

# UNIVERSITY OF NAPLES “FEDERICO II”



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## PhD Thesis

***“Abnormal invasive placenta: epidemiology, diagnosis,  
management, fetal and maternal implications”***

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*“The roots of education are bitter, but the fruit is sweet.”*

Aristotele

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## Introduction

### ***The relationship between abnormal invasive placenta (AIP), preterm delivery and brain injury.***

Abnormal invasive placentation (AIP) is a potentially life-threatening complication of pregnancy characterized by an abnormal adherence of the placenta to the uterine wall (1). Its clinical consequence is failure of placental separation leading to massive postpartum haemorrhage with a significant increase in maternal morbidity and mortality. The reported incidence of abnormal placentation is highly variable, ranging from 1:93 000 to 1:111 pregnancies (2). A deficit in the uterine wall thickness due to a scarred uterus or an abnormal placentation site in the lower segment is a major risk factor (3). An increasing incidence of AIP has been demonstrated to be related to higher rates of cesarean section (CS). Therefore, populations with a high CS rate, such as in southern Italy, are expected to have an increased incidence of AIP (4, 5). While obstetricians agree that a planned delivery with a multidisciplinary team is the best management option to optimize maternal outcomes, there is little evidence to guide the timing of delivery for previa-accreta patients. Choosing the timing of delivery is critical in terms of limiting both maternal and neonatal risk. Several studies have suggested the benefits of planned delivery in the reduction of maternal morbidity. An early delivery can be beneficial as it allows to arrange a multidisciplinary team and to avoid an emergency delivery because of bleeding or labour. However, a scheduled delivery often means delivery of a premature infant, and all the risks related to iatrogenic prematurity must be taken into account (6-8).

Placenta previa and AIP represent the second most common cause for indicated preterm delivery, accounting for 5.6-8.7% of iatrogenic preterm deliveries (9). Preterm delivery before 37 weeks represents a major burden worldwide, with 15 million preterm births per year. Preterm birth is associated with many specific acute complications of immaturity. In almost all high- and middle-income countries, preterm birth is the leading cause of child deaths. In addition to its contribution to mortality, preterm birth can have lifelong effects on neurodevelopment, with increased risks of cerebral palsy, impaired learning, and mental disorders (10). Of 15 million (12.3–18.2 million) preterm births per year, 13.0 million (12.7–14.3 million) are estimated to survive the neonatal period. Among them, 0.9 million (uncertainty range: 0.8–1.1 millions) of these survivors will suffer long-term neurodevelopmental impairment with 345,000 moderately or severely affected (11).

Preterm brain injury results from developmental vulnerability given that the brain weighs only 65% of its full-term weight at 34 weeks and glial cell migration continues to 36 weeks. Gyral and sulcal development is still incomplete late preterm. The cortical volume in the late preterm infant is only 53% of the term volume, with approximately half the volume to be obtained in the last 6 weeks before 40 weeks. Brain insults in the late preterm brain can also alter the trajectory of specific programs in neuronal and glial development, as they do in the very premature brain, thereby contributing to the neurological disabilities of the survivors (12).

Ideally we would deliver patients with AIP at the gestational age at which lowest morbidity for the mother coincides with lowest morbidity for the infant. As the second leading cause of iatrogenic prematurity, during this PhD programme research has

been focused on the epidemiology, diagnosis, and management of AIP, trying to provide more evidence to restrict the earliest planned AIP deliveries to situations with demonstrated benefit.

### **PhD research: objectives and sessions**

The aim of this research project was to exploit the epidemiology, diagnosis and management of abnormally invasive placenta:

- The Session A was developed in the years before the beginning of the PhD and represents a starting point for the line of research developed afterwards. This is a retrospective study investigating the epidemiology of AIP in terms of incidence and risk factors in our population in the last 3 decades. The results of the study have been published in a peer reviewed journal (5).
- The Session B has been developed in the first two years of research and it encompasses two studies investigating the aspects of the diagnosis of the AIP. The first one is a multicentre study including data from 11 hospitals in Italy which has been recently accepted for publication on Gynecologic and Obstetric Investigation (manuscript No.: 201803046). The second study is a systematic review and meta-analysis on the predictive accuracy of different Color Doppler signs for the diagnosis of AIP. This study has been submitted for publication and is currently under peer review.
- The Session C has been developed in the third year of research and it deals



with the problem of the management of AIP. Two studies are included in this section. The first one is the result of the international collaboration with the International Society for Abnormally Invasive Placenta (IS-AIP), of which our centre is part of. This study represents the first ever published evidence based guidelines for the management of IS-AIP and it is currently under peer review. The second study is a prospective research conducted in our centre, dealing with the problem of the gestational age at delivery in women with AIP, trying to optimize maternal outcomes and to reduce unnecessary neonatal prematurity.

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## **Section A – Epidemiology**

### **Placenta accreta: incidence and risk factors in an area with a particularly high rate of cesarean section.**

*Morlando M. et al. Placenta accreta: incidence and risk factors in an area with a particularly high rate of cesarean section. Acta Obstet Gynecol Scand 2013; 92:457–460.*

#### **Background**

Placenta accreta (PA) is a potentially life-threatening complication of pregnancy characterized by an abnormal adherence of the placenta to the uterine wall (1), secondary to an absence or deficiency of Nitabuch's layer of the decidua (2). The term abnormal placentation is colloquially used for the three known variants of placenta accreta, increta or percreta (1). The clinical consequence of abnormal placentation is failure of placental separation leading to massive postpartum hemorrhage with a significant increase in maternal morbidity and mortality (1). The reported incidence of abnormal placentation is highly variable, ranging from 1:93 000 to 1:111 pregnancies (4). A deficit in the uterine wall thickness due to a scarred uterus or an abnormal placentation site in the lower segment is a major risk factor (5). An increasing incidence of abnormal placentation has been considered most likely related to much higher rates of cesarean section (CS) (5,6). Countries with a high CS rate, such as Italy (7), are expected to have an increased incidence.

We have investigated the changes in the incidence of PA and associated risk factors

along four decades from 1970s in a tertiary south Italian center.

## **Material and Methods**

A retrospective study of medical charts to identify all patients with PA was conducted. To evaluate incidence variation from the 1970s to 2000s we analysed all cases of PA (increta and percreta are included as they could often not be safely distinguished from accreta) in a sample triennium for each decade. Printed copies of the clinical notes were available starting from the 1976. The first triennium sample was considered from January 1976 to December 1978; then in any 10-year interval, an analogue three-year period at was studied, i.e. 1986–1988, 1996– 1998 and 2006–2008.

Placenta accreta was defined as any abnormal adherence of the placenta to the uterine wall (“accretism”) (1). Diagnosis had to be based on clinical and histological findings (4,6,8), using (i) histopathologic confirmation on a hysterectomy specimen by absence of the intervening layer of decidua, Nitabuch’s layer (2), between placenta and myometrium, (ii) incomplete manual removal of the placenta despite active management of the third stage of labor or (iii) heavy continued bleeding from the implantation site of a well-contracted uterus after difficult removal of the placenta during CS.

Variables included in the analysis were: maternal age, parity, previous abortions and curettages, CS, any other uterine surgery, placenta previa according to third trimester ultrasound examination, in vitro fertilization, uterine artery embolization in a previous pregnancy, female new- born gender (3–5,8,9). Risk factors for PA were analysed using the chi-squared test for categorical variables, and an ANOVA test for continuous variables. P-values <0.05 were considered significant. The institutional ethical committee approved the study.

## Results

During the four triennia there were 30 491 deliveries at our center, from which 50 cases of PA were diagnosed (Table 1). The incidence of PA grew from 0.12% (1/833) during 1976–1978, to 0.31% (1/322). At the same time, CS rate went from 17 to 64% during the last triennium (Figure 1).

Of the PA cases, nine women delivered vaginally. Among them, seven had blood products transfusions, five had dilatation and curettage, one of whom required a hysterectomy. Among women delivering vaginally, there were four hysterectomies due to uncontrollable bleeding.

Forty-one women were delivered by CS: 23 had trans-fusions, three were successfully treated with curettage and 26 required a hysterectomy. One woman had hypogastric artery ligation as adjuvant treatment to reduce hemorrhage during the cesarean hysterectomy. Twelve women were successfully treated by uterine packing only. There were 30 hysterectomies. In nine cases (30%) the histology confirmed the PA (four increta, five percreta); in 14 the histological result was negative (46%). Seven of the early cases from the first triennia could not be reviewed due to lost or destroyed documents. There were 13 primiparous women, three of whom delivered vaginally, while CS was carried out in 10 for different obstetrical indications. There were no cases of maternal death.

Table 1 shows risk factors in the four decades. No significant differences were seen for any of the most common variables, except previous CS ( $p < 0.05$ ).

## Discussion

This observational study shows an increasing incidence of PA over time from the

1970s to the 2000s. Risk factors did not change to any significant degree over the last four decades except for CS.

Due to the absence of 23% of histology reports, the diagnosis was based mostly on clinical criteria. The literature is controversial on the sensitivity and specificity of the clinical criteria compared with histological diagnosis (3,4,8,10). The exclusion of the cases with negative histological examination may underestimate the real incidence (3). The absence of indicative histological features in cases of clinically suspected PA does not exclude the diagnosis (10). We excluded all cases of simple retained placenta. Most of the cases were discovered at CS and a senior consultant was always involved in the management. It is therefore unlikely that the PA false-positive rate would have influenced the incidence rate, even if some cases of retained placenta were considered PA.

Other authors have reported rising rates of PA in the last decades (4,6). To the best of our knowledge, this is the longest observed period reporting the last 40 years of PA frequency variance. The incidence in the last decade is comparable with more recently published studies (0.01– 0.9%) (4,6,8).

The high CS rate was the only characteristic significantly different from 1970s to 2000s (from 18 to 63%). The possible explanation for this has been investigated previously. The human embryo develops in a relatively hypoxic environment, and data from in vitro studies suggests that oxygen tension determines whether cytotrophoblasts proliferate or invade, thereby regulating placental growth (11). Embryos may preferentially implant into areas of uterine scarring because of the lower vascularization and lower oxygen tension.

Our study has several limitations, including the retrospective evaluation of case notes where reporting was not consistent with regard to histology and data entry, affecting

the reliability of the clinical diagnosis. Moreover, electronic databases were not available from the 1970s and 1980s and this leads us to assume that a considerable amount of missing data cannot be recovered to evaluate the real incidence of PA in the last 40 years. Whether the four sample triennia are representative of the entire decade cannot be verified.

Considering the inevitable worldwide increasing rate of CS, further efforts should be spent on screening and management to prevent the consequent rise in maternal morbidity and mortality due to PA (6).

### **Acknowledgements**

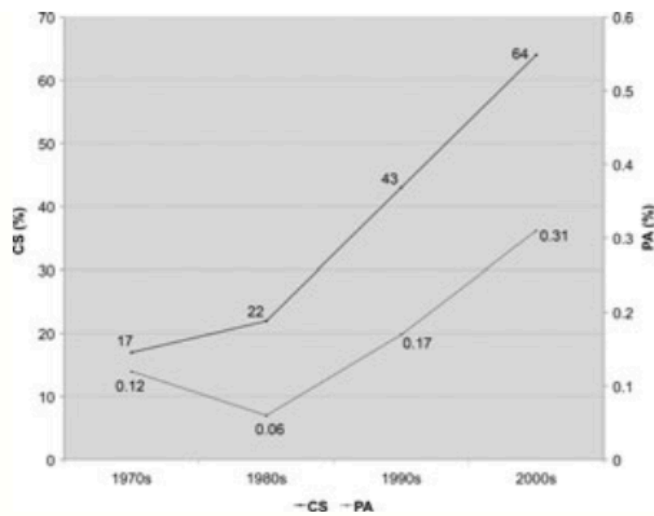
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**Figure 1**



**Figure 1.** Rates (%) of placenta accreta (PA, *dashed line*) and cesarean section (CS, *solid line*) at our center in the last four decades (1970s–2000s). Note that different scales for placenta accreta (right axis) and cesarean section (left axis) are used.

**Table 1**

**Table 1.** Risk factor for PA in the four decades and in the total cohort. Prior CS is the only risk factor significantly different between the four decades.

	1970s		1980s		1990s		2000s		Total	
	n	%	n	%	n	%	n	%	n	%
PA cases	11	0.12	4	0.06	15	0.17	20	0.31	50	
Prior cesarean section*	4	36	2	50	3	20	14	70	23	46
1	2	18	0		0		5	25	7	14
≥ 2	2	18	2	50	3	20	9	45	16	32
Age ≥ 35 years	5	45	2	50	3	20	7	35	17	34
Placenta previa	5	45	2	50	3	20	12	60	22	44
Parity ≥ 2	7	64	3	75	3	20	10	50	23	46
Prior curettage	4	36	0		9	60	8	40	21	42
Other prior uterine surgery	2 (18)		0		0		0		2	4
IVF	0		0		0		1	5	1	2
Prior uterine embolization	0		0		0		1	5	1	2
Uterine malformation	1	9	0		0		0		1	2
Female sex of newborn	9	82	2	50	6	40	11	55	28	56
Prior cesarean section*, mean ± sd	0.6 ± 1		1.2 ± 1.5		0.4 ± 0.8		1.3 ± 1		0.9 ± 1	
Maternal age, mean ± sd	32 ± 5.5		32.7 ± 6.8		32.8 ± 5		33.5 ± 5		32.9 ± 5.1	
Parity, mean ± sd	2 ± 1.3		2 ± 1.4		0.9 ± 0.7		1.4 ± 1.2		1.4 ± 1.2	
Prior curettage, mean ± sd	0.5 ± 0.9		0		1 ± 0.9		0.5 ± 0.6		0.6 ± 0.8	

\*Statistically significant ( $p < 0.05$ ).

PA, placenta accreta; IVF, in vitro fertilization.

## **Section B – Diagnosis (I)**

### **Clinical and ultrasound predictors of placenta accreta in pregnant women with antepartum diagnosis of placenta previa: a multicenter study.**

*De Vita et al. Clinical and ultrasound predictors of placenta accreta in pregnant women with antepartum diagnosis of placenta previa: a multicenter study. Accepted on Gynecologic and Obstetric Investigation (manuscript No.: 201803046).*

#### **Background**

Abnormally invasive placenta (AIP) defines a placenta that doesn't separate spontaneously at delivery and its removal causes abnormally high blood loss; AIP encompasses the histopathological diagnosis of placenta accreta, placenta increta and placenta percreta [1]. Placenta accreta is more common in women with a history of multiple caesarean section and the presence of a placenta previa than women without these risk factors. Placenta accreta increases the risk of major complications, such as fetal loss [2], bleeding [3], and hysterectomy [4]. Due to an increasing proportion of caesarean deliveries [5], the risk of placenta accreta has increased in the last two decades [6]. Silver et al. 2006 [7] reported that placenta accreta was present in 15 (0.24%), 49 (0.31%), 36 (0.57%), 31 (2.13%), 6 (2.33%), and 6 (6.74%) women undergoing their first, second, third, fourth, fifth, and sixth or more caesarean deliveries, respectively. AIP should be investigated in women with previous uterine surgery [8-9] and women with placenta previa [8]. Several ultrasound features have been suggested for diagnosis of placenta accreta such as: irregularly shaped placental lacunae (vascular spaces), thinning of the myometrium overlying the placenta, loss of

the retroplacental “clear space”, protrusion of the placenta into the bladder, increased vascularity of the uterine serosa/bladder interface, and turbulent blood flow through the lacunae on Doppler ultrasonography [10]. Magnetic resonance imaging (MRI), even if used widely in cases of suspected AIP, has yet to be showed to clearly to improve pregnancy outcome. Furthermore, diagnostic accuracy depends on the training and level of experience of the physician, irrespective of the imaging technique [1]. Ultrasound is the primary tool to diagnose AIP in women at risk, such as those with placenta previa and a prior cesarean section, whereas prenatal magnetic resonance imaging (MRI) is usually reserved for cases with inconclusive ultrasound assessment [11]. In fact, ultrasound had an overall good diagnostic accuracy in identifying the depth of placental invasion with sensitivities of 90.6%, 93.0%, 89.5%, and 81.2% for placenta accreta, increta, accreta/increta, and percreta, respectively [12].

Here we aimed to assess whether ultrasonography might help identify predictors of placenta accreta and hysterectomy in a large group of pregnant women in Italy with antepartum diagnosis of placenta previa.

## **Material and methods**

### *Participants and clinical characteristics*

A cross-sectional study was performed in eleven centres placed in Italy. Caucasian women with an ultrasound diagnosis of placenta previa in pregnancy delivering at the participating centres were recruited between May 2015 and April 2016. Placenta previa was classified based on the relationship between the placental margin and the internal os. Antepartum diagnosis of placenta previa at ultrasound scan was defined when the placenta covers the internal os and marginal placenta, when it

is sonographically measured < 20 mm of the internal os. (Fig. 1). [13]. All women underwent a transabdominal ultrasound scan followed by transvaginal scan and placental evaluation performed from 25+0 weeks to 40 weeks of gestational age, investigating the following criteria [2]: (1) irregularly shaped placental lacunae (vascular spaces), (2) thinning of the myometrium overlying the placenta with a cut-off of 1 mm:, (3) loss of the retroplacental “clear space”, (4) protrusion of the placenta into the bladder, (5) increased vascularity of the uterine serosa/bladder interface, (6) and turbulent blood flow through the lacunae on Doppler ultrasonography (Fig. 2). Placenta accreta was defined as trophoblastic attachment to the myometrium without intervening decidua. If the trophoblast invades the myometrium, it is termed placenta increta, and if it invades through the myometrium beyond the serosa and into surrounding structures such as the bladder, it is termed a percreta. Often the term placenta accreta is used to refer to the entire spectrum of conditions including accreta, increta, and percreta as well as to cases of clinically apparent morbidly adherent placenta. In this study, the term “placenta accreta” refers to the entire spectrum unless specifically noted. AIP was established at postpartum histological evaluation. Placenta accreta was separated into 3 categories: placenta creta when the villi simply adhere to the myometrium, placenta increta (PI) when the villi invade the myometrium, and placenta percreta (PP) when the villi invade the full thickness of the myometrium. [14]. A detailed anamnesis was obtained including age, parity with number of vaginal deliveries and caesarean deliveries, previous myomectomies, curettages, and resectoscopies. The respective Ethical Committee of all participating sites approved the study and all patients provided written informed consent.

### *Statistical analysis*

Continuous variables were expressed as mean  $\pm$  standard deviation and compared with t test, if normally distributed, and with the Mann–Whitney U test, if not normally distributed. Normality of variables was tested using the Kolmogorov-Smirnov test. Categorical variables are expressed as proportions and compared using a  $\chi^2$  test. To determine the risk factors associated with placenta accreta and hysterectomy, logistic regression analyses (backward conditional) were performed including all the demographic, clinical and ultrasound features. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS 22.0) software (SPSS Inc., Chicago, Illinois). A  $P < 0.05$  was considered statistically significant.

## Results

242 women with antepartum diagnosis of placenta previa were included. The mean age  $\pm$  standard deviation (SD) was  $33.2 \pm 4.9$  years, mean number of vaginal deliveries  $\pm$  SD was  $2.2 \pm 1.9$  and mean number of caesarean deliveries  $\pm$  SD was  $1.0 \pm 1.1$ .

Sixty-six out of 242 (27.27 %) women were nulliparous, 82/242 (33.89%) had 1 previous cesarean section (CS), 64/242 (26.45%) had 2 previous CS, 26/242 (10.74%) had 3 previous CS, 4/242 (1.65%) had 4 previous CS. From the anamnesis 22/242 patients (9.09 %) had a myomectomy, 100/242 (41.32 %) had a curettage and 5/242 (2.07 %) had a resectoscopy. Ninety-eight out of 242 (40.49 %) patients had a histological diagnosis of placenta accreta after the delivery. Placenta accreta was reported in 12/98 (12.25%), 31/98 (31.63%), 36/98 (36.73%), 19/98 (19.39%) women undergoing their first, second, third, and fourth cesarean deliveries, respectively. Table 1 shows demographic, clinical and ultrasound features of women who had versus those who did not have a placenta accreta. Women with placenta accreta had higher

number of caesarean deliveries, older age compared to women with no abnormal placental adherence and higher probability to have at least one ultrasound feature among signs number 1, 2, 3, 4, 5 and 6. Higher number of caesarean deliveries (Odds ratio [OR]: 7.002, 95% Confidence Interval (CI): 2.119–23.135; P=0.001) and curettages (OR: 3.577, 95% CI: 1.160–11.037; P=0.027), older age of the woman at the delivery (OR: 1.116, 95% CI: 1.010–1.233; P=0.031) and lower number of vaginal deliveries (OR: 0.462, 95% CI: 0.265–0.804; P=0.006) were identified as risk factors for placenta accreta. At ultrasound, the presence of irregularly shaped placental lacunae (vascular spaces) (OR: 6.226, 95% CI: 2.076–10.673; P=0.008), protrusion of the placenta into the bladder (OR: 24.408, 95% CI: 5.359–111.179; P<0.0001), and turbulent blood flow through the lacunae (OR: 24.695, 95% CI: 2.278–267.711; P=0.008) were predictors for placenta accreta (Table 2). No other variables were significantly associated with the diagnosis of placenta accreta. Sixty-one out of 242 (25.21%) patients with diagnosis of placenta accreta had hysterectomy; 17 (6.9%) had hysterectomy without diagnosis of placenta accreta.

## **Discussion**

In an Italian population of 242 women with antepartum diagnosis of placenta previa. Ninety-eight (98/242, 40.49 %) had a histological diagnosis of placenta accreta and 61/242 (25.21 %) patients with diagnosis of placenta accreta had a hysterectomy at the time of the delivery. 17/242 (67,02%) had hysterectomy without diagnosis of placenta accreta. A prior delivery by caesarean section was the main risk factor for placenta accreta. History of previous myomectomy did not increase the risk. With regard to ultrasound findings, we found two strong predictors of morbidly adherent placenta: protrusion of the placenta into the bladder and turbulent blood flow through

the lacunae. Our data confirm that an increasing incidence of placenta accreta is mainly due to the increased number of deliveries by caesarean section. In almost all cases, an abnormal placental invasion was at the site of the uterine scar [15]. We also found that older maternal age and curettages are important risk factors for placenta accreta, as shown previously [16]. In fact, women at most increased risk of placenta accreta were those who had a history of curettages, no vaginal deliveries and previous caesarean sections with a placenta previa overlying the uterine scar. The antepartum identification of women at higher risk of placenta accreta is pivotal for the reduction of maternal/fetal morbidity and mortality by allowing clinicians to choose the best time and place of birth. Multidisciplinary surgical management, neonatal intensive care, uterine artery embolization and an adequate number of blood products available in the operating room can only be achieved effectively through early detection of the placental pathology [10]. Ultrasonography may be used for diagnosis of abnormal placental adherence, but diagnostic criteria and accuracy are still under debate [17-19]. Here, we found that having protrusion of the placenta into the bladder and turbulent blood flow through the lacunae would help to identify the vast majority of women who had a histological diagnosis of placenta accreta at the delivery. Ultrasound is the primary tool to diagnose AIP in women at risk, such as those with placenta previa and a prior cesarean section, whereas prenatal magnetic resonance imaging (MRI) is usually reserved for cases with inconclusive ultrasound assessment [11]. On the other hand, having turbulent blood flow through the lacunae on Doppler ultrasonography was already found in prior studies [17-20]. Recently, a systematic review and meta-analysis of D'Antonio et al. [21] summarized several papers showing that ultrasound signs of Abnormally Invasive Placenta (AIP) are already present during the first trimester of pregnancy, especially before 11 weeks of gestation. Low anterior



implantation of the placenta/sac close to or within the scar was the most common early US signs suggestive of AIP, although its individual predictive accuracy was not high.

Rac et al. [22] constructed a receiver operating characteristic curve with the combination of smallest sagittal myometrial thickness, lacunae, and bridging vessels, in addition to number of cesarean deliveries and placental location, yielding an area under the curve of 0.87 (95% confidence interval, 0.80-0.95). Using logistic regression, a predictive equation was generated, termed the "Placenta Accreta Index." Each parameter was weighted to create a 9-point scale in which a score of 0-9 provided a probability of invasion that ranged from 2-96%, respectively; they concluded that this Index may be helpful in predicting individual patient risk of morbidity adherent placenta. The main limitation of this study may be that the antepartum diagnosis was based only on ultrasound and no MRI evaluations have been performed. MRI may be helpful when the placenta is difficult to visualize on ultrasound due to patients' habitus or to a posterior location of the placenta [23-26]. However, it has been reported no statistical difference in sensitivity or specificity between ultrasound and MRI [27-28]. Planning individual management for delivery is possible only with accurate evaluation of prenatal risk of accreta placentation in women presenting with a low-lying placenta/previa and a history of prior cesarean delivery. Ultrasound is highly sensitive and specific in the prenatal diagnosis of accreta placentation when performed by skilled operators [29]. In conclusion, women with a prior delivery by caesarean section have a high incidence of placenta accreta among women with antepartum diagnosis of placenta previa.

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## **Section B – Diagnosis (II)**

### **Diagnostic accuracy of colour-Doppler ultrasound in detecting abnormally invasive placentation: a systematic review and meta-analysis**

*Morlando et al. (submitted, under peer review).*

#### **Background**

Abnormally invasive placentation (AIP) is a potentially life-threatening complication characterized by an abnormal adherence of the placenta to the uterine wall, secondary to a defect in the decidua basalis.<sup>1</sup> According to the degree of placental invasion, three different variants of AIP can be recognized: placenta accreta, increta and percreta. Placenta previa and previous uterine surgery<sup>2-4</sup> represent the main risk factors for the occurrence of this condition and the incidence of AIP has been shown to rise in the last decade most likely as the consequence of the increase in caesarean section rate.<sup>2,3,5</sup> AIP is associated with the occurrence of several major complications such as severe maternal hemorrhage, need for blood transfusion, peri-partum hysterectomy and damage to adjacent organs.<sup>6</sup>

Antenatal diagnosis of invasive placentation is associated with a reduced risk of maternal complications as it allows a planned management of this condition.<sup>7</sup>

Ultrasound is usually used as the primary modality for the antenatal diagnosis of invasive placental disorders and is carried out especially in the second and third trimester of pregnancy. A recent systematic review has shown that ultrasound can reliably diagnose invasive placentation antenatally and that color Doppler has the best combination of sensitivity and specificity in the detection of this condition.<sup>8</sup> Despite

this, a multitude of different color Doppler signs have been reported in the recent past and it is not entirely certain which sign should be used to diagnose AIP.<sup>8-19</sup> The aim of this review was to systematically report the predictive accuracy of different Color Doppler signs in identifying invasive placental disorders prenatally.

## **Material and methods**

This review was conducted according to a protocol designed a priori and in line with recommended procedure for systematic reviews and meta-analyses.<sup>20-23</sup> An electronic search on Medline, Embase, Cinhal and The Cochrane Library including The Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and The Cochrane Central Register of Controlled Trials (CENTRAL) was performed on the 27 March 2016, utilizing combinations of the relevant medical subject heading (MeSH) terms, keywords and word variants for 'placenta accreta', 'placenta increta', 'placenta percreta', 'ultrasound', 'invasive placenta' and 'Color Doppler', 'invasive placenta' and 'infiltrative placenta. The search and selection criteria were restricted to the English language. Reference lists of relevant articles and reviews were hand-searched for additional reports (Appendix Table 1).

### *Study selection*

Studies were assessed according to the following criteria: population, outcome, prenatal diagnosis of invasive placenta by Doppler ultrasound and study design. For the purpose of this study, AIP was defined based on histopathological diagnosis of trophoblastic invasion through the myometrium or clinical assessment of abnormal

adherence/evidence of gross placental invasion at the time of surgery in the absence of histo-pathological evidence.

The Color Doppler signs explored in this systematic review were classified according to their location within the uterine-placenta complex. Many analogous definitions of the Doppler signs were found in the papers included. For that reason, in order to combine data from different studies, the Doppler signs most commonly reported were grouped as follows:

- Placental lacunae – encompassing the following definitions: large linear lacunae with low velocities flow, diffuse or focal lacunar flow pattern, vascular lakes with turbulent flow, vascular lakes with turbulent flow with high velocity (PSV > 15 cm/s), dilated vascular channels with diffuse lacunar flow;
- Uterine serosa-bladder interface – encompassing the following definitions: hyper-vascularity/abnormal vascularity of serosa–bladder interface, defined as the presence of either an hyper vascularity of the serosa–bladder interface, vessels extending from the placenta to the bladder, vessels crossing the interface disruption site;
- Sub-placental zone – encompassing the following definitions: increased sub-placental vascularity in the retro-placental zone, markedly dilated vessels over peripheral sub-placental zone, prominence of sub-placental venous complexes, loss of sub-placental Doppler signal, absence of sub-placental vascular signals in the areas lacking the peripheral sub-placental hypoechoic zone or vessels bridging the placenta and the uterine margin, dilated peripheral sub-placental vascular channels with pulsatile venous type flow over the cervix;
- 3D power Doppler signs - encompassing the following definitions: hyper-vascularity of the bladder serosa interface in basal, coronal and axial view, irregular

intra-placental vascularization with tortuous confluent vessels across placental width, inseparable cotyledonal and intervillous circulations.

A detailed individual description of the different Color Doppler signs present in the studies included in this systematic review is reported in Appendix Table 2.

In cases where the overall performance of Color Doppler and the number of imaging criteria used to diagnose AIP were not stated, the sign showing the best predictive value was used as a surrogate of the final diagnosis. Prospective and retrospective cohorts, case-control studies, case reports and case series were analyzed. Only studies reporting a prospective diagnosis of invasive placentation and/or the evaluation of the single Color Doppler signs and studies for which the value of true positive, false positive, true negative and false negative were available were included in the final analysis. Opinions and studies carried out only in the first trimester of pregnancy were excluded. Case reports and case series with fewer than five cases were also excluded in order to avoid publication bias. Studies published before 2000 were not considered for the analysis; technical advances in ultrasound equipment has led to a profound change in imaging processing thus we decided to consider a relatively small time window in order to uniform the appearance of the explored signs; furthermore, imaging of placental invasive disorders is a relatively recent issue and only in the last decade maternal and fetal medicine specialist are becoming confident with the detection of these conditions.

#### *Data extraction*

Two reviewers (MM, FD) independently extracted data. Inconsistencies were discussed by the reviewers and consensus reached. For those articles in which



targeted information was not reported but the methodology was such that the information might have been recorded initially, the authors were contacted requesting the data.

### *Quality assessment*

Quality of studies was assessed by using the revised tool for the quality assessment of diagnostic accuracy studies (QUADAS-2) tool. Each item scored a “yes”, “no”, or “unclear” if there is not sufficient information to make an accurate judgment.<sup>24</sup>

### *Statistical analysis*

Summary estimates of sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR-) and diagnostic odds ratio (DOR) for the overall predictive accuracy of colour Doppler ultrasound overall and by Doppler sign location (Placental lacunar flow and Uterine-bladder interface) were computed using the hierarchical summary receiver operating characteristic (HSROC) model.<sup>25</sup> Rutter and Gatsonis HSROC parameterization was used because it models functions of sensitivity and specificity to define a summary ROC curve, and its hierarchical modelling strategy can be used for comparisons of test accuracy when there is variability in threshold between studies.<sup>26</sup> However, when the number of studies is small, the uncertainty associated with the estimation of the shape parameter could be very high, and models may fail to converge. Thus, for all meta-analyses in which less than four study estimates could be pooled, the DerSimonian-Laird random-effect model was used. The DOR is defined as the ratio of the odds of the test being positive if the subject has a disease, relative to the odds of the test being positive if the subject does not have the disease (PLR/NLR).<sup>27</sup> Potential publication bias was formally assessed through Egger's

regression asymmetry test and Begg's adjusted rank correlation test. Following specific indications for meta-analyses of diagnostic accuracy, we correlated individual study sample sizes with both sensitivity and specificity as measures of test accuracy.<sup>28</sup> Only the meta-analyses with more than 5 studies could be assessed, because both tests are unreliable when the number of primary studies is small.<sup>26</sup> Meta-Disc 1.429 and Stata command metandi (Stata Corp. College Station) were used to analyze the data.

## **Results**

### *General characteristics of the studies*

The search yielded 597 possible citations; of these, 540 were excluded by reviewing the title or the abstract. Of the remaining 57 full-text manuscripts that were retrieved, 46 studies were excluded because they did not meet the inclusion criteria (Appendix Table 3), thus 11 studies were finally included in the review.<sup>9-19</sup> These 11 studies included 891 pregnancies at risk for AIP. A summary of the identified studies is shown in Table 1; Appendix Table 2 shows the definition of the individual Colour Doppler signs reported in the studies included in this systematic review; a large heterogeneity in the description of the signs is present among the different studies.

Quality assessment based on QUADAS-2 guidelines was conducted on all 11 studies included for systematic review (Figure 2). Most of the studies were of high quality and there was a low risk of bias and low level of concern regarding the applicability of the studies. However, heterogeneity was found in the definition and description of the different colour Doppler signs among the included studies. The general characteristics of the included studies are reported in Table 1. As regard for publication bias, neither Begg's nor Egger's test showed significant p-values for any of the considered

outcomes. Although publication bias does not seem to be significant in the present meta-analysis, no method is currently validated to formally assess publication bias in meta-analyses of diagnostic tests.

### *Diagnostic accuracy*

The overall performance of Doppler ultrasound in the antenatal diagnosis of invasive placental disorders was as follows: sensitivity, 89.69% (95% CI 76.9-95.8); specificity, 95.81% (95% CI 80.6-99.2), LR+, 21.41 (95% CI 4.3-105.5), LR-, 0.11 (95% CI 0.04-0.25) and DOR, 199.03 (95% CI 40.5-978.9). Among the different colour Doppler signs both placental lacunar flow and abnormalities of the uterine bladder interface showed a good predictive accuracy for invasive placental disorders, while Doppler abnormalities in the sub-placental zone was not highly predictive for these conditions (Table 2). Only two studies (357 women) from which raw data could be extracted explored the diagnostic performance of 3D Power Doppler ultrasound;<sup>9,14</sup> 3D Power Doppler ultrasound showed an overall good predictive accuracy for AIP, although significant heterogeneity was found between these two studies.

## **Discussion**

### *Comparison with other systematic reviews*

A recent systematic review has shown that ultrasound can reliably detect AIP in a subset of women at risk on the basis of a previous history of caesarean section and placenta previa.<sup>8</sup> In that study, colour Doppler showed a better diagnostic performance than conventional 2D ultrasound. However, the study did not provide the predictive accuracy of individual colour Doppler signs.

### *Implication for clinical practice*

The increasing incidence of AIP has led obstetrician to the daily practice of these conditions. Previous uterine surgery and placenta previa represent the main risk factors for the occurrence of these conditions. The prevalence of AIP is highly variable and mostly dependent upon the population analysed and type of invasive placentation considered. A recent systematic review reported a prevalence of 19% in a sub-population of women with an anterior placenta previa confirmed in the third trimester of pregnancy and a previous uterine surgery.<sup>8</sup>

This high prevalence questions the fact whether all women with placenta previa confirmed in the third trimester and a previous caesarean section should be considered virtually affected by AIP until detailed prenatal imaging has ruled out this condition.

### *Main findings*

The findings from this systematic review show that placental lacunar flow and abnormalities at the uterine bladder interface have a good predictive accuracy in detecting AIP, while Doppler abnormalities in the sub-placental zone does not perform well in screening for these conditions. The value of 3D Colour Doppler ultrasound has to be further ascertained on the basis that only two publications explored the diagnostic performance of this new technique in detecting invasive placentation. However, a large heterogeneity was present in the description and definition of the individual Doppler signs.

### *Strengths and limitations*

In the current systematic review we have reported the diagnostic accuracy of different

colour Doppler signs in detecting AIP. Strength of this review is that the individual rather than the overall diagnostic accuracy of Colour Doppler signs was reported; this may help in guiding clinicians when facing women at high risk for the occurrence of disorders of invasive placental disorders. Furthermore, the current review showed the high variability in the definition of the different ultrasound criteria and the need for a standardization of the ultrasound diagnosis of AIP. The heterogeneity in study design, populations analysed and reference standards adopted among the different studies represents a major weakness of this meta-analysis and several factors such as gestational age at assessment, ultrasound setting, type of scan and operator's experience might have influenced the final results. Furthermore, as for several meta-analyses, the number of included studies was small and some of these studies also had a small sample size. In such situations, estimates of the variances of the random effects are subject to a high level of uncertainty, and caution is required when interpreting the results. A major limitation in the interpretation of our findings is the high degree of variability in the definitions of the Doppler signs adopted among the available studies. Different authors tend to define similar criteria in different ways. This makes a comparison or grouping difficult to be done. Furthermore, many Doppler signs were not consistently reported by all the authors, and many other signs were only reported in a single study. This background makes the task of assessing the predictive accuracy of colour Doppler even harder.

Prenatal diagnosis of AIP is primarily carried out by ultrasound, while MRI is usually adopted when ultrasound is not conclusive or to assess the extent of placental invasion.<sup>30,31</sup> A multitude of gray scale and Colour Doppler ultrasound signs, either 2D or 3D, has been described in the recent past, however it is not entirely certain yet how many and which ultrasound signs show the best combination of sensitivity and

specificity. A wide heterogeneity in the diagnostic performance of the same ultrasound signs among the different studies was observed in the current review; although the adoption of different reference standards for defining AIP, operators' experience, placental position and type of ultrasound scan play an important role in this scenario, the heterogeneity in the definition of the individual ultrasound criteria may account for these different results.

In the current review 3D ultrasound apparently shows a better accuracy in detecting AIP compared to traditional 2D colour Doppler ultrasound. This result should be interpreted with caution especially on the basis of the small number of studies included. Furthermore, 3D Colour Doppler is usually adopted only when conventional 2D colour Doppler has raised the suspicion of invasive placenta, thus the values reported in the current review may not reflect the actual diagnostic accuracy of 3D Doppler, but its performance only in a highly selected group of patients. Further studies assessing the role of 3D Doppler as a primary tool in detecting AIP are needed.

#### *Implication for research*

There is currently strong evidence that prenatal imaging techniques can reliably identify AIP in women at risk. Despite this, the large majority of the studies addressing the diagnostic ability of ultrasound in detecting invasive placentation differs as regard for several technical factors, such as the gestational age at assessment, ultrasound machine settings, imaging planes used, number of sonographic signs needed to label a scan as suggestive of the disease. Future research should aimed at objectively define ultrasound criteria suggestive for the presence of AIP, in order to develop a standardized technique for the assessment of women at risk for these conditions.

An objective description of the signs should be provided as regard for their appearance

in relation to the gestational age at scan, type of ultrasound scan (TA and TV), location within the utero/placental complex. Furthermore, the reproducibility of the imaging signs should also be addressed.

### *Conclusions*

Colour Doppler ultrasound is highly reliable in detecting AIP in women at risk; despite this accuracy a high variability persists in the definition of the sonographic criteria suggestive for these disorders. Further studies aiming at objectively defining the ultrasound criteria suggestive of AIP are urgently needed in order to standardize the diagnosis.

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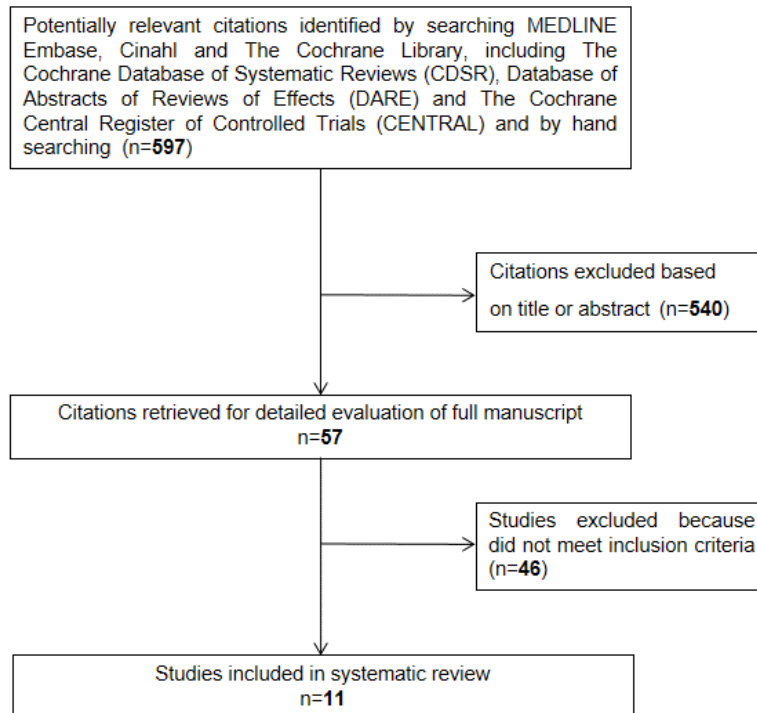


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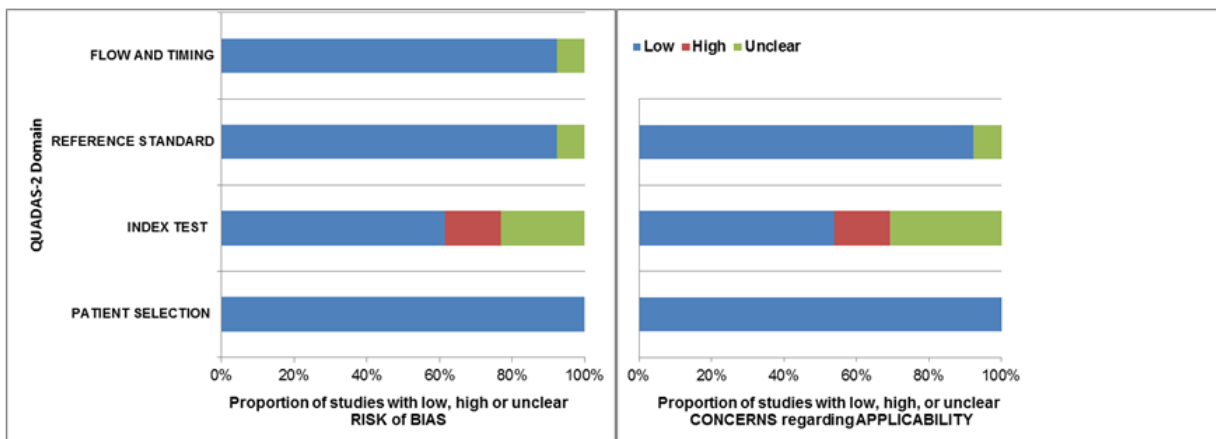
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**Figure 1: Systematic review flow-chart.**

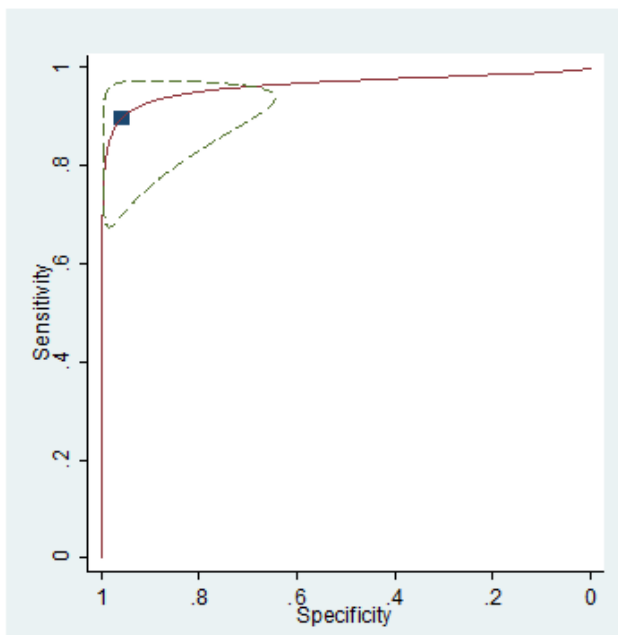


**Figure 2: Studies included in the review according to quality assessment of diagnostic accuracy studies (QUADAS-2) criteria: proportion of studies with low, high or unclear risk of bias (a) or concerns regarding applicability (b).**



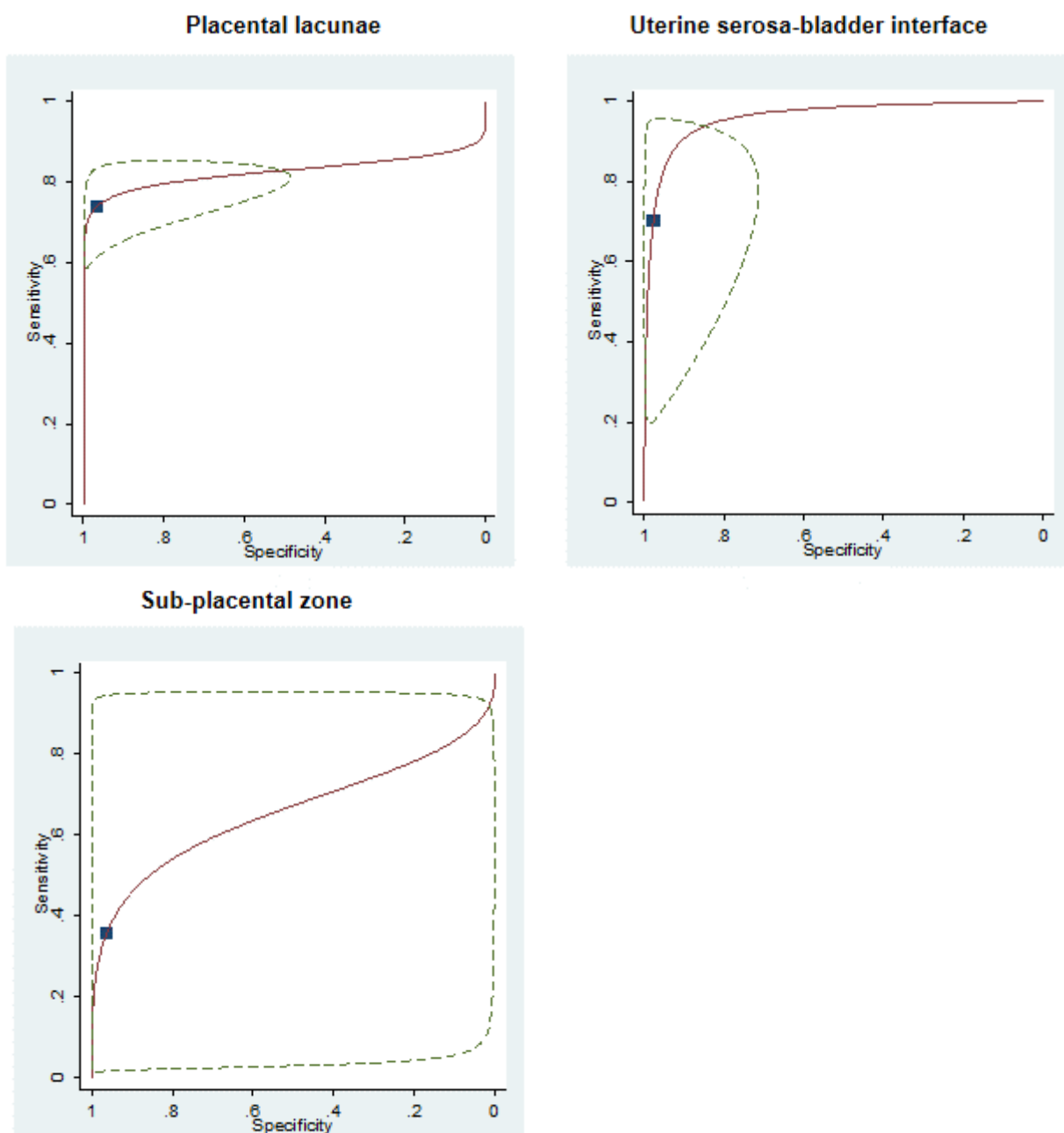
**Figure 3**

Predictive accuracy of overall Colour Doppler ultrasound in detecting invasive placentation disorders based upon hierarchical summary receiver operating characteristic (HSROC) model. The curve from HSROC model contains a summary operating point (■) representing summarized sensitivity and specificity point estimates for individual study estimates; dotted lines: 95% CI.



**Figure 4**

Predictive accuracy of different Colour Doppler signs in detecting MAP Depending on the number of studies, computations were based upon DerSimonian-Laird random-effect ( $\Psi$ ) or hierarchical summary receiver operating characteristic (HSROC) model ( $\blacktriangleright$ ). The curve from HSROC model contains a summary operating point ( $\blacksquare$ ) representing summarized sensitivity and specificity point estimates for individual study estimates; dotted lines: 95% CI.



**Table 1:** General characteristics of the included studies.

Author	Year	Study design	Inclusion criteria	USS techniques	Reference standard	Women (n)	Invasive placentas (n)	US Doppler signs analysed
Cali <sup>9</sup>	2013	Prospective	Placenta previa and previous uterine surgery	TA, TV	Pathology	187	41	1. Placental lacunae with turbulent flow with high velocity (PSV >15 cm/s). 2. Hypervascularity of uterine serosa-bladder interface. 3. (3D) Hypervascularity of uterine serosa-bladder interface. 4.(3D) Irregular intraplacental vascularization with tortuous confluent vessels across placental width.
Chalubinski <sup>10</sup>	2013	Retrospective	Placenta previa +/- previous cesarean section	TA, TV	Surgery/pathology	232	35	1. Placental lacunar flow
Pecker <sup>11</sup>	2013	Prospective	Placenta previa +/- previous cesarean section	TA	Pathology	40	20	1. Intraplacental lacunar turbulent flow with high velocity (PSV >15 cm/s). 2. Abnormal vascularization in the vesico-uterine plane.

Mansour* <sup>12</sup>	2011	Prospective	Placenta previa +/- previous uterine surgery	TA, TL	Surgery	35	15	1. Hypervascularity of the serosa-bladder interface.
El Behery <sup>13</sup>	2010	Prospective	Placenta previa +/- previous uterine surgery	TA, TV	Surgery/ pathology	35	7	1. Turbulent or diffuse flow within lacunae. 2. Vessel crossing the interface disruption site.
Shih <sup>14</sup>	2009	Prospective	Placenta previa +/- previous cesarean section	TA	Pathology	170	39	1. Diffuse or focal lacunar flow. 2. Vascular lakes with turbulent flow with high velocity (PSV >15 cm/s) and low resistance waveform. 3. Hypervascularity of the serosa-bladder interface. 4. Dilated vessels in the subplacental zone. 5. (3D) Intraplacental hypervascularity (lateral view). 6. (3D) Inseparable cotyledonal and intervillous circulations (lateral view). 7. (3D) Numerous coherent vessels involving the whole uterine serosa-bladder junction (basal view).
Miura <sup>15</sup>	2008	Prospective	Placenta previa +/- previous cesarean	Not stated	Pathology	12	4	1. Hypervascularity of the serosa-bladder interface.

			section					
Wong <sup>16</sup>	2008	Retrospective	Placenta previa or previous cesarean section of uterine surgery or previous history of invasive placentation	TA, TV	Surgery/pathology	66	9	1. Increased subplacental vascularity. 2. Placental lacunar flow. 3. hypervascularity of the serosa-bladder interface. 4. Vessels extending from the placenta to the bladder. 5. Vessels bridging the placenta and the uterine margin. 6. Vessels crossing the interface disruption site.
Japara <sup>17</sup>	2007	Prospective	Placenta previa and previous uterine surgery	TA, TV	Surgery/pathology	21	7	1. Dilated vascular channels with diffuse lacunar flow. 2. Interphase hypervascularity with abnormal vessels linking the placenta to the bladder. 3. Dilated peripheral subplacental vascular channels with pulsatile venous type flow over the cervix.



Chou <sup>18</sup>	2000	Prospective	Placenta previa+/- previous cesarean section	TA	Surgery/pathology	80	14	1. Diffuse lacunar flow with high-velocity pulsatile venous-type flow. 2. Focal lacunar turbulent flow. 3. Interphase hypervascularity with abnormal blood vessels linking the placenta to the bladder. 4. Dilated peripheral subplacental vascular channels with pulsatile venous-type flow over the uterine cervix. 5. Absence of subplacental vascular signals in the areas lacking the peripheral subplacental hypoechoic zone.
Twickler <sup>19</sup>	2000	Retrospective	Placenta previa+/- previous cesarean section	TA	Surgery/pathology	215	9	1. Large linear intraplacental lacunae with low velocities flow.

\*: additional data provided by the authors

**Table 2.** Summary estimates of sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR-) and diagnostic odds ratio (DOR) of Doppler ultrasound overall, 3D, and by colour Doppler sign location (Placental lacunar flow, Uterine-bladder interface, and sub-placental zone) to predict placental invasion. Depending on the number of studies, computations were based upon DerSimonian-Laird random-effect ( $\Psi$ ) or hierarchical summary receiver operating characteristic (HSROC) model ( $\Omega$ ).

	N. studies	N. accreta / Total sample	Sensitivity % (95% CI)	Specificity % (95% CI)	DOR (95% CI)	LR+ (95% CI)	LR- (95% CI)
Doppler (overall)	11 $\Omega$	169/891	89.69 (76.9-95.8)	95.81 (80.6-99.2)	199.03 (40.5-978.9)	21.41 (4.3-105.5)	0.11 (0.04-0.25)
Placental lacunar flow	9 $\Omega$	130/824	74.09 (64.5-81.8)	96.55 (73.3-99.6)	80.14 (11.6-554.2)	21.50 (2.8-162.4)	0.27 (0.20-0.36)
Uterine-bladder interface	9 $\Omega$	105/637	70.29 (35.7-91.0)	97.59 (87.2-99.6)	95.90 (12.0-768.5)	29.19 (5.3-162)	0.30 (0.11-0.84)
Sub-placental zone	4 $\Omega$	20/330	35.80 (14.9-63.9)	96.21 (54.4-99.8)	14.14 (0.8-262.9)	9.44 (0.6-156.3)	0.67 (0.45-0.99)
3D Doppler	2 $\Psi$	76/357	95.00 (87.7-98.6)	93.14 (89.5-95.8)	1020.81 (132.7-7852.5)	37.01 (0.2-7092.6)	0.06 (0.01-0.45)

## **Section C – Management (I)**

### **The International Society for Abnormally Invasive Placenta (IS-AIP) evidence based guidelines for the management of Abnormally Invasive Placenta (AIP)**

*Collins et al. (submitted, under peer review).*

#### **Background**

Abnormally invasive placenta (AIP), also called placenta accreta spectrum disorder (PAS), describes the clinical situation where a placenta does not separate spontaneously at delivery and cannot be removed without causing abnormal and potentially life-threatening bleeding<sup>1</sup>. There is increasing epidemiological evidence demonstrating that the incidence of AIP is rising worldwide<sup>2</sup>. This is most likely due to the rising rates of caesarean delivery, which is the greatest single risk factor for AIP in subsequent pregnancies. Optimal management requires both accurate antenatal diagnosis and a robust perinatal management strategy. However, even with the rising incidence, AIP is still rare (0.79-3.11 per 1000 births after prior cesarean)<sup>3</sup> and so defining an optimal management strategy remains extremely challenging. The literature contains a vast number of case reports, case-series and retrospective cohort studies looking at multiple management strategies but most studies are small and many are methodologically flawed limiting their utility. The situation is made even more

difficult by the spectrum of presentations being presented in most studies as a binary outcome ('AIP' or 'not AIP') with varying diagnostic criteria and no assessment of severity reported.

The International Society for Abnormally Invasive Placenta ([www.IS-AIP.org](http://www.IS-AIP.org)) evolved from the European Working group on AIP (EW-AIP) and currently consists of 42 clinicians, pathologists and basic science researchers from 13 countries. The IS-AIP's aim is to optimize the treatment of AIP, and to promote research and awareness of the condition internationally. The group has already published standardized descriptors to aid in the ultrasound diagnosis of AIP<sup>4</sup>. This paper aims to generate an evidence-based recommendation for the intra-partum management of AIP using the unique, international composition of the IS-AIP to provide expert consensus agreement where the evidence identified is weak, flawed or absent.

## **Materials and Methods**

The questions agreed by the IS-AIP membership to be pertinent to the management of AIP were framed and agreed on by 'round table consensus' at an IS-AIP meeting in Prague (October 2016). The search and assessment of the published evidence was then undertaken by an individual IS-AIP member according to a predefined pro forma (Supplementary material 1). In brief, this involved undertaking a full 'systematic review' process for each topic including formulating an appropriate question specific to AIP using the PICO framework<sup>5</sup> and searching all relevant medical databases (PubMed, EMBASE etc.) and, where appropriate, some non-medical databases (e.g. Google). All searches for

the 21 different topics were undertaken at various points during 2017. Full text versions of all potential papers were then obtained, assessed for relevance and critically appraised using the levels of evidence provided by the Centre for Evidence Based Medicine<sup>6</sup>.

All the completed pro formas detailing the search strategy, results and critical analysis for each topic were then sent to the entire membership for consideration. Where potential issues were identified (e.g. problems with search terms or the studies identified), a second IS-AIP member repeated the process to ensure no evidence had been missed. A few topics which revealed little high-quality evidence during the original 2017 search were searched again in 2018 to ensure no further evidence had been published. The results for each topic were then discussed by the membership at an IS-AIP meeting or using web conferencing and agreement was reached on the formal IS-AIP recommendation according to the level of evidence available. Where no evidence was found, the IS-AIP recommendation was generated by expert consensus after discussion.

## **Results**

### **What constitutes ‘expertise’ in management of AIP and/or defines a ‘Center of Excellence’?**

Evidence for what constitutes an ‘expert’ in the management of AIP is missing from the literature despite opening the search strategy to non-medical databases. Therefore, the IS-AIP recommendation is based on a consensus opinion (level 5 evidence) and is:

An expert is a person with significant experience in AIP and a high level of knowledge and/or skills relating to the condition (Grade D recommendation).

Whilst there are multiple retrospective cohort studies demonstrating decreased maternal morbidity when women are cared for in self-defined 'Centers of Excellence'<sup>7-10</sup> there was no definitive evidence for what should constitute such a 'Center of Excellence'. Therefore, the IS-AIP recommendation is based on a consensus opinion (level 5 evidence;) and is summarized in Table 1.

This recommendation was reached independently of the recently published FIGO consensus statement<sup>11</sup> but is in agreement with it.

### **Is there a reduction in morbidity if women antenatally diagnosed with AIP remain in hospital until delivery?**

There were no studies identified which specifically addressed the question of inpatient versus outpatient care for women antenatally diagnosed with AIP. As the majority of AIP cases are also placenta previa, an examination of the evidence available for placenta previa was also made. There were five publications reporting outcomes for expectant outpatient management of women with placenta previa (one small RCT<sup>12</sup> and four retrospective cohort studies<sup>13-16</sup>).

The oldest publication from 1984<sup>15</sup> presented data from a retrospective cohort of 38 women. The authors suggested significant improvement in neonatal morbidity and mortality for women with placenta previa who were managed as inpatients. However, there appeared to be significant recruitment bias, with the woman managed as outpatients being enrolled at significantly earlier gestations

compared to those managed as inpatients (Level 4 evidence).

A subsequent small RCT by Wing et al<sup>12</sup> reported the outcomes for 26 asymptomatic women with placenta previa managed at home compared with 27 who were hospitalized (level 2b evidence). The only significantly different outcome was length of hospital stay. Three retrospective cohort studies<sup>13, 14, 16</sup> examined the outcomes for a total of 305 women (level 2b evidence) and did not demonstrate any significant difference in either maternal or neonatal outcomes. All three studies concluded that in selected women with asymptomatic placenta previa outpatient management was both safe and cost effective. However, these were all retrospective cohort studies and there may have been individual circumstances which biased the selection of care settings for the women involved. This evidence for outpatient management of placenta previa was taken into consideration when reaching the consensus recommendation for the management of AIP.

In conclusion, there is no evidence for antenatal hospitalisation of asymptomatic women with antenatally diagnosed AIP, whether it is associated with placenta previa or not. Therefore, the IS-AIP recommendation is extrapolated from the small RCT for inpatient management of placenta previa<sup>12</sup> (level 2b evidence) and is as follows:

Expectant outpatient management of women with AIP, even in the presence of placenta previa, is acceptable treatment, as long as the woman is asymptomatic and has been appropriately counselled (Grade C recommendation). However, adequate resources must be available to allow rapid return to the hospital (Grade D recommendation).

Symptomatic women should be cared for according to local protocols and expertise (Grade D recommendation).

**Is there evidence of reduced morbidity in women antenatally diagnosed with AIP if they receive iron supplementation to optimize hemoglobin levels?**

There was no evidence available for the benefit of antenatal optimization of haemoglobin (Hb) specifically for cases of AIP. A single study nested in a community based RCT of treatments for severe anaemia in women from Zanzibar was identified which reported that women with Hb of <90g/L at delivery were at increased risk of blood loss both at the time of birth and in the immediate postpartum period, irrespective of mode of delivery<sup>17</sup> (level 1b evidence). This study was taken into consideration but it does not answer the original question posed therefore, the IS-AIP recommendation is based on a consensus opinion (level 5 evidence) and is as follows:

As soon as women are antenatally diagnosed with AIP they should have their Hb level measured. If it is low (<110g/l before 28 weeks' gestation or <105g/l after 28 weeks'), appropriate haematonic investigations should be undertaken and if indicated, iron supplementation (oral or intravenous) should be given to optimize their Hb level before surgery (Grade D recommendation).

This recommendation was reached independently but is in agreement with the UK RCOG prevention and management of postpartum hemorrhage guideline (Green-top number 52)<sup>18</sup> and the recent FIGO consensus statement<sup>11</sup>.



**At what gestation should women with antenatally diagnosed AIP be delivered?**

Six studies were found which reported maternal and neonatal outcomes for different gestational ages at delivery in women with an antenatal diagnosis of AIP<sup>8</sup>, 19-23. All six were retrospective observational studies (level 4 evidence). It was not possible to draw any firm conclusion on the optimal gestational age for delivery for woman with AIP, to reduce maternal and neonatal morbidity whilst still minimizing the rate of unplanned, emergency delivery. Therefore, although these studies were taken into consideration, the IS-AIP recommendation is based on a consensus opinion (level 5 evidence) and is as follows:

The timing of delivery should be tailored to each unique set of circumstances and based on the individual woman's risk of emergent delivery. To reduce the risk of neonatal morbidity it is reasonable to continue expectant management until after 36+0 weeks' gestation for women with no previous history of pre-term delivery (<36+0 weeks) and who are stable with no vaginal bleeding, PPRM, or uterine contractions suggestive of pre-term labor.

In the case of women with history of previous pre-term birth, multiple episodes of small amounts of vaginal bleeding, a single episode of a significant amount of vaginal bleeding or PPRM, planned delivery at around 34+0 week's gestation should be considered given the significantly increased risk of emergent delivery (Grade D recommendation).

**Is there evidence of reduced mortality or morbidity in neonates if women, with antenatally diagnosed AIP, receive corticosteroids for delivery**

### **occurring after 34+0 weeks' gestation?**

No prospective RCT exists evaluating the influence of AIP per se on neonatal respiratory morbidity beside the normal influence of prematurity when delivered between 34+0 and 37+0 weeks of gestation. One retrospective case series (level 4 evidence) of histopathologically diagnosed AIP compared the neonatal outcomes between antenatally diagnosed AIP and AIP cases diagnosed intrapartum 23. Although there was no significant difference between the gestation at delivery (33.9 vs 34.7 weeks;  $p=0.34$ ) for the two groups, those antenatally diagnosed were more likely to have received antenatal steroids (65% vs 16%;  $p<0.001$ ) yet still demonstrated a higher rate of admission to the neonatal intensive care unit (86% vs 60%;  $p=0.005$ ), and longer neonatal hospital stays (11 vs 7 days;  $p=0.006$ ). Interpretation of this dataset is difficult with regard to the specific question as there are likely to be considerable confounding factors.

There was no evidence available that the presence of AIP itself increases neonatal respiratory morbidity or mortality if the scheduled delivery takes place between 34+0 and 37+0 weeks of gestation. Therefore, the IS-AIP recommendation for antenatal glucocorticoid treatment to induce fetal lung maturation for a scheduled delivery after 34+0 weeks of gestation is based on consensus opinion (level 5 evidence) and is as follows:

An individualized approach for antenatal steroid administration should be employed, based on the current local guidelines for the specific gestation at delivery, irrespective of the suspicion or diagnosis of AIP (Grade D recommendation).

**Does routine pre-operative cystoscopy improve the accuracy of pre-operative diagnosis of AIP and/or reduce maternal morbidity in women with antenatally diagnosed AIP?**

No RCTs were found examining the efficacy of pre-operative cystoscopy for the management of AIP. One case series presented 12 patients with AIP and gross hematuria (level 4 evidence) who underwent pre-operative cystoscopy<sup>24</sup>. The authors reported that the procedure did not establish a preoperative diagnosis in any patient and concluded that cystoscopy had minimal diagnostic value.

The evidence that cystoscopic findings, even in the presence of gross hematuria, do not correlate to the level of bladder involvement was taken into account but, given the poor quality of this study, the recommendation is also supported by consensus opinion (level 5 evidence).

The IS-AIP does not recommend undertaking routine pre-operative cystoscopy. If pre-operative cystoscopy is performed for insertion of ureteric stents, the appearance of the bladder should not change the (imaging-based) plan of management (Grade D recommendation).

**Does routine ureteric stent placement reduce maternal morbidity in cases of antenatally diagnosed AIP?**

One retrospective cohort study<sup>25</sup> (level 2b evidence), of 57 cases of suspected AIP and 19 undiagnosed cases reported on ureteric stenting and unintentional urinary tract injury. Ureteric stenting was attempted in 25 of the suspected cases. The stent placement was achieved bilaterally in only 68% (17/25) of cases, on only one side in 16% (4/25) of cases, and neither side in 16% (4/25). Women with

bilateral ureteral stents had a lower incidence of early morbidity compared with women without stents (18% (3/17) vs. 55% (22/40),  $p = 0.018$ ). A non-significant reduction in ureteric injury was observed (0 vs. 7%).

A systematic review of 49 case series and case reports (level 3a evidence), including the above cohort study, attempted to examine the efficacy of approaches aimed at minimizing urinary tract injuries in AIP<sup>26</sup>. Of the 292 women with AIP, whether ureteric stents were successfully placed or not, was reported for 90 cases only. No details were available on the number in whom it was attempted but unsuccessful. The risk of urinary tract injury was significantly lower in the group with ureteric stents in situ (2/35) compared to those who were known not to have stents (18/55;  $p=0.01$ ).

On the basis of this evidence and consensus opinion (level 5 evidence) the IS-AIP recommendation is:

Placement of ureteric stents may be beneficial in preventing ureteric injury and early morbidity (Grade B recommendation). However, given the potential risks associated with stent placement, the evidence is not strong enough to recommend routine placement of ureteric stents for all suspected cases of AIP. The benefit from ureteric stents is probably limited to cases of percreta with significant invasion where hysterectomy is likely to be highly complex (Grade D recommendation).

**Does routine insertion of prophylactic balloon catheters into the pelvic vasculature reduce maternal morbidity in cases of antenatally diagnosed AIP?**

A systematic review has recently been published looking at endovascular interventional modalities for hemorrhage control in AIP<sup>27</sup>. This included both prophylactic arterial balloon occlusion and pelvic vasculature embolization. Only 16 of the 69 included studies were controlled with the remaining being cohort, case series or case studies (level 3a). The heterogeneity of the studies was reported by the authors to be significant. All grades of AIP (accreta/increta/percreta) were grouped together for the meta-analysis with no differentiation in severity, with some studies including only balloon occlusion and others using vascular embolization. The authors however, concluded that “endovascular intervention is effective in controlling hemorrhage in abnormal placentation deliveries”.

One small RCT (level 2b evidence)<sup>28</sup> was found that had been included in the systematic review<sup>27</sup>. This randomized 27 women with AIP and showed no difference in the number of packed red blood cell (RBC) units transfused for women who underwent placement of balloon catheters in the iliac arteries compared to those who did not. This RCT however, also reported that 15% of the women with balloon catheters experienced an interventional radiology (IR) related complication.

The IS-AIP considered the findings of both these two studies. The RCT is a much smaller data set but is more methodologically rigorous (level 2b evidence). The systematic review, whilst larger is heterogeneous and may be open to significant bias. Therefore, taking into account the quality of the evidence available the IS-AIP recommendation is as follows:

The effect of prophylactic arterial balloon catheters on bleeding and morbidity

among women with a prenatal diagnosis of AIP has yet to be confirmed. Significant adverse events have been reported from this procedure. Larger, prospective, appropriately controlled studies are needed to demonstrate both the safety and efficacy of prophylactic balloon occlusion. Given this, the IS-AIP cannot recommend routine use of prophylactic pelvic arterial balloon catheters for all cases of suspected AIP (Grade B recommendation).

This recommendation was reached independently of the recently published FIGO consensus statement<sup>11</sup> but is in agreement with it.

### **Is there an optimal maternal position for surgical delivery of women with antenatally diagnosed AIP?**

There are no publications which specifically address the question of maternal position for surgery for women with AIP. Therefore, the IS-AIP recommendation is based on consensus opinion (level 5 evidence) and is as follows:

When hysterectomy is either planned or likely, the woman should be placed in a position where the vagina is potentially accessible (such as lithotomy or legs straight on the operating table but parted) to facilitate manipulation of the cervix, if required to assist the hysterectomy. This will also allow easier assessment of any blood lost vaginally (Grade D recommendation).

### **Does routine vertical midline incision instead of using a transverse incision reduce maternal morbidity in cases of antenatally diagnosed AIP?**

No studies were found comparing either maternal or fetal outcomes for different skin incisions. In the few publications that mention the type of skin incision,

vertical midline incision appears to be used most frequently and is often anecdotally recommended. Other transverse incisions, such as Pfannenstiel and Maylard, have been reported and recommended based on both aesthetic considerations and the potential for a reduction in post-surgical complications. Given the lack of evidence, the IS-AIP recommendation is based on consensus opinion (level 5 evidence) and is as follows:

There is no evidence of benefit for routine use of a vertical, midline incision for all cases of antenatally diagnosed AIP. The decision regarding which type of skin incision is used, should be made by the operating team. The location of the placenta, degree of invasion suspected, likelihood of intraoperative complications, maternal body habitus, gestational age and preference of the operating surgeon/obstetrician, should all be taken into consideration (Grade D recommendation).

**Does making a uterine incision in the upper segment to avoid transecting the placenta reduce maternal morbidity in cases of antenatally diagnosed AIP?**

One retrospective case series (level 4 evidence)<sup>29</sup> reported blood loss after transverse fundal uterine incision to avoid the placenta in 34 women with placenta previa, 19 of whom had intraoperatively confirmed AIP. The average blood loss reported was 1,370g. There was no control group and the severity of AIP was not reported, yet the authors conclude that this blood loss “compares favourably with the volume lost during a routine transverse lower segment section performed in patients without placenta previa or accreta”. It is not possible to draw any firm

conclusion from this study therefore the IS-AIP recommendation is based on expert consensus (level 5 evidence) and is as follows:

Avoiding placental transection when making the uterine incision is essential if AIP is clearly evident on opening the abdomen, and is reasonable for women with antenatally suspected AIP but with no definite evidence seen at laparotomy, even if it means making an upper segment or fundal incision, as it is likely to reduce maternal blood loss from the placental bed (Grade D recommendation).

**Does routine intraoperative ultrasound (US) to map the placental edges before uterine incision reduce maternal morbidity in cases of antenatally diagnosed AIP?**

Several reports in the literature anecdotally recommend the use of intraoperative US usually with the probe directly placed on the uterus protected by a sterile cover. There is however, a theoretical risk of introducing infection. No publications were found which address either the risks or benefits of intraoperative ultrasound scanning for placental localization in women with suspected AIP. One study by Al-Khan et al.<sup>8</sup> retrospectively analyzed patients before and after an institutional protocol for AIP management was introduced. In their protocol, intraoperative US for placental localization is performed but the improvement in outcomes cannot be directly attributed to any individual measure. Therefore, the IS-AIP recommendation is based on a consensus of experts (level 5 evidence) and is as follows:

If the US scan is undertaken in an appropriately sterile manner, the small theoretical risk of introducing infection is outweighed by the benefit of ensuring



the incision is made away from the placental bed. Therefore, intraoperative US of the exposed uterus should be used, where possible, to locate the placental edge and assist decision-making regarding the uterine incision site (Grade D recommendation).

**Does routine prophylactic administration of oxytocin after delivery of the baby reduce maternal morbidity in cases of antenatally diagnosed AIP?**

There is evidence for the prophylactic administration of oxytocin after delivery at routine caesarean delivery to prevent PPH<sub>30</sub>. However, the use of routine oxytocin at caesarean in cases of antenatally suspected AIP, has not been addressed in any study. Therefore, the IS-AIP recommendation is based on a consensus of experts (level 5 evidence) and is as follows:

Prophylactic administration of oxytocin immediately after delivery increases contraction of the uterus which could be helpful for the assessment of placental separation. If the whole placental bed is abnormally invasive, uterine contraction will not result in any placental separation. If, however, the placenta is only partially adherent or invasive, uterine contraction may cause some separation leading to increased blood loss which could prompt the surgeon to forcibly remove the rest of the placenta or perform a more hurried hysterectomy. In light of this risk, the IS-AIP recommend that when AIP is suspected antenatally, prophylactic uterotonic agents should not be routinely given immediately after delivery of the infant. Instead a full assessment should be made in accordance with the intraoperative diagnosis recommendations (see next topic). Only if the placenta is removed, either fully or partially, or there is already significant bleeding, should

uterotonics be given (Grade D recommendation).

### **Is there an optimal method for intrapartum clinical diagnosis of AIP?**

No evidence was found for which clinical diagnostic method best correlates with the gold-standard histopathological diagnosis therefore, the IS-AIP recommendation is based on a consensus of experts (level 5 evidence) and is as follows:

The IS-AIP agree with the ACOG recommendation (level 5 evidence) that given the high risk of false positive with all methods of antenatal diagnosis there must be robust intra-partum evidence that there is actually significant AIP before surgical treatment is commenced. Care must be taken however, that major hemorrhage is not caused by inappropriate attempts to manually remove an AIP.

The IS-AIP recommend the following methods for clinically diagnosing AIP:

#### *At Vaginal delivery*

The diagnosis of AIP should not be made if the placenta spontaneously separates and is delivered by maternal effort, controlled cord traction or simple manual removal of an already separated placenta, even if there is a subsequent diagnosis of retained products of conception (RPOC). For the diagnosis of AIP, a manual removal of placenta is required and at the time of manual exploration of the uterine cavity, in the opinion of a senior, experienced obstetrician, no plane of cleavage can be identified between the placenta and the myometrium. This can be for the entire placenta bed or just in 'focal' areas. Major hemorrhage after piecemeal removal, removal of a 'ragged placenta' or discovery of subsequent RPOC is not sufficient to make the diagnosis of AIP (Grade D recommendation).

*At Laparotomy, at stepwise process should be followed:*

Step 1: On opening the abdomen the external surface of the uterus and the pelvis should be thoroughly inspected for frank signs of AIP which include:

- Uterus over the placental bed appears abnormal (can have a vascular, bluish/purple appearance) with obvious distension (a placental 'bulge').

- Placental tissue seen to have invaded through the surface of the uterus. This may or may not have penetrated the serosa. NB Care should be taken not to confuse this with a uterine 'window' which is a uterine scar dehiscence with the placenta visible directly underneath it. If it is a 'window' the surrounding uterine tissue will appear normal.

- Excessive, abnormal neo-vascularity in the lower segment (particularly with vessels running cranio-caudally in the peritoneum).

If these are clearly seen, AIP can be diagnosed confidently without recourse to any further procedures (Grade D recommendation).

Step 2: If these are not seen, then the uterine incision should be made according to the level of suspicion for AIP (see separate topic above). If the incision has been placed such that the placenta is undisturbed, then gentle cord traction should be attempted. If traction on the umbilical cord causes the uterine wall to be visibly pulled inwards in the direction of traction without any separation of the placenta (the 'dimple' sign) and there is apparent contraction of the uterus separate from the placental bed, then AIP can be diagnosed (Grade D recommendation).

Step 3: If AIP has not been diagnosed by the previous 2 steps, then gentle digital exploration can be attempted to assess if there is a plane of cleavage (following

method for diagnosis of AIP described for vaginal delivery). Care must be taken to avoid causing hemorrhage (Grade D recommendation).

In an attempt to assess severity, the IS-AIP use the clinical grading score in Table 2. This grading scale is also recommended by the recently published FIGO guidelines<sup>31</sup>.

**Is expectant management of clinically confirmed AIP effective and does it reduce maternal morbidity when compared to surgical treatment options?**

The 'leaving the placenta in situ' approach, or expectant management, consists of leaving the entire placenta untouched and waiting for its complete resorption. Attempting forcible removal significantly increases blood loss, hysterectomy rates, infection and disseminated intravascular coagulation<sup>32</sup> (level 2b evidence).

Kutuk et al<sup>33</sup> recently published a retrospective cohort study comparing women undergoing hysterectomy without placental removal (n=20), expectant management (n=15), and placental removal with uterus conserving surgery (n=11) (level 2b evidence). Two cases of percreta were planned to be conservative surgery but management was changed to expectant when the surgeons found that the placenta had infiltrated the parametrium and the cervix. There was significantly lower blood loss in the expectantly managed group (400 (250-2500) mL) than in both hysterectomy (2000 (500-3500) mL;  $p < 0.001$ ), and conservative surgery groups (3000 (1100-4000) mL;  $p < 0.001$ ). None of the expectantly managed women received blood products compared with

transfusions of 700 (200–2400) mL packed RBC in the hysterectomy group and 1200 (400–1800) mL in the conservative surgery group. Uterine preservation rates were not significantly different between the expectantly managed women and those having conservative surgery (14/15 [93%] vs 33/37 [89%];  $P>0.99$ ). Most studies use avoidance of hysterectomy as the outcome measure of successful expectant management. The single largest case series of expectant management published to date is a multicenter retrospective study which included 167 cases of AIP in 40 teaching hospitals (level 2b evidence)<sup>34</sup>. The overall success rate of uterine preservation was 78% (95% CI 71–84%), with severe maternal morbidity reported in 10 cases (6%). An empty uterus was obtained spontaneously in 75% of cases with additional hysteroscopic resection and/or curettage performed in 25%. One maternal death occurred as a direct result of methotrexate injection into the umbilical cord. Another smaller study of 36 women managed conservatively reported a success rate of 69%<sup>35</sup> (level 2b evidence). Three reviews of published case series report success rates of 85%<sup>36</sup>, 58%<sup>37</sup> and 60%<sup>38</sup>. Care must be taken interpreting this as these are not independent reviews, many cases are included in all three studies (level 4 evidence).

The IS-AIP recommendation is as follows:

When expectant management is planned and AIP confirmed at delivery, forced manual removal of the placenta should not be attempted (Grade B recommendation).

Expectant management appears to be associated with less blood loss and lower transfusion requirements than both hysterectomy and local resection and will be

successful for between 60% to 93% of women with the remainder undergoing hysterectomy, usually for secondary PPH or infection (Grade B recommendation). Therefore, this is an appropriate management strategy for women wishing to preserve their fertility and in cases where hysterectomy is considered to be at very high risk of surgical complications. If women choose this option they must be appropriately counselled including being informed that there is a 6% risk of severe maternal morbidity (Grade B recommendation).

**If expectant management is undertaken for women with AIP does the use of adjuvant therapies such as methotrexate and pelvic arterial embolization increase efficacy?**

#### *Methotrexate*

No solid evidence supports the use of methotrexate in cases of AIP left in situ. Only case reports and small series with no control groups have been reported therefore it is impossible to assess efficacy. Severe adverse effects such as pancytopenia and nephrotoxicity have been described with methotrexate<sup>34</sup>. One case of maternal death directly related to methotrexate was reported among the 21 patients who received methotrexate in the largest retrospective cohort of 167 women<sup>34</sup> (level 2b evidence).

The IS-AIP recommendation is therefore:

There is no evidence of significant benefit from the use of methotrexate when the placenta left in situ. As there is evidence for potential significant harm, the IS-AIP do not recommend the use of methotrexate for conservative management of AIP (Grade B recommendation).

### *Pelvic arterial embolization*

A systematic review published in 2015, included seven individual studies reporting on 177 cases of uterine artery embolization in women with AIP with planned conservative management<sup>39</sup> (level 2a evidence). Hysterectomy was avoided in 159 of these women (90%). The review did not report maternal morbidity other than to say “all patients survived”.

A retrospective cohort study of 45 patients with AIP compared prophylactic uterine artery embolization to no embolization for women undergoing conservative management<sup>40</sup> (level 2b evidence). No difference was observed in blood loss, hysterectomy rates or incidence of massive transfusion. However, one patient in the embolization group had uterine necrosis requiring hysterectomy.

A retrospective cohort of 12 patients having embolization to assist conservative management reported uterine necrosis requiring hysterectomy in one woman<sup>41</sup> (level 2b evidence). This study was included in the systematic review<sup>39</sup>.

The IS-AIP recommendation is therefore:

There is no evidence for prophylactic uterine artery embolization increasing efficacy of conservative management and two cases of uterine necrosis have been reported in two cohort studies (level 2b evidence). Therefore, the IS-AIP do not recommend prophylactic uterine artery embolization in women undergoing conservative management (Grade B recommendation). However, therapeutic embolization for postpartum hemorrhage in conservatively managed women may avoid hysterectomy (Grade D recommendation).

**Does local surgical resection reduce maternal morbidity in women**

**antenatally diagnosed with AIP when compared to other treatment options including hysterectomy and conservative management?**

Eleven original publications were found that reported on a variety of local resection techniques, seven were retrospective cohort studies, three prospective studies and 1 review. Only one retrospective cohort study<sup>42</sup> (level 2b evidence), compared planned hysterectomy to local resection and found less bleeding in the local resection group measured as packed RBC transfusion (1.1 units compared with 2.2 units;  $P < 0.05$ ). One retrospective cohort study<sup>43</sup> (level 2b evidence), compared a peripartum local resection technique known as the 'Triple-P' procedure to conservative management leaving the placenta partly or entirely in the uterus. Blood loss was lower in the 'Triple-P' group ( $1700 \pm 950\text{mL}$  vs  $2170 \pm 246\text{mL}$ ) but this difference was not statistically significant ( $P = 0.445$ ). The need for emergency peripartum hysterectomy was significantly lower in women undergoing the 'Triple-P' procedure than in the control group (0/19 (0.0%) vs 3/11 (27.3%),  $P = 0.045$ ).

Wei et al<sup>44</sup> published a retrospective, cohort study of 96 patients with histopathologically confirmed AIP who were treated by local resection with ( $n=45$ ) or without ( $n=51$ ) a Foley catheter tied around the lower uterine segment to enhance haemostasis (level 2b evidence). Use of the Foley catheter appeared to reduce blood loss and possibly also the hysterectomy rate (0 vs. 3).

Clausen et al<sup>45</sup> published a retrospective consecutive case series of placenta percreta treated with either hysterectomy or local resection (level 4 evidence). Of the 11 women requesting fertility preservation, nine were successfully treated with local resection with a blood loss of 1,300 to 6,000 mL. The eight women



undergoing hysterectomy had a blood loss of 450 to 16,000 mL. The difference in blood loss between the two treatments, however, does not reflect intention to treat. The one woman who had a 16,000mL blood loss had requested fertility preservation and local resection was attempted initially followed by a hysterectomy as the placenta had invaded into the cervix and parametrium.

Kutuk et al<sup>33</sup> published a retrospective cohort study comparing women undergoing hysterectomy without placental removal (n=20), expectant management (n=15), and women who underwent placental removal and uterine conserving surgery (n=11) (level 2b evidence); see the topic on expectant management for further details.

In all of the other studies the intended surgical procedure was local resection and there was no comparator group 46-51. The success rates for avoiding hysterectomy ranged between 67% and 100%.

In 2014 Clausen et al. published a review of 119 patients with placenta percreta stratified by mode of management<sup>37</sup> (level 4 evidence): 17 cases reported were local resection with no secondary hysterectomies; 36 cases were conservatively managed, of these 3 underwent a planned delayed hysterectomy and 18 had emergency hysterectomies; 66 had primary caesarean hysterectomies. Local resection was reported to be associated with a lower rate of complications including urinary tract injury, secondary hemorrhage and infection. However, there was no information provided regarding how the choice for local resection was made.

The evidence available for the efficacy of local resection is complicated by selection bias and poor comparator groups making interpretation of the results

difficult. However, the IS-AIP recommendation based on the available evidence and supported by consensus opinion, is as follows:

There is no evidence to demonstrate that routine local resection in all cases of AIP reduces maternal morbidity or mortality compared to other treatment methods. However, in appropriately selected cases, local resection appears to be reasonably successful (level 2b evidence) and may reduce blood loss and maternal morbidity compared to hysterectomy (level 2b/4 evidence) and requirement for emergency hysterectomy compared with conservative management (level 3b evidence). However, there is some evidence to suggest that attempting local resection may be detrimental in cases involving invasion into the uterine cervix and/or parametrium (level 4 evidence). Therefore, local resection should only be considered in selected cases where there is no invasion into the parametrium and/or uterine cervix (Grade C recommendation).

The IS-AIP expert consensus of what constitutes an 'appropriate case' for local resection is focal disease with an adherent/invasive area which is <50% of the anterior surface of the uterus (Grade D recommendation). More evidence is required to fully identify which women will most benefit from this management strategy (Grade D recommendation).

**Does performing a sub-total hysterectomy reduce maternal morbidity in women antenatally diagnosed with AIP when compared to total hysterectomy?**

Whilst several studies on AIP reported the actual numbers of sub-total and total hysterectomy performed in their cohorts, no evidence for the benefit of one type

of hysterectomy compared to another was presented. Wright et al<sup>52</sup> reported on 4967 retrospectively collected cases of peripartum hysterectomy performed in the USA (level 3b evidence). AIP was the stated indication for 1789 (36%) of these hysterectomies. No sub-group analysis of the AIP cases was presented. For the overall dataset of all peripartum hysterectomies, total hysterectomy was associated with more bladder injuries (10.2% vs. 7.2%,  $P<0.001$ ), an increased number of other operative injuries (10.4% vs. 8.3%,  $P=0.02$ ), more gastrointestinal complications (7.9% vs. 6.3%,  $P=0.04$ ) and a longer hospital stay ( $P<0.001$ ). Sub-total hysterectomy was associated with more secondary operations (5.0% vs. 3.6%,  $P=0.02$ ), higher rates of transfusions (52.4% vs. 42.7%,  $P<0.001$ ) and a higher perioperative maternal death rate (1.4% vs. 0.8%,  $P=0.04$ ).

Knight et al, on behalf of the UK Obstetric surveillance system (UKOSS), examined all the peripartum hysterectomies occurring in the UK over a 12 month period<sup>53</sup> (level 3b evidence). For the 318 hysterectomies performed there were no significant differences in outcomes between total and subtotal hysterectomy. One hundred and nineteen of the hysterectomies were performed for AIP, these were more commonly total hysterectomies but no sub-group analysis between the two methods was reported.

Another six small retrospective studies were identified (level 3b/4 evidence). Ogunniyi et al reported 32 cases of peripartum hysterectomy<sup>54</sup> and demonstrated that sub-total hysterectomy was associated with higher post-operative morbidity than total (55.6% vs 71.4%;  $p<0.01$ ). Roopnarinesingh et al. reported 52 cases in a single center in Dublin<sup>55</sup>. They found that total

hysterectomy was associated with a significantly higher transfusion rate (12.7 units vs. 9.4units;  $P<0.001$ ). Saeed et al reported on 39 cases from a single center in Pakistan<sup>56</sup> and found that total hysterectomy had a significantly higher number of postoperative complications than sub-total.

D'Arpe et al. reported on 51 cases from a single center in Italy<sup>57</sup>, Daskalakis et al. reported 45 cases from a single center in Athens<sup>58</sup>and Olamijulo et al reported on 34 cases from a single center in Nigeria<sup>59</sup>. No significant differences in morbidity were found in these studies (level 4 evidence).

No information was available in any study regarding how the decision was made regarding the method of hysterectomy. Therefore, the evidence available is highly likely to be complicated by considerable selection bias making interpretation of these results extremely difficult. Therefore, the IS-AIP recommendation is also supported by consensus opinion (level 5 evidence):

There is no evidence to demonstrate that routine sub-total hysterectomy in all cases of AIP reduces maternal morbidity or mortality compared to total hysterectomy, in fact the largest study published suggested that sub-total might be associated with a higher maternal mortality rate (level 3b evidence).

The type of hysterectomy performed therefore, should be individualized on a case by case basis, taking into account the site and degree of invasion both suspected antenatally and found at laparotomy, and the preference of the operating team (Grade C recommendation). In cases with cervical invasion total hysterectomy should be performed (Grade D recommendation).

**Does performing a planned delayed hysterectomy reduce maternal**

**morbidity in women antenatally diagnosed with AIP when compared to hysterectomy at the time of caesarean?**

A planned delayed hysterectomy involves leaving the placenta untouched in the uterus at the time of delivery with the intention of performing a hysterectomy at a later date for example 5 to 6 weeks after the caesarean delivery. Only one retrospective study was identified that attempted to compare planned delayed hysterectomy with immediate hysterectomy<sup>60</sup>. However, all the immediate hysterectomy cases presented as emergencies without antenatal diagnosis and with signs of shock from hemorrhage. The delayed cases were all antenatally diagnosed and underwent delivery in a haemodynamically stable condition (level 4 evidence).

This study was taken into consideration but as it is methodologically flawed, the IS-AIP recommendation is based on a consensus opinion (level 5 evidence) and is as follows:

Given the evidence for the success of expectant management for AIP, the IS-AIP recommend that the surgical choice should be between immediate surgical management (hysterectomy or local resection) and expectant management. There is no evidence of benefit of planned delayed hysterectomy, and the potential complications of performing a second intentional surgical procedure in a stable patient, outweigh the benefits (Grade D recommendation).

**What are the most effective intra-operative measures to treat life-threatening massive hemorrhage in women with AIP should it occur at the time of delivery?**

We found no RCTs providing direct comparison of different intraoperative strategies to reduce blood loss in the event of massive life-threatening hemorrhage.

#### *Pharmacological treatments*

There were no publications that specifically addressed the question of the effectiveness of uterotonics or hemostatic/pro-coagulant agents as life-saving measures to treat massive hemorrhage directly attributable to AIP. Therefore, the IS-AIP recommendation is based on consensus opinion (level 5 evidence) and is as follows:

Uterotonics should be considered in accordance with local protocols whenever massive uterine bleeding occurs until either hemostasis is achieved or the uterus is removed. Hemostatic/pro-coagulant agents can also be used in accordance with local protocols where the surgeon believes they will be of benefit (Grade D recommendation).

The benefit of early administration of tranexamic acid in reducing maternal mortality has been proven in a large multi-centre RCT of PPH from all causes, including AIP<sup>61</sup>(level 1b evidence). Therefore, the IS-AIP recommendation for its use is as follows:

Tranexamic acid should be administered whenever massive hemorrhage occurs, preferably as soon as possible after onset of significant bleeding (Grade A recommendation).

#### *Surgical treatments*

##### *Internal Iliac Artery Ligation*

Four retrospective studies were identified reporting a total of 105 cases of internal iliac artery ligation (IIAL) performed to reduce hemorrhage at deliveries complicated by AIP<sup>62-65</sup>. Three of these were retrospective cases series of women undergoing IIAL with no comparator group (level 4 evidence)<sup>62, 63, 65</sup> and one was a retrospective cohort study comparing outcomes for women with AIP treated with or without IIAL, at the time of delivery (level 4 evidence)<sup>64</sup>. The authors concluded that IIAL did not contribute to a reduction in blood loss however, as the indication for undertaking IIAL was not described, this study is highly likely to be confounded by selection bias. Consequently, it was not possible to appropriately evaluate the efficacy of IIAL for reducing blood loss.

#### *Uterine devascularization*

One retrospective study from Verspyck et al<sup>66</sup> reported immediate and long-term outcomes in six women undergoing surgical uterine devascularization at the time of caesarean followed by conservative management of their AIP. No conclusion can be drawn from this regarding the efficiency of the technique for hemorrhage control but the study demonstrated that uterine devascularization appears to be a reasonably safe technique as long as it is not associated with ovarian artery ligation.

#### *Uterine compression sutures*

Compression sutures after extirpation of placenta were reported in three retrospective studies<sup>67-69</sup> including a total of 47 women. Shahn et al reported 26 cases of had bilateral uterine artery ligation followed by insertion of a B-Lynch suture for major hemorrhage from AIP (level 4 evidence)<sup>67</sup>. Two of the 26 women died. Shazly et al reported a similar case series of seven women with hemorrhage

from AIP who underwent bilateral uterine artery ligation and then multiple compression suturing<sup>68</sup>. The authors reported that the procedure was successful. For both these studies it is impossible to assess the efficacy of compression sutures alone as the treatment also involved arterial ligation. The absence of a control group makes it impossible to assess the efficiency of this technique to reduce blood loss. Hwu et al reported a case series of 14 women who had a vertical compression suture involving both the anterior and posterior uterine walls to control bleeding from the placental bed<sup>69</sup> (level 4 evidence). One of these women was diagnosed with AIP. Again, there was no control group making assessment of efficacy in reducing blood loss impossible.

#### *Balloon tamponade*

One retrospective study<sup>70</sup> compared first-line hysterectomy (17 women) and balloon tamponade (19 women). Women who were assessed to have >50% invasion of the axial plane of the uterus were treated with immediate hysterectomy. The remainder had a balloon tamponade after extirpation of placenta with or without extra square compression sutures to the placental bed. Blood loss and transfusion amounts were significantly lower in the tamponade group ( $p < 0.05$ ) however the selection criteria used brings into question the appropriateness of the two groups. Also, it was not clear if the tamponade was used to prevent or treat hemorrhage. Three retrospective studies looking at treatment for PPH have also reported that the presence of an AIP is associated with a higher failure rate of balloon tamponade<sup>71-73</sup>.

#### *Pelvic Tamponade*

A variety of techniques have been described for pelvic tamponade in the case of



persistent bleeding post-hysterectomy. Ghourab et al<sup>74</sup> described five cases of pelvic packing with 10-12 dry abdominal swabs. Dildy et al<sup>75</sup> described a case series spanning 38 years of pelvic packing using a variety of materials, including pillow cases, gauze sheets, plastic X-ray cassette drapes and orthopedic stockings, filled with gauze rolls. Charoenkwan et al<sup>76</sup> reported a case series of three women treated with pelvic tamponade using a large volume Bakri balloon. There were no maternal deaths in any of the three reports. No comment can be made on which technique provides the most effective tamponade.

In light of the quality and potentially conflicting evidence available, the IS-AIP recommendations for the surgical procedures to be used in case of massive hemorrhage are mostly based on a consensus of experts (level 5 evidence) and are as follows:

If the woman is stable, the bleeding is not imminently life-threatening and a conservative approach was planned (either for maternal request or if hysterectomy is anticipated to be at very high risk of surgical complications), surgical uterine conserving procedures should be attempted before resorting to hysterectomy. The simplest techniques with the lowest complications should be performed first.

If the placenta has been removed, intra-uterine tamponade (e.g. balloon tamponade) should be the first line management. If this fails, or the placenta remains in situ, uterine devascularisation, with or without uterine compressive sutures, should be tried next. Internal iliac artery ligation has the highest risk of post-operative complications and therefore should only be performed if the previous steps have failed to control the bleeding.

If the woman is unstable or the bleeding is life-threatening, treatment must be focussed on the source of the blood loss, this will most often be the placental bed, so emergency hysterectomy should be performed as rapidly as possible. Vascular compression (common iliac arteries or aorta) can be used as a temporary measure to gain time to resuscitate the woman and complete definitive treatment.

In case of persistent pelvic bleeding following hysterectomy, internal iliac artery ligation and/or pelvic tamponade should be considered. Pelvic tamponade should be performed with appropriate, sterile equipment such as large abdominal swabs and broad-spectrum antibiotics given whilst they remain in situ (Grade D recommendation).

### **What is the likelihood of a further pregnancy for women who have had an AIP and successful uterine conservation?**

There are case reports<sup>77-81</sup> (level 4 evidence), case series<sup>46, 68, 82, 83</sup> (level 4 evidence), case-controlled<sup>84</sup> (level 3b evidence) and cohort studies<sup>85-89</sup> (level 2b evidence) which clearly demonstrate preservation of fertility after successful conservative management of AIP. There are however, no prospective or randomized studies.

The largest cohort of 131 women who had successful conservative management of AIP reported that 27 women expressed a desire for a subsequent pregnancy. Of these, 24 women (89%) had 34 spontaneously conceived pregnancies<sup>87</sup>. Another retrospective observational study assessed 46 women who had successful conservative management of AIP<sup>88</sup>, 12 (86%) of the 14 patients

desiring another pregnancy achieved a total of 15 pregnancies. The only other cohort study presenting outcomes for women desiring a subsequent pregnancy, reported five out of six women (83%) achieved a successful pregnancy<sup>85</sup>. These studies included women who had received a multitude of additional treatments including administration of methotrexate, embolization of uterine arteries, pelvic arterial ligation, hysteroscopic resection of retained tissues and segmental excision of the uterus. No study addressed the effect that these different management strategies had on fertility preservation or what degree of placental adherence/invasion each woman had prior to conservative management.

Two of the cohort studies also examined the recurrence rates for AIP. In the largest study<sup>87</sup>, AIP recurred in 6 (29%) of the 21 pregnancies which continued beyond 34 weeks' gestation and was associated with placenta previa in 4 cases. The other study reported that of the nine patients who delivered after 35 weeks' gestation, two had recurrence of placenta accreta (22%)<sup>88</sup>.

There is considerable evidence demonstrating that women who have successful conservative management of AIP may go on to have a successful future pregnancy. What remains unclear is what effect different methods used for conservative management, such as arterial embolization or uterine resection, have on fertility rates and what is impact the original degree of adherence or invasion. The IS-AIP recommend that:

Women wishing to preserve their fertility are counselled that this is possible (Grade B recommendation). If conservative management is successful, the subsequent pregnancy rate is between 86% and 89% (Grade B recommendation). There is no evidence regarding the association of AIP degree

(accreta/increta/percreta) or methods used for conservative management, and successful preservation of fertility.

Women wishing for fertility preservation should be managed by a team with appropriate resources and experience in conservative management according to that team's local protocols (Grade D recommendation). These women should be counselled that their risk of AIP in a subsequent pregnancy is between 22 and 29% (Grade B recommendation).

## **Discussion**

The paucity of robust evidence for the optimal management of this difficult and dangerous condition highlights the urgent need for large, multi-center collaborations. However, until the international community comes to an agreement on robust clinical definitions, diagnostic criteria and stratification of severity for AIP this problem will persist.

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## **Section C – Management (II)**

### **Fetal and maternal outcomes of women with antenatal suspected abnormally invasive placenta according to gestational age at delivery before and after 36 weeks of gestation.**

Morlando M. et al. (submitted, under peer review).

#### **Background**

Placenta accreta is a complication of pregnancy characterized by an abnormal adherence of the placenta to the uterine wall, secondary to a defect in the decidua basalis (1). When the placenta invades the myometrium, the term placenta increta is used, whereas placenta percreta refers to a placenta that has invaded through the myometrium and serosa, sometimes into adjacent organs. The term abnormally invasive placenta (AIP) is often used to describe all of these conditions. The reported incidence of abnormal placentation is highly variable, ranging from 1:93,000 to 1:111 pregnancies (2) The incidence of abnormal placentation is increasing, most likely related to increasing rate of cesarean delivery, one of the most important risk factor for AIP (3,4). The optimal gestational age at delivery for stable women with suspected AIP is still subject of debate (5-10). Choosing the timing of delivery is critical in terms of limiting both maternal and neonatal risk. Several studies have suggested the benefits of planned delivery in the reduction of maternal morbidity. An early delivery can be beneficial as it allows to arrange a multidisciplinary team and to avoid an

emergency delivery because of bleeding or labour. In addition to this, the difficulty of performing a caesarean hysterectomy in the presence of invasive placentation can be higher with advancing gestational age. However, as scheduled delivery often means delivery of a premature infant, all the risks related to iatrogenic prematurity must be taken into account. The American College of Obstetricians and Gynecologists (ACOG) recommends that the timing of delivery should be individualized but also that combined maternal and neonatal outcomes are optimized in stable patients with delivery at 34-35 weeks without amniocentesis (7). The Society for Maternal-Fetal Medicine (SMFM) also emphasize that delivery should be individualized due to the lack of randomized trial and of large observational studies (8). On the other side, the Royal College of Obstetricians and Gynaecologists (RCOG) recommends delivery for asymptomatic and stable women at 35+0 to 36+6 (9). The aim of this study is to compare maternal and fetal outcomes of women with confirmed AIP delivered before and after 36 weeks of gestation.

### **Material and methods**

This was a prospective cohort study. All consecutive pregnancies at risk of AIP because of persistent placenta previa in the setting of prior cesarean delivery who delivered at the University of Naples Federico II (Naples, Italy) from January 2006 to September 2018 were collected prospectively in a dedicated database. For this study, pregnancies with different degrees of invasive placentation, diagnosis of accreta, increta, or percreta were considered under the umbrella term of AIP. All women with placenta previa identified in the second trimester had a follow-up

ultrasound at 32-34 weeks. Only those with prior cesarean delivery in whom the placenta reached the level of the internal cervical os at the last ultrasound examination in the third trimester were considered as women with persistent placenta previa in the setting of prior cesarean delivery and therefore at risk of AIP. All women underwent transvaginal ultrasound exam. In most cases prenatal magnetic resonance imaging was requested to better define the risk of AIP (MRI). Women were considered with suspected AIP in case of diagnosis of AIP using prenatal MRI (11), or transvaginal ultrasound (12). Women were included only if AIP was confirmed either by intraoperative confirmation or by histopathology report on a hysterectomy specimen. Ultrasound diagnosis of AIP was made by using the standardized ultrasound descriptors for AIP by the European Working Group on Abnormally Invasive Placenta (EW-AIP), of which our center (University of Naples Federico II) is part of (12). The timing of delivery was defined according to the individual patient risk of based on anamnestic data, ultrasound and MRI signs. Reasons for earlier delivery included history of vaginal bleeding and spontaneous onset of labor. Cesarean delivery was planned without any attempt to remove the placenta. In cases with macroscopic evidence of uterine infiltration at the abdominal entry a cesarean hysterectomy was instantly performed. In all other cases hysterectomy was performed when no evidence of placental detachment, or heavy continued bleeding from the implantation site of a well-contracted uterus after difficult removal of the placenta were noticed. Maternal baseline characteristics examined were: maternal age, body mass index (BMI), smoke, number of prior cesarean deliveries, number of prior uterine curettages. Maternal outcome measures included: the overall length of stay, the



post-operative length of stay, the haemoglobin loss after caesarean section/hysterectomy, the need for blood transfusions, the total amount of blood and blood products transfused, the occurrence of any post-operative complication, the classification of the degree of AIP.

Neonatal outcomes measures included: birthweight, Apgar score at 1 and 5 minutes, umbilical cord pH, admission to neonatal intensive care unit (NICU), antenatal administration of corticosteroids (CCS). Outcomes were compared in cohort of women who were delivered before and after 36+0 weeks of gestation.

### *Statistical analysis*

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v. 20.0 (IBM Inc., Armonk, NY, USA). Data are shown as means  $\pm$  standard deviation (SD), or as number (percentage). Univariate comparisons of dichotomous data were performed with the use of the chi-square or Fisher exact test. Comparisons between groups were performed with the use of the T-test for continuous variables. Logistic regression, presented as unadjusted odds ratio (crude OR) or adjusted odds ratio (aOR) with the 95% of confidence interval (CI) was performed. We calculated two sided p-values. A p-value  $<0.05$  was considered to indicate statistical significance.

### **Results**

60 women were included in the present study. In 57 women (95%) AIP was suspected on the basis of the ultrasound examination. MRI was performed in 47 women (78%) and the presence of AIP signs was confirmed in 24 (53%) cases.

Only one woman with negative ultrasound was classified as being at high risk for AIP following the MRI. Two women with no antenatal suspicion of AIP, were included in the present study as they showed intraoperative findings of AIP at the time of delivery. On the basis of anamnestic data, ultrasound and MRI, 32 women (53%) were delivered before 36+0 weeks of gestation, while 28 (47%) were delivered at later gestations. Diagnosis was confirmed by intraoperative findings alone in 16 (27%) cases and by intraoperative findings and histopathology exam in 44 (73%) cases. All the women included in the present study underwent hysterectomy at the time of delivery, due to macroscopic evidence of uterine infiltration at the abdominal entry, no evidence of placental detachment, or massive bleeding. Table 1 shows the characteristics of the women delivered before and after 36+0 weeks of gestation. The two groups were similar in terms of maternal demographic characteristics, except for the number of prior caesarean sections, which was higher in the group of women who were delivered earlier (<36 weeks group) compared to those who were delivered later ( $\geq 36$  weeks group). Maternal outcomes were not different among women delivered before and after 36 weeks of gestation. There were no differences in post-operative haemoglobin drop, total and post-operative length of admission, rates of women transfused, number of blood products transfused, and in surgical complications. There were no differences in the severity of invasion of AIP among the 2 groups (table 2). As expected, fetuses delivered <36 weeks had lower birthweights (2216 gr vs 2875 gr,  $p < 0.0001$ ) and higher rates of NICU admission (50% vs 20%,  $p = 0.032$ ), compared to fetuses delivered at  $\geq 36$  weeks. Five minutes Apgar scores were also significantly lower in fetuses delivered <36

weeks (7,69 vs 8,36,  $p= 0,029$ ). After adjusting for the number of prior caesarean sections, differences in birthweight (aOR 1,86 - 95%CI 1,27 - 2,72) and 5 minutes Apgar score (aOR 7,98 - 95%CI 1,20 - 52,95) remained significant among infants delivered before and after 36+0 weeks. Umbilical cord pH, 1 minute Apgar scores and rates of antenatal corticosteroids administration were not different in the 2 groups (table 3).

## **Discussion**

In our population of women with AIP, delivery before 36 weeks is not associated with any improvement in maternal outcome in terms of post-operative haemoglobin drop, total and post-operative length of admission, need for transfusions, number of blood products transfused, and surgical complications. On a neonatal perspective, delivery before 36 weeks was associated with lower birthweights and lower Apgar scores at 5 minutes.

AIP is a major contributor to maternal morbidity and mortality in many countries (13-15). The optimal management regimen has yet to be defined because of the paucity of outcome data in the literature and the lack of randomized controlled trials. Choosing the timing of delivery is critical in terms of limiting both maternal and neonatal risk. An earlier delivery can be beneficial as it allows to arrange a multidisciplinary team and to avoid an emergency delivery because of bleeding or labour. In addition to this, the difficulty of performing a caesarean hysterectomy in the presence of invasive placentation can be higher with advancing gestational age. On the other side, a planned delivery at earlier gestations is associated with

a rise in all the risks related to iatrogenic prematurity for the neonate (16,17). Our data showed that delivery at earlier gestations did not reduce the maternal morbidity rate, but it was associated with the delivery of smaller infants with lower 5 minutes Apgar scores.

Prematurity is now the second leading cause of death in children under-5 years and the single most important direct cause of death in the critical first month of life. For the babies who survive, many face a greater risks of serious health problems, including cerebral palsy, intellectual impairment, chronic lung disease and vision and hearing loss (16). There is a well-recognized gradient of increasing risk of mortality and adverse developmental outcomes with decreasing gestational age at birth from early term (37–38 weeks) through to the most premature survivors. The 5% of those born at 32–36 weeks who survive the neonatal period are estimated to have some degree of long-term impairment, but this includes 85% of all preterm births, and hence, their contribution to the overall morbidity is substantial (17).

There are currently no RCTs or well-controlled observational studies to guide best practice in delivery timing of women with a diagnosis of AIP. In cases of suspected AIP, where significant blood loss and caesarean hysterectomy is anticipated, delivery at between 34 and 35 weeks of gestation has been proposed in order to avoid emergency delivery. A 2010 decision analysis supports this approach based on the increasing likelihood of emergency delivery as pregnancy goes beyond 34 weeks of gestation (6). Some recent retrospective cohort studies of women diagnosed prenatally with AIP have indicated that in the absence of

risk factors for preterm delivery, it is safe to plan the delivery at 36 weeks of gestation. In the first study the authors showed that as gestational age increased, the likelihood of vaginal bleeding necessitating urgent delivery decreased, and that the estimated blood loss at delivery was not greater among women delivered urgently for bleeding compared with those who underwent a scheduled delivery (5). This was similar to our findings, as we did not demonstrate a higher rate of maternal haemorrhagic complications in women delivered at later gestations. Another study of 84 women who had reached 34+0 weeks of gestation with a suspected praevia accreta found that those with no risk factors for preterm birth are at low risk for an unscheduled delivery prior to 36 weeks of gestation. The authors conclude that individual risk stratification is an essential component of the delivery planning in order to avoid unnecessary fetal prematurity (18). Concerning the fetal outcome in women with AIP the available studies reporting on this are limited. One study reporting on fetal outcome at different gestational ages at delivery in women with AIP was a retrospective one on 67 pregnancies. The incidence of neonatal complications (respiratory distress syndrome, anemia of prematurity, transient tachypnea of the newborn, cerebral hemorrhage, hypoglycemia, and apnea) was similar at each of the gestational ages investigated, with a decline in the rate of complications only at 36 weeks (19). These results are similar to our findings of a lower birthweight and lower Apgar score at 5 minutes in neonates delivered at < 36 weeks. An additional consideration is that the positive predictive value for radiographically-suspected AIP is not 100%, therefore unnecessary prematurity based on a false-positive diagnosis needs to be considered as a risk of early delivery timing (11).

From the analysis of the baseline characteristics of the included women, we found that in the <36 weeks group the number of previous sections was significantly higher. The number of previous sections is the main risk factor for AIP, and it is associated with a significant increase in the risk of AIP in women with a placenta previa (4, 20). The anamnestic data of a higher number of previous sections, in addition to the ultrasound and MRI features, might have led the attending clinicians to classify the women as being at higher risk and therefore to schedule them to an earlier delivery. This might have determined a selection of the most severe cases in the <36 weeks group. However, the analysis of the degree of invasion of AIP, did not show a difference in the rates of the most severe types of AIP in the group of women delivered earlier. At the same time, the management did not differ among the two groups, as all the included women underwent caesarean hysterectomy.

Our study has several strengths. The main strength is the prospective design, covering a wide period of time of 12 years. The population studied is characterised by a high caesarean section rate (approximately 60%) with a relatively high prevalence of AIP (4). Despite this, we acknowledge that some outcomes were underpowered and that the sample size might have limited to reach statistical significance for some measures of interest. One more limitation of our study is that this a non-randomized comparison.

This poses the attention on the need for larger multicentre studies on delivery timing for AIP, with well-defined protocols for the diagnosis and the management of this condition. Future research should also aim at improving the prediction of

maternal morbidity, including specific anamnestic and ultrasound findings, which may be useful to obtain a delivery planning individualized for the single woman. With this purpose our centre is part of the International Society for Abnormally Invasive Placenta (IS-AIP - <http://www.is-aip.org>), aimed at enhancing the understanding of the pathophysiology, diagnosis and management of AIP with a view of improving outcomes for women worldwide.

We conclude that delayed delivery at  $\geq 36$  weeks of gestation for women with AIP may help to reduce unnecessary neonatal risks of prematurity and may ensure a similar rate of morbidity for the mother. Efforts should be made to restrict the earliest AIP deliveries to situations with clear benefits. Further research is needed to reach individualized care that will provide the optimal delivery plan for women with AIP to optimize both maternal and neonatal outcomes.

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**TABLE 1: Maternal baseline characteristics.**

Data are presented as number (percentage %), or as mean (standard deviation). Boldface data, statistically significant. BMI, body mass index.

	<b>&lt; 36 weeks</b>	<b>≥ 36 weeks</b>	<b>p-value</b>
<b>Age</b>	34,31 (4,23)	34,43 (5,34)	0,927
<b>BMI</b>	27,33 (7,60)	29,68 (4,75)	0,153
<b>Smokers</b>	8 (25%)	7 (25%)	1
<b>Prior cesarean deliveries</b>	<b>2,34 (1,18)</b>	<b>1,64 (0,68)</b>	<b>0,006</b>
1	6 (19%)	11 (39%)	
2	17 (53%)	15 (54%)	
3 or more	9 (28%)	2 (7%)	
<b>Prior uterine curettage</b>	0,81 (0,93)	0,80 (1,45)	0,8

**TABLE 2: Maternal outcomes.**

Data are presented as number (percentage %), or as mean (standard deviation). Boldface data, statistically significant. ICU, intensive care unit.

	<b>&lt; 36 weeks</b>	<b>≥ 36 weeks</b>	<b>p-value</b>
<b>Overall length of stay (days)</b>	23,19 (15,34)	18 (10,09)	<i>0,133</i>
<b>Post-operative stay (days)</b>	11,06 (6,07)	10,46 (5,77)	<i>0,698</i>
<b>Hemoglobin loss</b>	2,94 (1,32)	2,82 (1,79)	<i>0,774</i>
<b>Need for transfusion</b>	25 (78%)	21 (75%)	<i>1</i>
<b>Total units transfused</b>	6,31 (7,2)	4,54 (4,82)	<i>0,261</i>
Red blood cells (units)	3,44 (3,69)	2,79 (2,35)	<i>0,412</i>
Fresh frozen plasma (units)	2,94 (3,98)	1,75 (2,86)	<i>0,186</i>
<b>Maternal complications</b>	13 (40%)	9 (32%)	<i>0,595</i>
Bladder injury	6 (18,8%)	7 (25%)	
Injury to other organs	2 (6,2%)	2 (7,1%)	
ICU admission	7 (21,9%)	4 (13,4%)	
Need for re-intervention	1 (3,1%)	2 (7,1%)	
Other severe complications	2 (6,2%)	3 (10,7%)	
Maternal death	1 (3,1%)	0	
<b>Hystological diagnosis</b>			<i>0,864</i>
Previa	9 (28%)	7 (25%)	
Accreta	8 (25%)	9 (32,1%)	
Increta	7 (21,9%)	7 (25%)	
Percreta	8 (25%)	5 (17,9%)	

**TABLE 3: Fetal outcomes.**

Data are presented as number (percentage %), or as mean (standard deviation). Boldface data, statistically significant. NICU, intensive care unit. CCS, corticosteroids. \*Adjusted for prior caesarean section (Table 1).

	< 36 weeks	≥ 36 weeks	crude OR (95% CI)	aOR (95% CI)*	<i>p</i>
<b>Birthweight (decagrams)</b>	<b>22,16 (4,57)</b>	<b>28,75 (3,82)</b>	<b>1,69 (1,26 - 2,26)</b>	<b>1,86 (1,27 - 2,72)</b>	<b>0,000</b>
<b>Apgar 1 min</b>	6,19 (1,89)	6,82 (1,36)	1,28 (0,91 - 1,79)	0,46 (0,18 - 1,16)	0,139
<b>Apgar 5 min</b>	<b>7,69 (1,49)</b>	<b>8,36 (0,73)</b>	<b>2,06 (1,05 - 4,07)</b>	<b>7,98 (1,20 - 52,95)</b>	<b>0,029</b>
<b>PH</b>	7,33 (0,04)	7,33 (0,05)	0,00 (0,00 - .)	0,00 (0,00 - .)	0,568
<b>NICU</b>	<b>16 (50%)</b>	<b>6 (20%)</b>	<b>0,27 (0,09 - 0,85)</b>	1,19 (0,15 - 9,35)	<b>0,032</b>
<b>Antenatal CCS</b>	26 (81%)	20 (71%)	0,58 (0,17 - 1,93)	0,44 (0,05 - 3,64)	0,54