Effectiveness of Contingent screening for Placenta Accreta Spectrum disorders based on persistent low-lying placenta and previous uterine surgery

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Contribution:

What are the novel findings of this work?

Routine contingent screening for placenta accreta spectrum disorders based on the finding of placenta previa and previous uterine surgery is effective in a public healthcare setting.

What are the clinical implications of this work?

A contingent screening strategy for placenta accreta spectrum disorders is feasible in an ultrasound service where placenta localization is routinely performed. When linked to a placenta accreta diagnostic and surgical management service, adoption of such a screening strategy has the potential to significantly reduce the maternal morbidity and mortality associated with this condition.

ABSTRACT

Objectives: Maternal mortality related to the placenta accreta spectrum (PAS) disorders remain substantial when an unexpected diagnosis is made at delivery. The aim of this study was to evaluate the effectiveness of a routine contingent ultrasound screening program for PAS.

Methods: A retrospective study conducted between 2009 and 2019 involving two groups: a screening cohort of unselected women attending for routine mid-trimester ultrasound assessment and a diagnostic cohort comprised of referrals to the PAS diagnostic service with a suspected diagnosis of PAS in women with placenta previa and previous uterine surgery. Ultrasound assessment by the PAS diagnostic service was comprised of two-dimensional greyscale and color Doppler ultrasonography, and women with a diagnosis of PAS were usually managed with conservative myometrial resection. The final diagnosis of PAS was based on a combination of intraoperative clinical findings and histopathological examination of the surgical specimen.

Results: 57,179 women underwent routine mid-trimester fetal anatomy assessment with a third trimester diagnosis of placenta previa in 220 (0.38%). Seventy-five of these women were referred to the PAS diagnostic service because of a history of previous uterine surgery, where 21 of 22 cases of PAS were correctly diagnosed (sensitivity of 95.45%, 95%CI: 77.16-99.88% and specificity of 100%, 95%CI: 99.07-100%). Univariate analysis demonstrated that two or more previous Cesarean sections (OR 94.20, 95%CI 22.00-656.00) and placenta previa (OR 20.50, 95%CI 4.22-369.00) were the strongest risk factors for PAS. In the diagnostic cohort, there were 173 referrals with one false positive and three false negative diagnoses – resulting in a sensitivity 96.63% (95%CI: 90.46-99.30%) and specificity 98.81% (95%CI: 93.54-99.97%).

Conclusion: A contingent screening strategy for PAS is both feasible and effective in a routine healthcare setting. When linked to a placenta accreta diagnostic and surgical management service, adoption of such a screening strategy has the potential to reduce the maternal morbidity and mortality associated with this condition. Larger prospective studies are necessary before implementing this screening strategy into routine clinical practice.

INTRODUCTION

Placental accreta spectrum (PAS) disorders are a recognized cause of major maternal morbidity and mortality, with a reported prevalence of between 0.01% to 1.1% of pregnancies [1]. The incidence of PAS is increasing worldwide - attributed to the rising rate of cesarean section (CS) [2–5]. Previous Cesarean birth is associated with an almost three-fold increase in risk of PAS in the next pregnancy compared to those with a previous vaginal delivery [6]. The main risk factor for PAS in the current pregnancy is a diagnosis of placenta previa, with more than 90% of PAS cases being associated the diagnosis of placenta previa combined with a previous history of uterine surgery [7–9]. PAS is associated with a significant increase in maternal morbidity and mortality from massive peripartum hemorrhage [10,11]. However, hemorrhagic morbidity can be significantly reduced when a diagnosis of PAS is made prior to admission at the time of delivery [12]. Systematic screening and diagnosis of PAS would permit referral of these high-risk women to tertiary hospitals with specialized multidisciplinary teams experienced in the management of pregnancies complicated by PAS [13,14].

Antenatal ultrasound diagnosis of PAS is possible with close to 90% accuracy in specialist referral centers with expertise in the diagnosis of PAS [15,16]. However, the diagnostic accuracy for PAS in non-specialist referring hospitals is only 50% as clinical suspicion for PAS and/or knowledge of risk factors is low [17,18]. There is a clinical need for an effective and systematic screening program for PAS in referring hospitals, so that cases suspected with PAS can be referred to a PAS diagnostic center, and if confirmed, for subsequent specialist surgical management to prevent the maternal morbidity associated with undiagnosed PAS. The aim of this study is to evaluate the effectiveness of a contingent

screening program for identification of pregnancies with PAS based on persistent low-lying placenta in the third trimester in women with a history of previous uterine surgery or Cesarean section.

METHODS

This is a retrospective cohort study conducted between 2009 and 2019 in the Fetal Medicine Unit of St George's University Hospitals NHS Foundation Trust, London, UK. Two cohorts of patients were included in this study: a 'screening cohort' of unselected women attending for routine mid-trimester ultrasound assessment and a second 'diagnostic cohort' comprised of local and external referrals to the diagnostic service because of a suspicion of PAS. In the 'screening cohort', women diagnosed to have a low-lying placenta (leading edge less than 2cm from the internal cervical os) at the mid-trimester fetal anomaly assessment were scheduled for a 32-34 week placental localization scan [19]. At the 32-34 week assessment, placenta previa was confirmed if the placental leading edge was within 2 cm of the internal os [19,20]. Patients with confirmed placenta previa with a history of previous uterine surgery or Caesarean section were referred to the PAS diagnostic service. Women with a low-lying placenta at the mid-trimester ultrasound who transferred care for management in another center before placental localization at 32-34 weeks were excluded from the analysis.

All women undergoing routine ultrasound screening in pregnancy were assessed by qualified sonographers and any cases with fetal or maternal complications were managed by maternal-fetal medicine specialists. In particular, the PAS diagnostic service was run by two consultants (BT, AB) with significant experience and expertise in the prenatal diagnosis of PAS. Ultrasound assessment by the PAS diagnostic service was comprised of two-dimensional (2D) grey-scale ultrasound and color Doppler ultrasonography as previously described [21,22]. The following markers were assessed: 1) the presence of multiple irregular lacunar spaces within the placenta with turbulent

blood flow on Doppler ultrasonography (peak systolic velocity often >10 cm/s); 2) Loss of the 'clear zone', the normal hypoechoic line between the placenta and myometrium; 3) Myometrial thinning of the retroplacental area; 4) Lower uterine segment placental thickness; 5) Bladder wall interruption defined as the loss or irregularity of the hyperechoic line between uterine serosa and bladder. Color Doppler was only used at discretion of the examiner and mainly to differentiate lacunae from placental lakes [21–23]. The presence of two or more of ultrasound signs was considered diagnostic of PAS, one isolated sign was labelled as equivocal and the absence of any ultrasound signs was considered negative for a PAS diagnosis. Magnetic resonance imaging (MRI) was only performed in cases where ultrasound signs of extra-uterine invasion of the placenta (focal exophytic mass, distortion of cervix or parametrial anatomy) was suspected. Women with a diagnosis of PAS were referred to the PAS surgical team for further management – usually with a conservative surgical technique (Triple P procedure) which is recommended by the International Federation of Gynecology and Obstetrics (FIGO) as an alternative to peripartum hysterectomy [14,24,25].

Eligible pregnancies were identified by searching the electronic database (ViewPoint version 5.6.26.148, ViewPoint Bildverarbeitung GMBH, Wessling, Germany), review of the surgical notes and histological records. Demographic, surgical and histological data and obstetrical history were retrieved from the clinical records. The final diagnosis of PAS was based on intraoperative clinical findings and histopathological examination of the surgical specimen [26]. A histological diagnosis of placenta accreta, increta and percreta were only possible when hysterectomy or partial myometrial resection specimens were accessible for examination. If a histological specimen was not available, the final PAS diagnosis was based on the surgical record of adherent placenta. Ethics approval and signed patient consent was not required as per the UK

Health Regional Authority (HRA) decision tool. The findings of this study were reported in agreement with the STROBE Statement [27].

Statistical analysis

Comparisons between continuous and categorical variables were performed using Kruskall-Wallis test for the former and χ^2-square or Fisher's exact test for the latter. Univariate binomial logistic regression analysis was carried out to determine which risk factors were associated with PAS in women with placenta previa in the screening cohort. Due to the limited number of PAS cases, forward stepwise multivariable logistic regression analysis was performed to determine which factors identified in univariate analysis contributed to the prediction of PAS in women with placenta previa and previous Cesarean section. All data analyses were carried out using the statistical software package *R* version 4.0.1 (2020-06-06) and MedCalc for Windows, version 19.4.1 (MedCalc Software, Ostend, Belgium). Statistical significance was defined as a p value <0.05.

RESULTS

Screening Cohort

A total of 57,179 women underwent routine mid-trimester fetal anatomy assessment at 18 to 23 weeks' gestation between 2009 and 2019. Among the 4486 (7.8%) women with a repeat scan scheduled for a low-lying placenta, a total of 415 (9.2%) had a diagnosis of low-lying placenta at 32-34 weeks' gestation (Figure 1). A total of 220 women had a final diagnosis of placenta previa at subsequent scan assessments, and 75 (34.1%) of these women were referred to the PAS diagnostic service because of a history of previous uterine surgery. This final cohort contained 22 cases of PAS, of whom 21 cases were correctly identified by the PAS diagnostic service and managed surgically (Supplementary Table). Additionally, there were five women who were followed up serially from the first trimester for a diagnosis of scar implantation who underwent emergency delivery before 32 weeks' gestation and a further case of focal PAS in the non-placenta previa cohort in a woman with a previous myomectomy. The overall performance of a contingent PAS screening program where women with a diagnosis of placenta previa and previous uterine surgery are referred to a specialist PAS diagnostic service was: sensitivity 95.45% (95%CI: 77.16-99.88%), specificity of 100% (95%CI: 99.07-100%) with a 99.75% (95%CI: 98.30-99.96%) negative predictive value and 100% (95%CI: not calculable) positive predictive value.

The demographic characteristics and risk factors for women with a low-lying placenta in the third trimester who had confirmed PAS or no evidence of abnormal placental invasion are shown in Table 1. Univariate analysis demonstrated that multiparity $\geq$2 (OR 35.50, 95%CI 6.90-649.00), two or more previous Cesarean sections (OR 94.20, 95%CI 22.00-656.00) and placenta previa (OR 20.50, 95%CI 4.22-369.00) were the strongest risk factors for PAS.

Smoking (OR 1.12, 95%CI 0.06-5.92), body mass index >24kg/m^2 (OR 1.04, 95%CI 0.95-1.11) and other previous uterine surgeries (OR 3.49, 95%CI 0.77-11.60) were not associated with PAS in this cohort. Paired stepwise multivariate logistic regression demonstrated that the strongest risk factors beyond the number of previous Cesarean section were variables related to placental localization and ethnicity (Table 2). Maternal age, Asian ethnicity and multiparity were no longer associated with an increased risk of PAS after controlling for the number of previous Cesarean section.

Diagnostic Cohort

There were 173 (local 99 and referred 74) suspected cases of PAS referred to the diagnostic service between 2009 and 2019 (Figure 2). There was one false positive and three false negative diagnoses of PAS in this cohort. The overall performance of the PAS diagnostic service was: sensitivity 96.63% (95%CI: 90.46-99.30%), specificity 98.81% (95%CI: 93.54-99.97%), positive likelihood ratio 81.17 (95%CI: 11.56-569.76) and negative likelihood ratio 0.03 (95%CI: 0.01-0.10).

DISCUSSION

Routine contingent screening for PAS based on the finding of placenta previa in the third trimester and a history of previous Cesarean section is both feasible and effective. The ability of such a screening program to result in improved clinical outcomes is contingent on access to a multidisciplinary PAS diagnostic and surgical service.

Comparison with other studies

The prevalence of placenta previa (0.4%) and PAS (0.04%) in our screening cohort are consistent with what has been previously described in a meta-analysis of population-based studies of 0.56% for placenta previa and 0.07% for PAS – consistent with the assertion that the study was performed on a routine pregnancy population [28]. The finding that number of previous Cesarean sections and diagnosis of placenta previa were the most important risk factors for PAS are consistent with the reports from previous systematic reviews of PAS [1,6,7]. Even one previous Cesarean section increased the odds for PAS by over 25-fold in a cohort of women with placenta previa and the majority of PAS cases in our cohort had only one previous Caesarean section. Other uterine surgeries were not associated with PAS in this cohort, in contrast to the findings in some previous studies [29,30]. It is difficult to conclude whether the lack of an association between other uterine surgery and PAS is a consequence of the small number of cases or a true finding in this study [30,31].

Afro-Caribbean ethnicity remained associated with PAS even after statistical correction for previous Cesarean section. This finding has not been previously reported and might be explained either by socio-economic determinants of health in black and minority ethnic populations, or more likely, from residual confounding from the relatively low number of patients with PAS in the

screening cohort and the increased likelihood for Cesarean birth in Afro-Caribbean women.

Despite general consensus amongst international guidelines that women with previous uterine surgery and low-lying placenta are at increased risk of PAS, there has been no previous systematic evaluation of the effectiveness of such a contingent screening program [9,21]. A first trimester screening strategy for PAS based on the identification of low-lying placenta in women with previous uterine surgery between 11 and 13 weeks has been described [32]. Although the benefits of such early screening would be to provide women with an option to have a first trimester abortion, the drawbacks are number of additional follow-up visits and low specificity resulting in high volume referrals to a PAS diagnostic service. The contingent screening described in the current study does not require additional routine scan visits and still resulted in high PAS detection. The SGH PAS diagnostic service correctly identified 86 out of 89 cases of PAS using ultrasound alone resulting in sensitivity and specificity of greater than 95%, which are superior to retrospective studies (sensitivity 88%, 95%CI 81.0-93.0; specificity 90%, 95%CI 88.0-93.0) and comparable to prospective diagnostic studies (sensitivity 97%, 95%CI 93.0-99.0; specificity 97%, 95%CI 97.0-98.0) [9].

Clinical Implications

Effective prenatal screening that correctly identifies pregnancies complicated by PAS would significantly improve maternal outcomes due to scheduled birth in a center with tertiary level facilities specialized in PAS care [12]. The need for such screening is compounded by the continuing global trend for an increase in both Cesarean section rates and PAS disorders [33]. We have shown that contingent screening for PAS in women with previous Cesarean section and a current diagnosis of placenta previa is both feasible and effective. This screening and

triage strategy is possible in lower-resource medical settings with basic obstetric ultrasound facilities and does not require additional visits beyond those that are indicated routinely. The success of such a screening program depends on access to both a specialized PAS diagnostic service with experienced operators and a management service at a tertiary level hospital where, if the diagnosis of PAS is confirmed, safe delivery can be arranged [34].

Strengths and Limitations

The major strengths of the present study are related to the relevant sample size in both the screening and diagnostic cohorts. Additionally, significant expertise has been combined with a robust surgical service with distinctive skills in the conservative management of PAS to allow linkage of antenatal ultrasound findings with surgical and histological records. The Triple P procedure used includes myometrial excision alongside preservation of the uterus and allows a full histological diagnosis in the majority of cases [26].

An obvious limitation is the retrospective nature of the study and there is a need to validate these findings in prospective studies set in populations with variable Cesarean section rates in order to ensure validity in a wide range of settings. The absolute number of cases affected by PAS in the screening cohort was small, and as a consequence, it was not possible to undertake a detailed analysis of risk factors in the prediction of PAS. Finally, our screening protocol failed to detect focal PAS following myomectomy because PAS was evident despite the placenta being clear of the lower uterine segment.

Conclusions

A screening program for PAS based on the identification of women with persistent placenta previa in the third trimester and a history of previous Cesarean section was both feasible and highly effective. This contingent

strategy has the potential to improve antenatal PAS detection rates and decrease maternal morbidity and mortality related to undiagnosed PAS.

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FIGURE LEGENDS

Figure 1. Patient flowchart of the routinely screened cohort, where women with a diagnosis of placenta previa and a history of previous uterine surgery were referred to the placenta accreta spectrum diagnostic service for further management.

Figure 2. Patient flowchart of the referred cohort showing the diagnostic accuracy of the placenta accreta spectrum service.

Supplementary Table 1. Description of the findings in women with placenta accreta spectrum (PAS) assessed in the screening study

Table 1. Comparison of risk factors and univariate analysis for confirmed versus unconfirmed diagnosis of placenta accreta spectrum (PAS) disorders in women with a diagnosis of low-lying placenta in the third trimester of pregnancy. Data shown as median (IQR), number (%), odds ratio (OR) and 95% confidence interval (95% CI). *Reference: 35 years, #Reference: 24Kg/m^2.

Variable	No PAS (n=393)	PAS (n=22)	OR (95%CI)	*p* value
Maternal age* (years)	35.0 (32.0-38.0)	39.0 (35.0-40.7)	1.11 (1.02-1.21)	**0.018**
Ethnicity				
Caucasian	243 (61.8)	3 (13.6)	Reference	
Asian	94 (23.9)	6 (27.3)	5.17 (1.34-24.90)	**0.022**
Afro-Caribbean	46 (11.7)	11 (50.0)	19.40 (5.79-88.10)	**<0.001**
Smoking	16 (4.1)	1 (4.5)	1.12 (0.06-5.92)	0.913
Assisted conception	62 (15.8)	0 (0.0)	-	-
Body mass index# (Kg/m^2)	24.2 (21.9-27.6)	25.9 (22.9-28.3)	1.04 (0.95-1.11)	0.368
Parity				
0	180 (45.8)	1 (4.6)	Reference	
1	142 (36.1)	7 (31.8)	8.87 (1.55-167.00)	**0.042**
2 or more	71 (18.1)	14 (63.6)	35.50 (6.90-649.00)	**<0.001**
Previous Cesarean section				
0	314 (79.9)	2 (9.1)	Reference	
1	64 (16.3)	11 (50.0)	27.00 (7.03-177.00)	**<0.001**
2 or more	15 (3.8)	9 (40.9)	94.20 (22.00-656.00)	**<0.001**
Previous pre-labor Cesarean section	35 (9.1)	8 (47.1)	8.89 (3.16-24.70)	**<0.001**
Previous intrapartum Cesarean section	36 (9.4)	7 (41.2)	6.79 (2.34-18.80)	**<0.001**
Previous other uterine surgery	17 (4.3)	3 (13.6)	3.49 (0.77-11.60)	**0.061**

Fibroids	21 (5.3)	3 (13.6)	2.80 (0.62-9.07)	0.119
Placenta covering internal cervical os	128 (32.6)	20 (90.9)	20.70 (5.92-231.00)	**<0.001**
Placenta within 2cm of internal cervical os	199 (50.6)	21 (95.5)	20.50 (4.22-369.00)	**0.030**
Anterior placenta at last scan	91 (23.2)	18 (81.8)	14.90 (5.41-52.70)	**<0.001**

Table 2. Paired stepwise multivariable logistic regression analysis of risk factors for placenta accreta spectrum disorders in women with a diagnosis of low-lying placenta in the third trimester of pregnancy. Data shown as odds ratio (OR) and 95% confidence interval (95% CI) for risk factors in addition to previous Cesarean section.

Variable	**OR (95%CI)**	***p* value**
Number of previous Cesarean section		
One previous	23.88 (6.16-157.49)	**<0.001**
Two or more previous	90.33 (20.93-631.93)	**<0.001**
Previous Cesarean sections and…		
Maternal age (years)	1.08 (0.98-1.20)	0.11
Asian	4.16 (0.98-21.39)	0.06
Afro-Caribbean	17.37 (4.54-87.93)	**<0.001**
Para 1	0.70 (0.02-19.31)	0.809
Para 2 or more	2.56 (0.10-66.77)	0.513
Placenta covering the internal cervical os	20.32 (5.19-139.06)	**<0.001**
Placenta within 2cm of the internal cervical os	17.59 (3.35-236.74)	**0.007**
Anterior placenta	12.35 (4.04-47.65)	**<0.001**