical performance of the checklist itself has not been assessed.

Our objective was to assess the diagnostic accuracy of the Maternal-Fetal Medicine (MFM) sonologist's overall impression of PAS using the EW-AIP checklist, and to further evaluate the interrater reliability and diagnostic performance for each of the characteristics.

Materials and Methods

We conducted a multi-site, blinded, retrospective review of 26-32 week (inclusive) ultrasound studies ~~fo~~including~~r~~ subjects prospectively enrolled at ~~from~~ a single United States referral center with suspected PAS and confirmed on hysterectomy specimen between 2016 (when the EW-AIP checklist was published and adopted at our institution) and 2020. We retrospectively identified a 1:1 control cohort of subjects without PAS clinically or on the final pathology report~~, imaged antenatally at the same diagnostic center and undergoing cesarean delivery at the same hospital as the PAS subjects~~ (incidental diagnoses on placental specimens were not included).~~.~~ In an effort to control for expected bias influenced by clinical risk factors for PAS, we best-matched the control cohort using a greedy-matching algorithm for pre-defined clinical characteristics listed in the ACOG Obstetric Care Consensus[3], including placenta previa, number of prior cesarean deliveries, prior dilation and curettage (D&C), and in vitro fertilization (IVF). Additionally, we matched clinical characteristics influencing image quality including body mass index (BMI) at first prenatal visit, multiple gestation, and gestational age at the time of the ultrasound. Thus, the control cohort was created by including subjects with imaging conducted at the same diagnostic center and cesarean delivery conducted at the same labor and delivery during the same timeframe, then excluded those with PAS on final pathology or on review of operative note. The last step was matching the pre-defined clinical characteristics as the disease cohort.

Ultrasounds studies from 26-32 weeks gestation were chosen for review, as this timing was the institutional standard for follow up for suspected abnormal placentation diagnosed during routine anatomy scan. Regardless of the disease severity, subjects with anticipated PAS were cared for by a multidisciplinary care team and, with intraoperative confirmation and the

patient's consent, adherent placenta was managed with cesarean hysterectomy. Of note, while not all subjects with ~~anticipated~~ PAS may have been~~were~~ managed with hysterectomy at our institution, a hysterectomy was required as part of the present study design as histology was the primary outcome to test the sonographic checklist.

After the PAS and control cohorts were created, the lead author (who did not participate in interpreting the ultrasound studies) selected transabdominal ~~ultrasound images and cine clips of the~~images of the placenta, cervix, and placental cord insertion obtained during a detailed second trimester ultrasound (CPT 76811) or follow up ultrasound (CPT 76816). Selected images included both still and cine clips, and greyscale and color Doppler images – no dedicated image of the placenta, cervix, or cord insertion was excluded, as the EW-AIP checklist did not have a prescribed number of images. ~~.~~The ultrasound images ~~s~~were de-identified, randomized, and then interpreted by 9 Maternal-Fetal Medicine (MFM) sonologists blinded to final histology. The blinded sonologists were aware that the ultrasound series included matched controls, but were not aware of the specific ratio for matching. The 9 sonologists were from 5 United States referral centers (7 MFM faculty and 2 MFM fellows), recruited by email after an annual professional conference, and prior familiarity with the EW-AIP checklist was not required.[9] For each ultrasound, the sonologists were provided the gestational age and the matched clinical characteristics from the Obstetric Care Consensus[3], such as number of prior cesarean deliveries or prior D&Cs. To simulate a workflow at an antenatal diagnostic center, 5 minutes were suggested to review each ultrasound and the sonologists were permitted to move between images and cine clips as necessary. Consistent with the EW-AIP checklist, the nine sonologists could choose "present", "absent", or "unsure" for each sonographic sign, and then prompted to predict whether there was a low or high probability of PAS on pathology. To preserve integrity of

statistical analysis, each sonologist was required to review 100% of the ultrasounds studies, or their responses were discarded.

Baseline demographics of the PAS and control cohorts were assessed using Chi-Square or ANOVA F-Test, depending on whether the demographic was binary or continuous, respectively. For the primary outcome, to measure the strength of agreement between sonologists' interpretation and histologic diagnosis, a dichotomous sensitivity and specificity table was created using the sonologists' aggregate overall impression. Two separate sensitivity analyses were performed: 1) we excluded subjects with mild disease (i.e. excluding subjects with histologic accreta and only including subjects with histologic increta and percreta on hysterectomy specimen); 2) we excluded interpretations from the 2 MFM fellows who were most junior in experience with ultrasound interpretation. We performed these analyses to assess how disease severity and sonologist experience affected the performance of the checklist.

For secondary outcomes, we analyzed the interrater reliability of the sonologists' responses, using Kappa statistics to compute an interrater correlation coefficient (ICC) to assess the agreement for each characteristic between the 9 sonologists. Additionally, to compute the aggregate sonologists' responses for individual characteristics to the true histologic diagnosis of PAS, we used Cohen's Kappa, which provided a numerical summary between -1 and 1, where 0 indicates no agreement beyond what is expected by chance, 1 indicates perfect agreement, and -1 indicates perfect disagreement.

The images were anonymized and exported from the clinical picture archiving and communications system (Viewpoint 6.11, General Electric) onto an encrypted, cloud-based content management platform (Box Service, 2022). The checklist for each subject was completed on REDCap 12.0.2. Statistical software used was SAS 9.4 (SAS Institute, Cary, NC). The study

was approved by the institutional review board at each of the five participating institutions and a data transfer agreement was executed to facilitate transfer of the de-identified images. The de-identified images and code used for analysis are available upon request for either research or education purposes.

Results

Subject recruitment is demonstrated in Figure 1. In total, there were 39 subjects with PAS that met inclusion criteria including: a) performance of an ultrasound between 26-32 weeks gestation, b) hysterectomy performed between 2016-2020 with histology confirming PAS. After pooling the PAS cohort's pre-defined risk factors, the 1:1 control cohort was identified by querying 3,348 subjects who had a cesarean delivery at the same center during the same time period, but without PAS suspected clinically or on final pathology. Baseline demographics between the PAS and control cohorts were statistically similar, including presence of placenta previa on ultrasound (64.1% vs 59.0%, p=0.64), median (25^{th}, 75^{th} percentile) number of prior cesarean deliveries (2 [1, 3], for both cohorts, p>0.99), prior D&Cs (23.1% vs 25.6%, p=0.79) and IVF conception (2.6% for both cohorts, p>0.99). Furthermore, factors influencing image quality were statistically similar including BMI, multiple gestation, and gestational age of ultrasound (Table 1). Of note, although study sonologists were unaware of this fact, there were more images for PAS subjects than control subjects (median 23.0 [13.0, 33.0] versus 16.0 [9.0, 20.0], respectively, p=0.002).

Each of the 9 sonologists completed the checklist for all subjects. The median (25^{th}, 75^{th} percentile) years of MFM experience was 5.0 (2.8, 8.0), with a range of 1-22. Seven sonologists were practicing MFM faculty (6 board-certified, 1 board-eligible), and 2 were active MFM fellows.

Primary outcomes are listed in Table 2. The sensitivity (95% Confidence Interval, CI) of the EW-AIP checklist detecting histologic PAS was 76.6% (63.4%-90.6%) and specificity (95%

CI) was 92.0% (63.4%-99.9%), yielding a positive likelihood ratio to detect PAS of 9.6, and a negative likelihood ratio to exclude PAS of 0.3. When excluding mild cases (~~,~~ or histologic accreta (n=10), and assessing only histologic increta and percreta)~~,~~ the sensitivity (95% CI) increased to 84.7% (73.6%-96.4%) and specificity remained the same with a narrowed CI, 92.0% (83.2%-99.9%). When excluding the responses of the two MFM fellows, the sensitivity and specificity were negligibly affected, 78.0% (64.8%-91.2%) and 93.0% (85.0%-99.9%), respectively.

For secondary outcomes, the interrater classification coefficient (which reflects the degree of correlation and agreement between measurements among 9 sonologists) is shown in Table 3. The two characteristics with the most agreement between sonologists was abnormal placental lacunae (0.4) and uterovesical hypervascularity (0.41), indicating good reliability between reviewers. Bladder wall interruption (0.19) and focal exophytic mass (0.05) were noted least consistently, indicating poor reliability. In the sensitivity analysis, sonologist agreement for each of the 11 characteristics increased with more severe histologic disease. Additionally, when excluding the responses of the most junior sonologists, there was an increase in agreement for each of the 11 characteristics, even if this did not change their overall diagnostic impression.

Table 4 lists the performance of individual characteristic against histologic PAS, or in other words, the predictive value of histologic PAS if the individual characteristic was identified. Each of the characteristics had a positive association with histological PAS, with the highest agreement being myometrial thinning (0.56), loss of clear zone (0.55), and ~~bladder wall interruption (0.34).~~ placental bulge (0.48). The least correlated with severe disease was the parametrial involvement, with a kappa of 0.05. Similarly, the agreement between sonographic

characteristic and true PAS diagnosis improved with more severe disease, as well as excluding the responses from the two junior sonologists.

Discussion

Principal Findings

Using a consensus expert opinion initially proposed in 2016 by EW-AIP and endorsed in 2018 by FIGO and SMFM, we assessed the clinical performance of an ultrasound checklist for the histologic diagnosis of PAS. The sensitivity (95% CI) was 76.6% (63.4%-90.6%) and specificity (95% CI) was 92.0% (63.4%-99.9%) in predicting PAS, yielding a positive likelihood ratio to detect PAS of 9.6, and a negative likelihood ratio to exclude PAS of 0.3. The performance of the checklist to predict histologic PAS improved with more severe disease (increta and percreta) and maintained a strong performance when employed by less experienced sonologists (MFM fellows).

Results in the context of what is known

As our understanding of the pathophysiology of PAS evolves from a model centering on *placental-invasion* to a model of *uterine-dehiscence*[10], reporting radiologic, clinical, or pathologic PAS has moved away from categorical "accreta", "increta" and "percreta" terminology to a more descriptive approach. For example, in 2018 FIGO sought to standardize intraoperative findings with a clinical criteria that describes pelvic involvement of placentation[11] rather than using categorical terms. Additionally, a consensus panel of clinical pathologists have replaced the categorical terminology to a 10 characteristic, descriptive grading system[12]. Similarly, driven by the need to standardize sonographic PAS markers, multiple professional societies have called for a systematic approach to the evaluation of the uterus and

placenta. EW-AIP put forth a proposed checklist in 2016, reviewing 23 manuscripts and drafting a list of 11 PAS ultrasound markers (6 markers are greyscale, 4 are 2D color Doppler, and 1 is 3D power Doppler)[6]. The present study now provides clinical performance outcomes for the expert-consensus checklist put forward by EW-AIP.

Research implications

Studies assessing predictive value of ultrasound markers for PAS are limited by small sample sizes, retrospective designs without a control cohort, and heterogenous definitions of PAS. For example, the sensitivity and specificity of hypervascular uterovesical interface ranges widely from 11-100% and 36-100% respectively[13,14]. Given the broad range of predictive values for each characteristic within the checklist, the EW-AIP consensus stresses that all markers should be systematically assessed and unambiguously reported until further research clarifies their individual utility. Therefore, the primary outcome of this study was to report the performance of the "bundle" of sonographic markers in a checklist format that may be readily adopted by antenatal diagnostic centers.

An interesting finding was that responses from the MFM fellows did not significantly impact overall predictive performance, suggesting that this checklist may have an early learning curve if adopted as a part of MFM training. While the independent items within the checklist had more variability, the overall impression was similar to experienced clinicians. Components of the checklist may be helpful for training in familiarity and recognition, but the overall impression is the most clinically relevant. Checklists have emerged for the management of complex conditions to standardize evidence- or consensus-based processes and promote high quality and consistent care. Accordingly, SMFM has created a checklist for surgical planning for

anticipated and unexpected PAS[15]. Establishing a clinically validated checklist for the systematic evaluation of placenta and uterus is imperative for education, training, and research.

Strengths and limitations

There are two key, related limitations to this study. Although the study involved blinded interpretations by sonologists from multiple institutions, it is retrospective in design. Therefore, images were not systematically procured in a checklist manner to capture or exclude components of the checklist itself. We suspect that this limitation is pertinent to the secondary outcomes, assessing the individual characteristics of the checklist. We therefore recommend caution in interpreting Table 4 as these may underreport the performance against the true PAS diagnosis. Second, there were more images within the PAS cohort than the control cohort, likely reflecting the sonographers internal assessment as they were obtaining images for interpretation or requested additional focus. While the sonologists in this study were blinded to the clinical outcome, a potential bias is introduced. The lead author intentionally did not control this known discrepancy in advance to avoid introducing a selection bias by "cherry picking" included images for blinded review (aside from removing non-placental images).

There are four strengths to the study. First, the use of a control cohort matched comprehensively for PAS risk factors is an effort to neutralize the impact of knowing the patient's clinical history before reading the images. Mimicking real world ultrasound reading, sonologists had the basic clinical information prior to reading the scan, such as number of prior cesarean or IVF conception, and the clinical characteristics were comparable between the PAS and control cohorts. Second, both the PAS and control cohort were selected from the same referral center, therefore standardizing variables such as sonographer education, image procurement, and ultrasound machines used. Additionally, to reduce the risk of recall bias,

images were blinded and reviewed by sonologists from four external institutions that did not participate in the subjects' clinical care and therefore had never seen the images previously. Lastly, the planned sensitivity analysis assessed the impact of disease severity as well as sonologist training in order to assess potential uptake of the checklist as a part of clinical care or education.

Conclusion

Our multi-site study has assessed the diagnostic accuracy of an ultrasound checklist for the detection of placenta accreta spectrum, with a high likelihood ratio. The routine incorporation of this checklist may contribute to decreased unanticipated PAS cases and timely referral to PAS centers, as well as standardize research terminology.

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Table 1: Baseline demographics between PAS and 1:1 matched control cohort

	PAS on hysterectomy specimen (n=39)	Control cohort without PAS (n=39)	*p* value
Placenta previa	25 (64.1%)	23 (59.0%)	0.64[1]
Number of prior cesarean	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	>0.99[2]
IVF	1 (2.6%)	1 (2.6%)	>0.99[1]
Prior D&C	9 (23.1%)	10 (25.6%)	0.79[1]
BMI (kg/m^2)	29.3 (24.5, 36.1)	28.5 (22.6, 37.6)	0.82[2]
Multiple gestation	1 (2.6%)	1 (2.6%)	>0.99[1]
US gestational age (weeks)	28.0 (26.0, 29.0)	29.0 (26.0, 29.0)	0.93[2]
Number of images per US	23.0 (13.0, 33.0)	13.0 (9.0, 20.0)	0.002[2]
Indication for US in control cohort			
Placental reassessment		30 (76.9%)	
Fetal Indication		6 (15.4%)	
Anatomy		3 (7.7%)	
Final pathology			<0.001[1]
No PAS	0 (0.0%)	39.0 (100.0%)	
Accreta	10 (26.3%)	0 (0.0%)	
Increta or percreta	29 (76.3%)	0 (0.0%)	

Binary variables are represented number (%)
Continuous variables are median (25th percentile, 75th percentile)
IVF: *in vitro* fertilization; US: ultrasound; BMI: body mass index; PAS: placenta accreta spectrum
[1]Chi-square; [2]ANOVA F-Test

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Table 2: Primary outcome – performance of EW-AIP checklist on detection of PAS

	All cases (n=78)	**Excluding histologic accreta (n=68)**	**Excluding 2 MFM fellows (n=78)**
Sensitivity	76.7% (63.4%-90.6%)	84.7% (73.6%-96.4%	78.0% (64.8%-91.2%)
Specificity	92.0% (63.4%-99.9%)	92.0% (83.2%-99.9%)	93.0% (85.0%-99.9%)
Positive Likelihood Ratio	9.6	10.6	11.8
Negative Likelihood Ratio	0.3	0.2	0.2
Sensitivity and specific above measured with 95% confidence interval			

Table 3: Secondary outcome – interobserver variability of individual characteristics

	All cases (n=78)	**Excluding histologic accreta (n=68)**	**Excluding 2 MFM fellows (n=78)**
Loss of clear zone	0.25	0.49	0.50
Myometrial thinning	0.29	0.53	0.58
Abnormal placental lacunae	0.40	0.54	0.57
Bladder wall interruption	0.19	0.34	0.35
Placental bulge	0.22	0.48	0.50
Focal exophytic mass	0.05*	0.12*	0.10
Uterovesical hypervascularity	0.41	0.62	0.61
Subplacental hypervascularity	0.33	0.62	0.48
Bridging vessels	0.23	0.44	0.44
Placental lacunae feeder vessels	0.30	0.43	0.40
Parametrial involvement	0.23	0.02*	0.03*

*Mixed-effects model did not converge.

Inter-characteristic correlation (ICC) with no restrictions is 0.71 which indicates a reasonable sonologist-to-sonologist reliability. Estimates closer to this number indicate more reliable performance measures.

Table 4: Secondary outcome – performance of individual characteristics

	All cases (n=78)	**Excluding histologic accreta (n=68)**	**Excluding 2 MFM fellows (n=78)**
Loss of clear zone	0.55	0.63	0.59
Myometrial thinning	0.56	0.64	0.61
Abnormal placental lacunae	0.44	0.52	0.45
Bladder wall interruption	0.34	0.45	0.36
Placental bulge	0.48	0.59	0.54
Focal exophytic mass	0.11	0.17	0.13
Uterovesical hypervascularity	0.44	0.49	0.45
Subplacental hypervascularity	0.33	0.38	0.34
Bridging vessels	0.35	0.41	0.35
Placental lacunae feeder vessels	0.23	0.32	0.30
Parametrial involvement	0.049	0.045	0.12

To check agreement between sonologists' individual (binary) responses (e.g., loss of clear zone) and the true case/control status we used Cohen's kappa. This provided us with a numerical summary between -1 and 1 for each sonologist, where 0 indicates no agreement beyond what is expected by chance, 1 indicates perfect agreement, and -1 indicates perfect disagreement.