Prenatal Ultrasound Diagnosis and Outcome of Placenta Previa Accreta after Caesarean Delivery: A Systematic Review and Meta-Analysis

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Condensation: Ultrasound imaging is effective in diagnosing placenta previa accreta in women with prior caesarean delivery and presenting with a placenta previa.

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Key Words: Placenta accreta; ultrasound; caesarean delivery; placenta previa; prenatal diagnosis.

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Abstract

Background: Women with a history of previous caesarean delivery, presenting with a placenta previa have become the largest group with the highest risk for placenta previa accreta.

Objective: To evaluate the accuracy of ultrasound imaging in the prenatal diagnosis of placenta accreta and the impact of the depth of villous invasion on management in women presenting with placenta previa or low-lying placenta and with one or more prior caesarean deliveries.

Study design: **Data sources:** We searched PubMed, Google Scholar, clinicalTrials.gov and MEDLINE for studies published between 1982 and November 2016. **Study eligibility criteria:** Cohort studies which provided data on previous mode of delivery, placenta previa or low-lying placenta on prenatal ultrasound imaging and pregnancy outcome. The initial search identified 171 records of which five retrospective and nine prospective cohort studies were eligible for inclusion in the quantitative analysis. **Study appraisal and synthesis methods:** The studies were scored on methodological quality using the Quality Assessment of Diagnostic Accuracy Studies tool.

Results: The 14 cohort studies included 3889907 pregnancies presenting with placenta previa or low-lying placenta and one or more prior caesarean deliveries screened for placenta accreta. There were 328 (8.4%) cases of placenta previa accreta out of which 298 (90.9%) were diagnosed prenatally by ultrasound. The incidence of placenta previa accreta was 4.1% in women with one prior caesarean and 13.3% in women with ≥ 2 previous caesarean deliveries. The pooled

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performance of ultrasound for the antenatal detection of placenta previa accreta was higher in prospective than retrospective studies with diagnostic odds ratios of 228.5 (95% confidence interval [CI], 67.2–776.9) and 80.8 (95% [CI], 13.0–501.4), respectively. Only two studies provided detailed data on the relationship between the depth of villous invasion and the number of previous caesarean deliveries. Independently of the depth of villous invasion., Aa caesarean hysterectomy was performed in 208 out of 232 (89.7%) cases for which detailed data on management were available. Positive correlations were found in the largest prospective studies between the cumulative rates of the more invasive forms of accreta placentation and the sensitivity and specificity of ultrasound imaging but not with diagnostic odds ratio (DOR) values. We found no data on the ultrasound screening of placenta accreta at the routine mid-trimester ultrasound examination- from non-expert ultrasound units by non-expert operators.

Conclusions: Planning individual management for delivery is only possible with accurate evaluation of prenatal risk of placenta previa accreta placentation in women presenting with a low-lying placenta/ previa and a history of prior caesarean delivery. Ultrasound is highly sensitive and specific in the prenatal diagnosis of accreta placentation when performed by skilled operators in women presenting with placenta previa and a history of prior caesarean delivery. Developing a prenatal screening protocol is now essential to further improve the outcome of this increasingly more common major obstetric complications.

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Introduction

Placenta accreta is a complication of human placentation first defined in 1937 by Irving and Hertig, as the "abnormal adherence of the afterbirth in whole or in parts to the underlying uterine wall".[1] Histopathologically, placenta accreta is now universally defined by a partial or complete absence of decidua basalis, resulting in placental villi being attached to or invading into the scarred myometrium underneath.[2-4] Pplacenta accreta is graded according to the depth of villous invasiveness into placenta creta or vera when the villi adhere to the myometrium without invading it, placenta increta when the villi invade the myometrium and placenta percreta when the villi invade down to or penetrate through the uterine serosa.[2-4]

Abnormal adherence or invasion results in the failure of the placenta to separate normally from the uterine wall at delivery. When unsuspected at the time of delivery, attempts to manually remove a placenta accreta typically provoke massive haemorrhage leading to high maternal morbidity and mortality. There is increasing evidence that multidisciplinary management of patients with suspected placenta accreta is superior to standard obstetric care.[5-7] For such care to be organized, the diagnosis must be made prenatally.[8-10] Recent population studies have shown that accreta placentation remains undiagnosed before delivery in half[11,12] to two-third of the cases.[13] Even in series from specialist centres ~~around~~ up to a third of cases of placenta accreta are not diagnosed during pregnancy.[14]

The incidence of placenta accreta is directly linked with the increase in caesarean delivery.[13-19] The main additional factor for the risk of placenta accreta after a previous caesarean delivery is placenta praevia. The risks of both placenta praevia and placenta accreta in subsequent pregnancies increase with the number

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of previous caesarean deliveries[13,16,20,21] and is higher in women with a previous classical caesarean delivery.[21] A large multicenter cohort study has noted that for women presenting with placenta praevia and prior caesarean delivery the risk of accreta placentation is 3%, 11%, 40%, 61%, and 67% for first, second, third, fourth, and fifth or more cesarean deliveries, respectively.[17] These risks are independent of other maternal characteristics, such as parity, body mass index, tobacco use, and coexisting hypertension or diabetes. [2,4,14,15,17]

Given these data, the identification at the mid-trimester ultrasound examination of an anterior placenta praevia or low-lying placenta in a woman with a history of caesarean delivery should prompt a more detailed search for signs of placenta accreta and evaluation of the depth of villous myometrial invasion. The main objective of this review is to evaluate the accuracy ultrasound imaging in diagnosing placenta previa accreta in women presenting prenatally with prior caesarean delivery. Cases of placenta accreta following other types of uterine surgeries were excluded from our review and analysis. We will have also evaluated the impact of the prenatal diagnosis of placenta praevia accreta on pregnancy management and outcome and address the issues in screening for these high-risk cases in the growing number of women with a history of caesarean delivery in the general population.

Material and Methods

Systematic review information sources and search strategy

We undertook a PubMed, Google Scholar, clinicalTrials.gov and MEDLINE search for studies published between the first prenatal ultrasound description of placenta accreta in 1982 by Tabsh[22] et al and 1st of November 2016. The search protocol

was designed a priori and registered on PROSPERO (#42016049990)

(http://www.crd.york.ac.uk/PROSPERO). The search strategy consisted of MeSH

headings for placenta accreta, placenta increta, placenta percreta, abnormally

invasive placenta, morbidly adherent placenta which were combined with terms

regarding placenta previa, low-lying placenta, sonography, ultrasound diagnosis,

ultrasound screening, prenatal diagnosis, caesarean section, or caesarean delivery.

Title, abstracts and full-text were independently assessed by the authors for content,

data extraction and analysis. References of included studies were also reviewed.

The search was limited to articles published in English. We contacted the authors for

clarification where 2 x 2 tables could not be constructed from the published data.

Systematic review eligibility criteria

The primary eligibility criteria were articles which correlated prenatal ultrasound

imaging with pregnancy outcome in women with a history of previous caesarean

delivery and presenting with a placenta previa or low-lying placenta. We included

retrospective and prospective cohort studies. The index test consisted of at least one

ultrasound evaluation performed during pregnancy with the specific aim of

diagnosing placenta accreta. The reference standard for confirmation of accreta

placentation after delivery was histopathologic observation of placental villi directly

attached to the myometrium or invading the uterine wall, or at delivery by direct

observation by the operating surgeon.

Systematic review study selection

The initial database search provided 166 reports and cross-referencing provided an

additional five reports, making a total of 171 records after removal of three duplicates

(Fig. 1). Out of the 171 records screened, 86 did not include data on prenatal

ultrasound imaging of placenta accreta and were therefore excluded. After a second

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selection, case reports and letters with no description of the case were excluded. The full-text of 26 articles identified on second selection were read independently and examined in detail the authors. A further 12 reports where antenatal ultrasound was performed but the cohort studies did not include data on previous uterine surgery were excluded leaving 14 reports for the quantitative analysis.

The authors independently assessed inclusion criteria, data extraction and analysis. The studies were scored on methodological quality using the Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2) using four key domains: 'patient selection', 'index test', 'reference standard' and flow and timing'.[23] The quality items assessed were study design and the conduct and analysis of all included studies. Each item was scored 'high' or 'low', or 'unclear' if there was insufficient information to make an accurate judgment on the risk for bias. When there was inconsistency in study selection or quality assessment, we solved it by weighing arguments.

We constructed two-by-two tables, cross-classifying the outcome of the index test against the outcome of the reference standard. Authors were contacted for additional data if it was not possible to create two-by-two tables. Heterogeneity was identified using Cochran's Q test and the I^2 statistic, in which $P<0.05$ and $I^2 \geq 50\%$ indicate significant heterogeneity as previously described.[24] According to the results of heterogeneity testing, we chose a random statistical model to pool data with 95% confidence interval (CI) on sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR–) and the diagnostic odds ratio (DOR) 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. Data analysis was performed using the statistical software package Meta-DiSc

(http://www.hrc.es/investigacion/metadisc_en.htm) and visualized using a Forest plot.

Clinical study characteristics were subsequently extracted using a predesigned data extraction form including: year of publication, number of cases of placenta praevia screened, number of placenta accreta in the study population, gestational age at diagnosis and histopathological confirmation (primary outcome). In addition, data on outcome were extracted including gestational age at delivery, type of management and depth of villous invasiveness (secondary outcome).

StatGraphic data analysis and statistical software package (Manugistics, Rockville, MD) was used to calculate relationships between parameters when required. A P value of <.05 was considered significant.

RESULTS

Systematic review report characteristics

The final selection included five retrospective[25-29] and nine prospective[30-38] cohort studies. The summarized QUADAS-2 assessment is shown in figure 2. Reference standard was scored unclear risk of bias in every study due to:

1. Histopathology was not available in women not suspected of normal placentation who were correctly diagnosed by ultrasound.
2. It was not generally possible to blind the pathologist to the ultimate diagnosis, since hysterectomy is not commonly performed in pregnancy, and invasive placentation is a recognised indication for Caesarean hysterectomy.

Systematic review synthesis of results

Table 1 displays the primary outcome characteristics of the 14 studies. These cohort studies included 3907 3889 pregnancies presenting with a placenta previa or a low-

lying placenta screen for placenta accreta. The largest cohort studies were US-based.[25,27,29,30-33] In total, there were 328 (8.4%) pregnancies complicated by placenta accreta. The incidence of placenta accreta was 14.9% (range: 7.5-29.4%) and 6.4% (range: 0.7-47.2%) in the retrospective and prospective cohort studies, respectively. Five studies included both low-lying and placenta previa in their screening population of women with a previous caesarean delivery.[25,26,29,32,38] In only one of these studies[29], the low-lying placenta was described as a placental edge within 2 cm of the cervical os but not covering it. The incidence of placenta accreta was lowest (0.7-8.9%) in those studies where the authors did separate low-lying placental position from placenta previa.[25,26,32,37]

The distribution of the number of previous caesarean deliveries in women presenting with a placenta previa accreta confirmed at delivery was reported by eight authors.[27-29,31,33,36-38] When pooled these data showed that out of 214 placenta previa accreta cases included in these studies, 50 (23.4%) women had a history of one previous caesarean delivery and 164 (76.6%) had $\geq$2 previous caesarean deliveries. When referred to the total number of women screened in those studies (n=1233), the incidence of placenta previa accreta was 4.1% in women with one previous caesarean delivery and 13.3% in women with $\geq$2 previous caesarean deliveries.

Overall, 298 (90.9%) cases of placenta accreta were diagnosed prenatally by ultrasound and confirmed clinically at delivery and/or by histopathology. The pooled performance of ultrasound for the prenatal diagnosis of placenta previa accreta in the retrospective studies was as follows: sensitivity, 88.0% (95% confidence interval [CI], 81.0–93.0); specificity, 90.0% (95% CI, 88.0–93.0) and DOR, 80.8 (95% CI, 13.0–501.4) (Fig.3). Positive and negative likelihood ratios were 8.8 and 0.13

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respectively. In the prospective studies, the pooled performance was higher with a sensitivity of 97.0% (95% CI, 93.0–99.0); specificity of 97.0% (95% CI, 97.0–98.0) and DOR of 228.5 (95% CI, 67.2–776.9). (Fig.4). Positive and negative likelihood ratios were 32 and 0.03 respectively. All authors, except two[30,32] used colour-Doppler imaging to diagnosed accreta placentation and five authors[25,27,34,36,37] used MRI to confirmas an aid to the ultrasound diagnosis. Transvaginal ultrasound was reported to be used by six authors[25,29,30,32,37,38] and one author reported on the use of trans-labial ultrasound.[36]

Table 2 presents the secondary outcome characteristics of the 14 studies. Overall there was one maternal death and no neonatal mortality. In tFor the ten studies, for which detailed data on the management of placenta previa accreta at delivery were available, 208 out of 232 (89.7%) cases had an elective or emergent caesarean hysterectomy. Conservative management was attempted in seven cases, including in four cases a focal myometrial resection of the accreta area. Five of these cases failed to control the bleeding and the total number of secondary hysterectomy i.e. (performed as a second procedure after the baby was delivered)delivery was 22.

Only one small retrospective study has reported data on the depth of accreta placentation.[26] Five retrospective studies and one prospective study (without outcome data)[36] were not included in the secondary analysis. The pooling of data of the remaining studies included 84 placenta accreta vera, 53 placenta increta and 37 placenta percreta. Two studies[31,38] provided detailed data on the relationship between the depth of villous invasion and the number of previous caesarean deliveries with the following distribution: five placenta acreta, one placenta increta and two placenta percreta after one caesarean delivery; seven placenta acreta, seven placenta increta and 11 placenta percreta after two caesarean deliveries; and

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six placenta acreta, three placenta increta and eight placenta percreta after more than two caesarean deliveries. Positive correlations were found in the largest prospective studies[30-32,34,35,37,38] between the cumulative rates of the more invasive forms of accreta placentation and the sensitivity (F= 0.91; R= 15.4; P=0.39) and specificity (F= 1.35; R= 21.3; P= 0.29) of ultrasound imaging but not with DOR values (F= 0.34; R= 6.4; P=0.58).

We found no data on the role of ultrasound in the screening of placenta accreta at the routine mid-trimester ultrasound examination by non-expert operators.

COMMENT

Principal findings of the study

This is the first systematic review were the inclusion criteria are restricted to women presenting in the second trimester with a low anterior placenta/placenta previa and a prior caesarean delivery and the first to evaluate the relationship between the depth of placental invasion, outcome and management. Our results show that the accuracy of both grey-scale and colour-Doppler ultrasound imaging in diagnosing placenta previa accreta in the second trimester in women presenting with a low placenta or placenta previa with one or more previous caesarean delivery is high when performed by expert operators. Data on the relationship between the depth of villous invasion are limited and caesarean hysterectomy is the ~~preferred~~ most common management approach for placenta previa accreta when diagnosed prenatally. Conservative management failed to prevent a secondary hysterectomy in the majority of attempted cases.

Comparison with existing literature

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Overall, we found a 3.2-fold increase in the risk of placenta accreta after more than one caesarean deliveries in women presenting with placenta previa confirming the data of previous epidemiological studies.[11,16,39,40] With the continuing increase in the number of caesarean section it is likely that the prevalence of placenta accreta will increase in the general population. Women with a previous history of caesarean delivery, presenting with a low-placenta or placenta previa in the second trimester of pregnancy have become the largest group of women at the highest risk of placenta accreta.

We found a pooled sensitivity of 88% (95% CI, 81–93) and 97% (95% CI, 93-99) in retrospective and prospective studies, respectively. Ultrasound imaging techniques used for the prenatal diagnosis of placenta accreta have included grey-scale imaging, colour-Doppler imaging and three-dimensional ultrasound. Ultrasound machines equipped with colour-Doppler imaging and three-dimensional ultrasound are less widely available than grey-scale imaging machines and require more skills and experience. The results of well conducted prospected cohort studies by Finberg et al[30] and Comstock et al[32] have indicated that the sensitivity and specificity of grey-scale imaging alone in diagnosing for placenta previa accreta are high when performed by experience operators. Finberg et al[30] reported a sensitivity for grey-scale imaging alone of 93% (95%CI, 68-100) and Comstock et reported an overall sensitivity of grey-scale ultrasound diagnostic criteria of 86%. This which is contrast with the data from recent population studies reporting prenatal detection rates for placenta accreta as low as 29% including in women with prior caesarean delivery and diagnosed prenatally with placenta previa.[13] These data suggest that colour-Doppler imaging and three-dimensional ultrasound are not essential to the screening and diagnosis of accreta placentation.

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In the prospective cohort studies included in the present review, the pooled accuracy of ultrasound imaging was higher in women presenting with a placenta previa or low-lying placenta than those reported in a previous general systematic review on the prenatal diagnosis of placenta accreta by ultrasound.[2441] The present systematic review is different as we only included women with placenta previa and one or more prior caesarean deliveries. In all the subsequent cohort study on the prenatal diagnosis of placenta accreta, except one[38], the authors also included women with a previous history of other uterine surgery, mainly myomectomy, curettage and manual delivery of the placenta. Inclusion of women with previous uterine surgery other than a caesarean section is likely to weaken the accuracy of prenatal ultrasound diagnosis in women at risk of placenta accreta as the ~~damage~~ scar area can be anywhere in the uterine cavity and likely to be smaller and more superficial than that of a caesarean section scar.

Clinical implications

Accurate prenatal diagnosis is essential for women with placenta previa accreta, as access to the fetus during caesarean delivery is often an issue due to the anterior placental position. In cases of false negative prenatal diagnosis, ~~and~~ accreta placentation may not be detected by the surgeon during delivery and a routine low transverse uterine incision will lead to major placental blood loss, even before the fetus is delivered. By contrast, a false positive diagnosis of accreta placentation will lead to an unnecessary midline vertical skin incision and a fundal uterine incision increasing the risks of intra-operative and post-operative complications and the risks of placenta accreta and uterine rupture in subsequent pregnancies.

Regionalization of care for women in centre of excellence by multidisciplinary

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team requires accurate prenatal diagnosis of placenta previa accreta.[5-10] Prenatal evaluation of the depth of placental invasion can also be useful for planning of individual management of women diagnosed with accreta placentation.[412] In particular, determining the degree of accreta invasion before delivery is essential to consent procedure, deciding on the optimal gestational age for delivery and planning the corresponding multidisciplinary team expertise for delivery. In a recent systematic review, we found that no single ultrasound sign or a combination of ultrasound signs were specific of the depth of accreta placentation, but that some signs like placental lacunae and bulge and a focal placental exophytic mass were more often associated with deeper invasion of the myometrium.[423] In the present review, eight out of the nine prospective studies provided detailed information on the depth of invasion and ultrasound findings but not on the relationship between the grade of accreta placentation and outcome. In the cases included in seven prospective cohorts, we found positive correlations between the cumulative rates of the more invasive forms of accreta placentation and sensitivity (P=.39) and specificity (P=.29) of ultrasound imaging. There is a need for more prospective data on the accuracy of ultrasound imaging in determining the depth of villous invasion in women diagnosed with placenta previa accreta and its impact on clinical outcome.

~~There are no randomized control trials comparing different surgical and non-surgical approaches for placenta previa accreta suspected or diagnosed antenatally. Both conservative and radical surgical approaches can be associated with a high maternal morbidity, although the value of an experienced team in a centre of excellence decreases the risk significantly.[6,7]~~ Thurn et al have recently indicated that hysterectomies were performed more often in the management of placenta accreta when the diagnosis ~~of placenta accreta was~~is made prenatally than at delivery.[13] The

present review ~~support these findings with~~indicate that almost 90% of women diagnosed prenatally with placenta previa accreta hav~~ing~~e an elective or emergent caesarean hysterectomy. Emergency peripartum hysterectomy is associated with considerable morbidity and mortality and the risks are directly related to a previous caesarean delivery.[4~~3~~4] Recent data from the Perspective database on the risks of peripartum hysterectomy based on placenta previa and prior caesarean delivery delivered in the U.S. between 2006 and 2014 have indicated that high-risk cases are being increasingly referred to a tertiary care hospital.[4~~4~~5] These data also highlight the potential benefits of prenatal screening and diagnosis of placenta previa accreta on clinical outcome.

The data of the present review underscore the pivotal role of prenatal ultrasound diagnosis in optimizing the counseling, management, and outcome of individual women with placenta previa accreta. Ultrasound screening and diagnosis of placenta accreta is not routinely taught during ultrasound training courses in the U.K.[4~~5~~6] Introducing such a screening program has been discussed but never implemented.[4~~6~~7] However, such ultrasound training and screening programs have existed for more than two decades for the detections of fetal anomalies such as congenital heart defect.[4~~7~~8,4~~8~~9] In countries where such a program exists, women at high risk of specific fetal abnormalities and those presenting with ultrasound markers ~~suggesting a~~suspicious of a congenital cardiac defect are referred to a specialist ultrasound unit for a~~n~~ expert review. Considering the increased incidence of placenta previa accreta in women with prior caesarean delivery and the high maternal morbidity and mortality at delivery of undiagnosed cases, similar international screening protocols with standard anatomical views should be developed. These obstetric risk factors of accreta placentation should be identified and integrated in the

clinical assessment at the first antenatal visit and at the mid-gestation routine ultrasound screening for fetal anomalies to improve the detection rate of placenta previa accreta during the second trimester of pregnancy.

Strengths and weaknesses

The main strengths of this review are the comprehensive search strategy, the identification of cases of placenta previa accreta in cohort studies on prenatal imaging and specific inclusion criteria (exclusion of cases with no history of caesarean delivery). We have also correlated ultrasound features of accreta placentation with obstetric outcomes highlighting the impact of prenatal diagnosis on management and emphasised the use of the corresponding ultrasound signs in screening women at high risks during the second trimester of pregnancy.

The main limitations of this review are the publications bias of retrospective studies on the accuracy of ultrasound diagnosis, the heterogeneity of some of the studies in the diagnosis of placenta previa and variability in gestational age at diagnosis. Unlike, MRI, ultrasound examination is operator-dependent and thus single center studies often overestimate the accuracy of ultrasound because they are conducted by skilled operators in specialized centers and the overall numbers of cases of placenta accreta diagnosed prenatally in some cohorts are small.

The ultrasound definition of placenta previa initially included all types of abnormally low placentation i.e. with the placenta edge inside the lower uterine segment. Placenta previa were then graded according to their relationship and/or the distance between the placental edge and the internal os of the uterine cervix.[4950] The use of transvaginal ultrasound has allowed for a more accurate evaluation of the relationship between the placental edge and the internal os and it has been recently

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recommended to use the term "placenta previa" only for those placenta overlying the internal os and to refer to the others as "low lying".[50+] Several authors in our review have included both low-lying and placenta previa in their cohort[25,26,29,32,37], do not report on the use of transvaginal ultrasound in the evaluation[26-28,31,34] and/or have used different terminology to describe the position of the placenta inside the lower uterine segment. The diagnosis of placenta praevia is overestimated in pregnancies at less than 16 weeks of gestation and 90% of the low-lying placenta diagnosed at the mid-gestation scan resolved before the term.[4950-534] This can explain the wide range (0.7-47.2%) in the incidence of placenta previa accreta reported in the cohort studies included in this review.

Conclusions

The sensitivity and specificity of ultrasound imaging in diagnosing placenta previa accreta in women with prior caesarean delivery, presenting with anterior low placenta or placenta previa are above 95% in prospective series, when performed by skilled operators. Women with a history of previous caesarean delivery, presenting with a placenta previa have become the largest group with the highest risk of placenta previa accreta. These specific obstetric risk factors of accreta placentation should be identified and integrated in the general clinical assessment at the first antenatal visit and at the routine mid-gestation ultrasound examination to further improve the detection rate of placenta previa accreta during the second trimester of pregnancy. Developing protocols for the screening of placenta previa accreta in women with prior caesarean delivery presenting with a low-lying or a placenta previa has become essential to improve the outcome of this increasingly more common major obstetric complication at national and international levels. Skills and expertise in identifying the main ultrasound signs of accreta placentation should be included in

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the general training of sonographers who are performing the routine mid-trimester detailed fetal anatomy ultrasound examination.

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