



## Lower uterine segment placental thickness in women with abnormally invasive placenta

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Figure 2. Measurement of maximum placental thickness in the lower segment in a typical case with normal placentation.

Upper border of the urinary bladder marks the limit of the lower uterine segment. Note the absence of other ultrasound signs of AIP.

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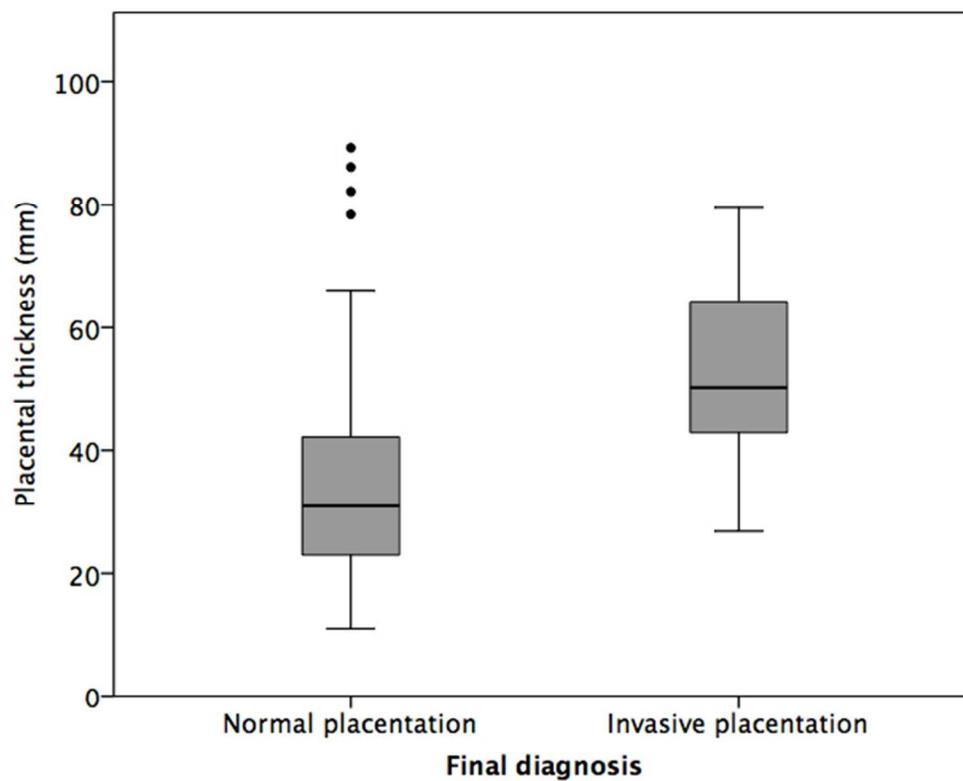


Figure 3. Maximum placental thickness in the lower segment in women with and without morbidly adherent placentation.

Box represents the median, 1st and 3rd quartiles.

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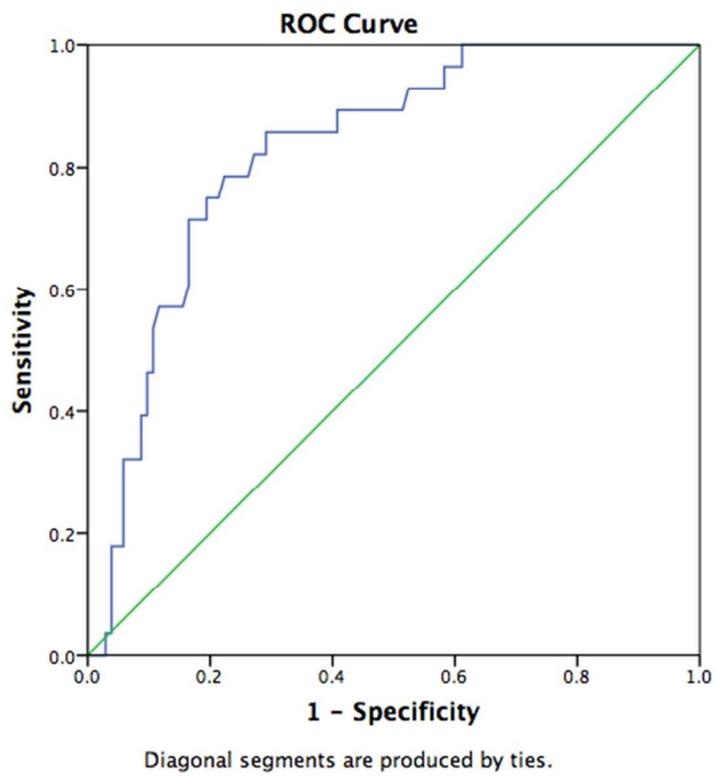


Figure 4. Receiver operating characteristic (ROC) curve of lower segment placental thickness and morbidly adherent placentation.

The area under the curve = 0.826 (95% CI: 0.749 to 0.904).

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**Lower uterine segment placental thickness in women with ~~morbidly adherent~~abnormally  
invasive placenta**

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**Running headline:** Placental thickness and ~~morbidly adherent~~abnormally invasive placenta

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Medicine in Dallas, January 29 – February 3, 2018.

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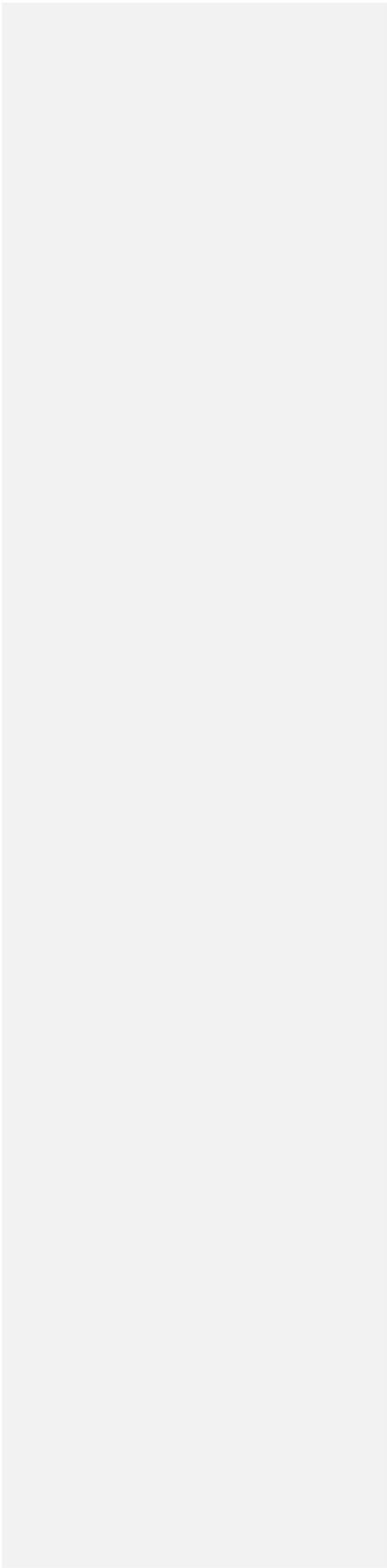
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**ABBREVIATIONS**

~~MAP-AIP – Morbidly adherent~~Abnormally invasive placenta  
SGA – Small for gestational age

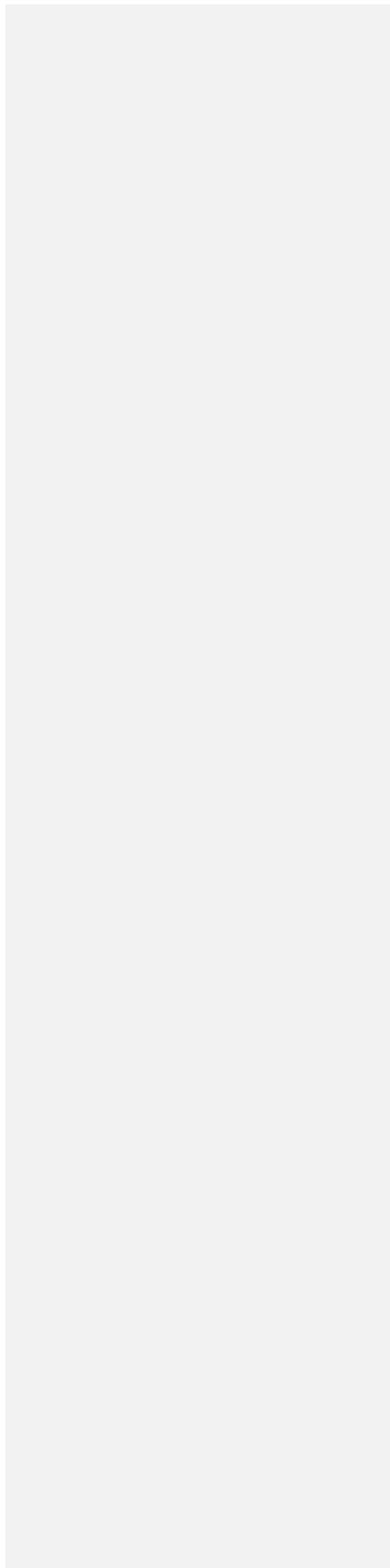
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**Conflicts of Interest notification:** The authors report no conflict of interest.

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**ABSTRACT**

**Introduction:** Ultrasound signs of abnormal placental invasion are subjective in nature. We tested the hypothesis that placental thickness in the lower uterine segment is increased when there is ~~morbidly adherent~~Abnormally invasive placenta (MAIP) in women with a low-lying placenta.

**Material and methods:** Retrospective analysis of data of placental thickness in women with ultrasound evidence of major placenta previa or a low-lying anterior placenta. The diagnosis of MAPAIP was confirmed both intraoperatively and on histopathology for those managed by partial myometrial excision with uterine conservation or by hysterectomy.

**Results:** One hundred and thirty-one records were available for analysis after exclusion of 33 cases due to unsuitable images and 8 cases without pregnancy outcomes. The diagnosis of MAPAIP was confirmed in 28 (21.4%) of the 131 cases. The lower segment placental thickness was significantly higher in women with MAPAIP (median=50.3mm, IQR: 42.7 to 64.3) compared to those with normal placentation (median=30.9mm, IQR: 22.9 to 42.2,  $p<0.001$ ). Logistic regression analysis showed that previous Caesarean section and placental thickness on ultrasound were independent predictors for MAPAIP.

**Conclusion:** Lower uterine segment placental thickness is increased in women with MAPAIP compared to those with non-invasive placentation. This association constitutes a pragmatic objective sign and may be of clinical value in improving prenatal detection of MAPAIP in women with placental implantation in the lower uterine segment. Prospective studies are necessary to ascertain lower segment placental thickness as a predictor for MAPAIP.

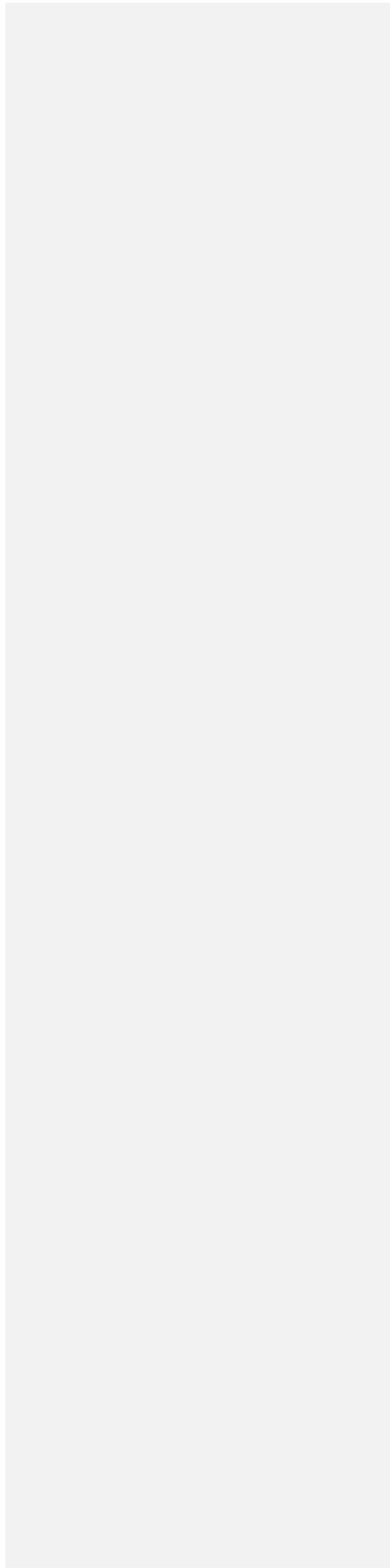
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**Key words:** Placenta accreta, Ultrasound, Placental thickness, Abnormal invasive placenta~~Morbidly adherent placenta, Abnormal invasive placentation~~

**Key message:** Placental thickness in the lower uterine segment is significantly greater in women with ~~morbidly adherent~~abnormally invasive placenta as compared to those with normal placentation. This is a useful objective sign to improve prenatal detection of abnormal placental invasion.

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## INTRODUCTION

~~Abnormally invasive~~~~Morbidly adherent~~ placenta (~~MAPAIP~~), also sometimes termed as Abnormally invasive placentation (AIP) is an uncommon complication, but is associated with serious maternal morbidity and mortality(1, 2). The incidence of ~~MAPAIP~~ appears to be increasing, with the rising rate of Caesarean section birth thought to be a major predisposing factor to this complication(3). Prenatal diagnosis of ~~MAPAIP~~ has been shown to reduce maternal morbidity associated with this condition, most likely due to the opportunity to plan management in advance(4). Ultrasound is the primary investigation for prenatal diagnosis of morbidly adherent placenta, and the diagnostic accuracy is good both in retrospective, as well as prospective case series(5, 6). Nevertheless, many markers of invasive placentation are subjective in nature. Objective markers are likely to improve reproducibility.

Antenatal diagnostic signs of morbidly adherent placenta are best described in the cohort of women with previous Caesarean birth and anterior low-lying placenta/placenta previa(6). Implantation of the placenta in the Caesarean scar is considered the most likely etiology of ~~MAPAIP~~ with placenta previa. Indeed, there is a growing body of evidence suggesting that a vast proportion of Caesarean scar pregnancies progress to ~~MAPAIP~~ in the absence of medical intervention(7-9). Presence of placental lacunae on ultrasound is a reliable sign of ~~MAPAIP~~(10, 11), and is thought to occur because defective placentation from high velocity jets of maternal blood into the placental sinuses.

With placental implantation into the Caesarean section scar, the center of the placental disc would be in the vicinity of the lower uterine scar. On the other hand, if placental implantation was near the scar but not in it, only the thinner placental margin may encroach into the lower uterine segment. We therefore hypothesized that the placenta is thicker with ~~MAPAIP~~ in women with a low-lying placenta or placenta previa.

## MATERIALS AND METHODS

We searched the computerized database of the Obstetric ultrasound unit to identify all women with a third trimester diagnosis of complete placenta previa or anterior low-lying placenta. Placenta was defined as low lying if the leading placental edge was within 20 mm from the internal os(12). The lower uterine segment was identified as the part of the uterus between the cervix and the top of the urinary bladder(13). The maximum placental

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6 thickness in the lower uterine segment was measured on stored digital images (Figure 1). 2-  
7 D images obtained using trans-abdominal ultrasound scan were used. For the image to be  
8 deemed suitable, a midline sagittal section of the lower uterine segment (with the  
9 implanted placenta) and the cervical canal, with the intervening urinary bladder was  
10 required. The measurement was performed by a researcher (AL) blinded to the final  
11 diagnosis. When there was more than one third trimester ultrasound examination  
12 performed, the one when the patient was first seen for ultrasound scan, was selected for  
13 image retrieval. The largest measurement was included if more than one digital images  
14 were stored. Basic demographic and pregnancy information, including gestational age was  
15 also retrieved. We retrieved information regarding morbidity associated with the surgical  
16 procedure, and use and volume of transfusion of blood products. The diagnosis of morbidly  
17 adherent placentation was based on intra-operative findings and histopathological  
18 examination of the surgical specimen when available. Written confirmation was obtained  
19 from the ethics committee that a formal approval was not necessary to analyze routinely  
20 collected data retrospectively.  
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30 Distribution of data was tested for normality with Kolmogorov Smirnov test. Accordingly,  
31 appropriate tests were used to compare data from women with or without invasive  
32 placentation. Chi squared test was used for comparing proportions, and Spearman's rho to  
33 test the correlation between gestational age at ultrasound and placental thickness. In order  
34 to control for the effect of gestational age, we conducted a logistic regression analysis using  
35 gestational age at ultrasound, placental thickness and previous Caesarean delivery as  
36 covariates. Maternal demographics in excluded cases were compared with the study  
37 dataset to explore if there were systematic differences between the two. Statistical Package  
38 for Social Sciences (SPSS) version 20 (IBM Corp, 2011) was used for all statistical analysis.  
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44 Statistical significance was set at  $p < 0.05$ .  
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47 [Ethical approval: National guidance in the UK mandates that formal ethics approval is not](http://www.hra-decisiontools.org.uk/research/docs/DefiningResearchTable_Oct2017-1.pdf)  
48 [necessary for retrospective analysis of de-identified patient data \(http://www.hra-](http://www.hra-decisiontools.org.uk/research/docs/DefiningResearchTable_Oct2017-1.pdf)  
49 [decisiontools.org.uk/research/docs/DefiningResearchTable\\_Oct2017-1.pdf\).](http://www.hra-decisiontools.org.uk/research/docs/DefiningResearchTable_Oct2017-1.pdf)

## 50 RESULTS

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6 The pregnancy records of 172 women were identified and recovered. 41 records were  
7 excluded because either stored images were unsuitable (n=33) or outcome of pregnancy  
8 was not available (n=8), leaving complete data from 131 records available for analysis. Of  
9 these 131 women 28 (21.3%) had abnormally invasive placenta. The mean maternal age,  
10 height, booking weight, body mass index was no different in women with or without MAP  
11 AIP (Table 1). All women with AIP were parous and all but one woman (96%) had given birth  
12 previously by Caesarean section, compared to 33 (33%) with normal placentation ( $p <$   
13  $0.001$ ).

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18 The maximum lower segment placental thickness was significantly greater in women with  
19 MAPAIP as compared to those without ( $p < 0.001$ , Table 1, Figure 2). Figure 3 shows receiver  
20 operating characteristic (ROC) curve for the prediction of MAPAIP by lower segment  
21 placental thickness, with an area under the curve of 0.826 (AUC 95% CI: 0.749 to 0.904).

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24 Details of the pregnancy outcome are shown in Table 2. Gestational age at delivery was  
25 significantly earlier in women with MAPAIP. Although the median birthweight was  
26 significantly lower in women with MAPAIP, it was due to earlier delivery since the  
27 birthweight centiles were no different (Table 2). As expected, the median blood loss and use  
28 of blood products were significantly higher in women with invasive placentation.

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32 The gestational age at which the ultrasound examination was performed at which placental  
33 thickness measured was no different in the two groups. A significant correlation was found  
34 between gestational age at ultrasound and maximum placental thickness (spearman's  $\rho =$   
35  $-0.188$ ,  $p = 0.031$ ). Logistic regression analysis showed that only previous Caesarean birth  
36 and placental thickness, but not gestational age at ultrasound, were independent predictors  
37 for MAPAIP (Table 3). For each millimeter increase in placental thickness above the  
38 expected normal median, the odds for MAPAIP increased 1.051 (95% CI: 1.018 to 1.085).  
39 Prior Caesarean birth considerably increased the odds for invasive placentation by 40-fold  
40 (Table 3).

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45 Excluded cases were significantly younger, and were less likely to have undergone a  
46 previous Caesarean section. Maternal height, BMI, parity, mode of conception, smoking  
47 status and gestational age at the ultrasound scan were no different between the two groups  
48 (data not shown). There were no cases of MAPAIP in cases with unsuitable images, and the  
49 gestational age at delivery was no different from that of the study group.  
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## DISCUSSION

The results of the study show that, in women with a low-lying placenta/placenta previa, the maximum placental thickness is significantly higher in the presence of MAPAIP compared to normal placentation. These findings support the hypothesis that scar implantation is a likely etiological factor for the development of MAPAIP. The strength of the association seen suggests that there is significant predictive value for the prospective identification of MAPAIP in these women.

Antenatal detection is particularly important in cases of clinically relevant MAPAIP(14). Indeed, in the current study, average blood loss was 1700mls in women with MAPAIP and 11/28 (40%) needed transfusion of blood products despite the use of intra-arterial occlusive devices. The frequency of need for blood products in those with low anterior placenta or placenta previa where the placenta was not morbidly adherent was lower (20%). Previous reports have shown that the accuracy of ultrasound for the prenatal detection of MAPAIP is high, but not diagnostic(5, 6, 10). This is likely because many of the ultrasound markers are subjective, relying on visual appearances rather than objective ultrasound measurement. The findings of this study, that a mean difference of 20mm in placental thickness between MAPAIP and normal placentation confers an odds ratio of 20 for MAPAIP, suggests the potential for the use of this marker. Further, prospective, studies are needed to assess whether this could be a good first line screening tool for referral of women with low placenta for expert assessment. The combination of such an objective ultrasound measure, together with the history of previous Caesarean birth, may well provide improved antenatal detection of MAPAIP in the future.

Maximum placental thickness increases with gestational age, with a thickness in excess of 50mm between 32 and 34 weeks' gestation being above the 90<sup>th</sup> centile(15). It is interesting to note that 12 of the 28 (42%) women with MAPAIP showed an abnormally thick placenta at this stage, where the expected number with this thickness would have been three (10%).

Why the prevalence of abnormally thick placenta is higher in women with MAPAIP is uncertain, but this may be due to positioning or implantation of the placenta in the

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Caesarean scar, thereby limiting migration of the placenta. This may result in a mushroom-like thickening of the placenta out of the scar defect rather than the usual pancake-like spread of the placenta over the uterine mucosa. It has been reported that lateral growth of the placenta occurs by trophoblast cell invasion of the decidual veins(16). The Cesarean scar tissue is avascular and lacks decidua. This may explain why the placenta is thicker in the lower uterine segment in women with morbidly adherent placenta.

In an earlier publication, excessively thick placenta was associated with a higher proportion of small for gestational age (SGA) babies(15). The prevalence of SGA fetuses in the current study was not unusually high, and no significant differences were seen between the birthweight centiles of cases with and without invasive placentation. This may be because the area of defective placentation is localised, and the rest of the placenta is able to function normally, compensating for the defective part of the morbidly adherent placenta.

The study is retrospective, and therefore placental thickness was not measured prospectively. This means that thickness was measured only on stored 2-D images, which may not have been representative of maximal placental thickness. However, the presence of other ultrasound signs suggestive of MAPAIP is unlikely to have influenced measurement of placental thickness, as operators were not cognizant of the potential importance of placental thickness at the time. ~~The retrospective nature of the study means that thickness was measured only on stored 2-D images, which may not have been representative of maximal placental thickness in the lower segment.~~ It is important to acknowledge that suitable images to assess placental thickness were not available in 33 women. Suitable images may not have been found if the placenta was not implanted in the anterior lower uterine segment. A vast majority of MAPAIP are thought to be related to a defect in the Caesarean section scar. This scar is expected to be on the anterior lower uterine segment. It is interesting that MAPAIP was not seen in any of these 33 women from whom suitable images were not available. This sign may not work for MAPAIP extending in the parametrium. Finally, the preliminary findings should be examined in prospective studies with specific reference to the sensitivity and specificity for AIP.

In conclusion, lower uterine segment placental thickness is increased in low-lying placentae of women with MAPAIP compared to those with non-invasive placentation in this

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6 retrospective study, however, there is overlap in the two groups. This simple and pragmatic  
7 sign may be of clinical value in improving prenatal detection MAPAIP in women with  
8 placental implantation in the lower uterine segment. Prospective studies are necessary to  
9 ascertain the screening performance of placental thickness for MAPAIP.  
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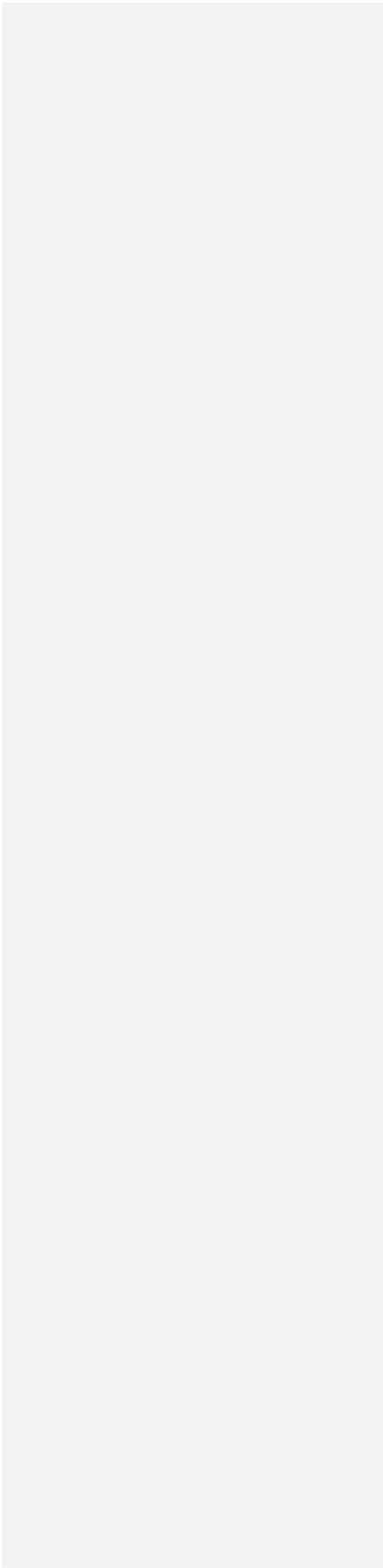
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**FIGURE LEGENDS**

**Figure 1:** Measurement of maximum placental thickness in the lower segment in a typical case with ~~morbidly adherent~~abnormally invasive placenta.

The placental thickness is significantly increased. Note also the presence of lacunae in the placenta.

**Figure 2:** Measurement of maximum placental thickness in the lower segment in a typical case with normal placentation.

Upper border of the urinary bladder marks the limit of the lower uterine segment. Note the absence of other ultrasound signs of MAPAIP.

**Figure 3.** Maximum placental thickness in the lower segment in women with and without morbidly adherent placentation.

Box represents the median, 1<sup>st</sup> and 3<sup>rd</sup> quartiles.

**Figure 4.** Receiver operating characteristic (ROC) curve of lower segment placental thickness and morbidly adherent placentation.

The area under the curve = 0.826 (95% CI: 0.749 to 0.904).

**Table 1** Baseline characteristics of the study population

Parameter	Morbidly adherent	Normal	Significance
	placenta-tion	placenta-tion	
	n = 28	n = 103	
Maternal age in years, Median (IQR)	36 (32.5 – 39.8)	34 (32.0 – 38.0)	0.507
Maternal height in cm, Mean(SD)	161.5 (5.6)	162.6 (6.4)	0.315
Maternal weight in Kg, Median (IQR)	68 (61.8 – 80.2)	67 (60.3 – 75.0)	0.431
Maternal BMI, Mean (SD)	27.4 (5.7)	26.1 (5.5)	0.166
Nulliparity (n)	0	14	<b>0.03*</b>
Smoker (n)	3	6	0.07*
IVF/ICI conception (n)	0	6	<b>0.037*</b>
Previous Caesarean delivery	27	33	<b>&lt;0.001*</b>
Gestational age at ultrasound in weeks, Median (IQR)	34.5 (31.0 – 36.1)	35.6 (32.9 – 36.6)	0.137
Mean booking Hb in gm/L (SD)	115 (13)	118 (11)	0.238
Lower segment placental thickness in mm, Median (Range(IQR))	50.3 (42.7 – 64.3) 26.8 – 79.5)	30.9 (10.9) 22.9 – 89.2) 42.2)	<b>&lt;0.001</b>

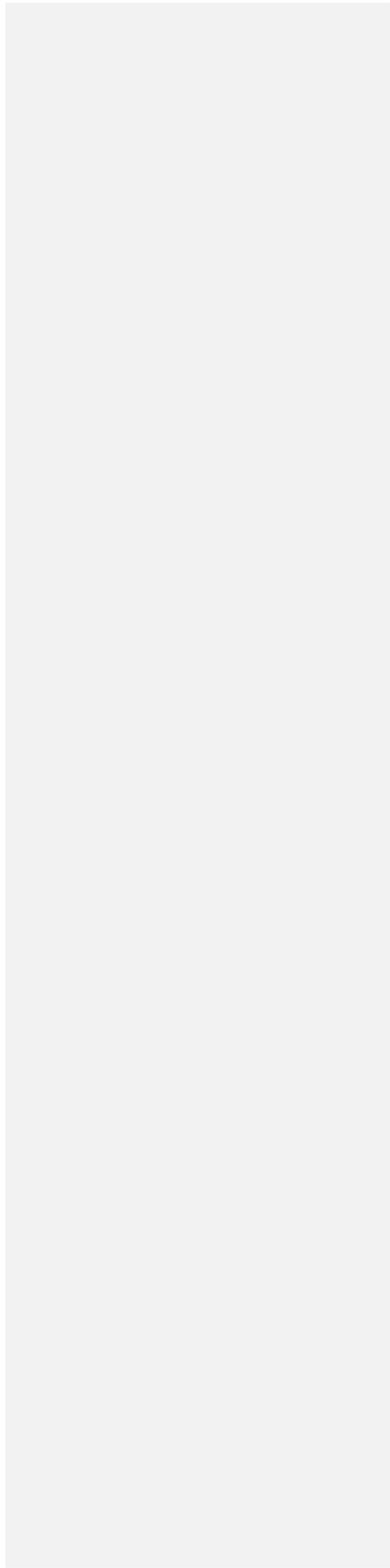
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Values expressed as mean(SD) or median (IQR). Independent sample t test or Mann-Whitney U test used for comparison as appropriate. \* = Chi squared test

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**Table 2.** Pregnancy outcome

Parameter	Morbidly adherent placentation n = 28	Normal placentation n = 103	Significance
Gestation at birth in weeks, Median (IQR)	36.1 (33.4 – 37.4)	38.0 (36.7 – 38.5)	<b>0.004</b>
Birthweight in g, Median (IQR)	2715 (2133 – 2995)	3000 (2640 – 3358)	<b>0.007</b>
Birthweight centile (SD)	41.3 (27.0)	44.4 (26.8)	0.758
Male sex (n, %)	14 (50.0%)	65 (63.1%)	0.246
Hysterectomy (n)	3	0	<b>0.009*</b>
Operative blood loss in ml, Median (IQR)	1700 (1195 – 4500)	800 (600 – 1200)	<b>&lt;0.0005</b>
Blood transfusion (n, %)	11 (39.3%)	20 (19.4%)	<b>0.001*</b>
Lowest post-op Hb in g/L, (SD)	92 (13)	99 (12)	0.081

Values expressed as mean (SD) or median (IQR). Independent sample t test or Mann-Whitney U test used for comparison as appropriate. \* = Chi squared test

**Table 3.** Results of the logistic regression analysis for the association with **MAPAIP**

Variable	Adjusted odds ratio (95% CI)	Significance
Placental thickness (mm)	1.051 (1.018 – 1.085)	<b>0.003</b>
Gestational age at ultrasound (weeks)	0.955 (0.823 – 1.107)	0.538
Previous Caesarean delivery	40.6 (5.1 – 320.8)	<b>&lt;0.005</b>

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