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## **Rethinking Prenatal Screening for Anomalies of Placental and Umbilical Cord Implantation**

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**Running title: Screening placenta and cord implantation anomalies**

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**Precis**

**The increasing frequency of anomalies of placental and umbilical cord implantation require new strategies for prenatal screening.**

**ABSTRACT**

The most common anomalies of implantation of the placenta and umbilical cord include placenta previa, placenta accreta spectrum, and vasa previa and are associated with considerable perinatal and maternal morbidity and mortality. There is moderate quality evidence that prenatal diagnosis of these conditions improves perinatal outcomes and the performance of ultrasound imaging in diagnosing them is considered excellent. The epidemiology of placenta previa is well known and it is standard clinical practice to assess placental location at the routine screening second trimester detailed fetal anatomy ultrasound examination. In contrast, the prevalence of placenta accreta spectrum and vasa previa in the general population is more difficult to evaluate as detailed confirmatory histopathologic data are not available in most studies. The sensitivity and specificity of ultrasound for the diagnosis of these anomalies is also difficult to assess. Recent epidemiologic studies show an increase in the incidence of placental and umbilical cord implantation anomalies, which may be due to increased use of assisted reproductive technology and caesarean delivery. There is good evidence to support targeted standardized protocols for women at high risk and that screening and diagnosing placenta accreta spectrum and vasa previa should be integrated into obstetric ultrasound training programs.

Anomalies of implantation of the placenta and umbilical cord include placenta previa, placenta accreta spectrum and velamentous insertion of the cord.<sup>1</sup> When undiagnosed before delivery, placenta previa and placenta accreta spectrum are associated with high maternal morbidity and some mortality whereas velamentous insertion of the cord when presenting with vasa previa leads to high fetal mortality.<sup>2</sup> The perinatal complications associated with placenta previa and vasa previa have been recognized for centuries.<sup>3,4</sup> Accordingly, determining placental location was one of the first aims of prenatal obstetric ultrasound examination.<sup>5</sup>

The American College of Obstetricians and Gynecologists (ACOG) with the Society for Maternal-Fetal Medicine (SMFM), The Royal College of Obstetricians and Gynaecologists (RCOG) and the Society of Obstetricians and Gynecologists of Canada (SOGC) recently updated their national guidelines or developed new guidelines on the diagnosis and management of placenta previa<sup>6</sup>, placenta accreta spectrum<sup>6-8</sup> and vasa previa.<sup>9-11</sup> All guidelines agree on the pivotal role of prenatal ultrasound imaging to reduce peri-partum complications of placenta and cord implantation anomalies for both mothers and babies. However, recommendations on screening strategies for placenta accreta spectrum and vasa previa and corresponding training are limited.

Epidemiologic studies show that the prevalence of implantation anomalies of the placenta and cord has increased due to an increase in use of caesarean delivery and assisted reproductive technologies over the last two decades.<sup>12-15</sup> Caesarean scars and transcervical embryo transfer after in vitro fertilization (IVF) increase the incidence of placentation in the lower segment uterine.<sup>1</sup> The pathophysiology of low blastocyst implantation in those cases has been linked to scar tissue in the lower uterine segment modifying the directionality of the

physiological uterine peristaltic waves, and thus the flow of intrauterine endometrial secretions.<sup>1</sup> The higher incidence of velamentous cord insertion and anomalies of the placental shape in IVF conceptions have been associated with blastocyst malrotation at implantation secondary to changes in the physiological interaction between the blastocyst and the endometrium.<sup>16</sup>

Since the rise in the prevalence and incidence of anomalies of placental and umbilical cord implantation are largely a consequence of modern obstetric and reproductive practices, they are likely to become increasingly common as couples delay childbearing, require more reproductive assistance and are more frequently delivered by caesarean.<sup>1</sup> In the present article, we review recent literature and evaluate the possible impact of new data on current screening strategies for placenta previa, placenta accreta spectrum and vasa previa.

## **PLACENTA PREVIA**

The prevalence of placenta praevia at term is estimated as 0.14 to 29.8 per 1000 live births.<sup>17</sup> Both the prevalence in the general obstetric population and incidence in women with prior caesarean delivery or after IVF depends on the definition used to define location of the lower placental edge and gestational age at diagnosis.<sup>18</sup>

The use of transvaginal ultrasound (TVS) has revolutionised the diagnosis of placenta previa by allowing accurate measurements of the distance between the low placental edge and the internal os.<sup>19</sup> The American Institute of Ultrasound in Medicine (AIUM) proposed that the term “placenta praevia” is only used when the placenta lies directly over the internal os and should be described as “low lying” when its edge is 0.5-2 cm from the internal os on TVS.<sup>20</sup>

Reporting on the placental position has been an integral part of the mid-trimester fetal anatomy detailed ultrasound examination in most countries around the world for at least

three decades. However, the UK National Screening Committee has never recommended a national screening program for placenta previa as this practice is not supported by strong evidence ([www.screening.nhs.uk/policies](http://www.screening.nhs.uk/policies)).<sup>21</sup> On the other hand, it has supported identifying and follow-up of placenta previa at the routine mid-pregnancy (18<sup>+6</sup>–21<sup>+6</sup> weeks of gestation) ultrasound examination in women whose placenta extends inside the low uterine segment towards the internal cervical os. The new version of the RCOG guidelines on the diagnosis and management of placenta previa and placenta accreta recommend as best practice that the mid-pregnancy routine fetal anomaly scan should include placental localization thereby identifying women at risk of persisting placenta previa or low-lying placenta.<sup>6</sup>

TVS in women suspected of placenta previa on transabdominal scan has a high accuracy in predicting placenta praevia.<sup>22</sup> A prospective study including 1214 women who had both transabdominal ultrasound examination and TVS, showed that a placenta-cervix distance cut-off of 4.2 cm on transabdominal scan during the second trimester is 93.3% sensitive and 76.7% specific for the detection of previa with a 99.8% negative predictive value at a screen-positive rate of 25.0%.<sup>23</sup> These data suggest that at centres with limited expertise in TVS, transabdominal placenta-cervix distance cut-offs at the time of the the routine mid-pregnancy scan can optimize the identification of patients who require follow-up.

So-called placental “migration” results in the resolution of low-lying placenta in over 90% of cases before 37 weeks of gestation<sup>7</sup> but a recent systematic review and meta-analysis could not define a cut-off value due to heterogeneity between studies that included all women at high risk for previa.<sup>24</sup> Only 5% of women diagnosed with a low-lying placenta at 20-24 weeks of gestation still have a low-lying placenta at 32-36 weeks and the distance between the placental edge and the internal os on TVS could be reduced from 20 mm to 5 mm as a threshold to recommend follow-up sonograms.<sup>25</sup>

## **PLACENTA ACCRETA SPECTRUM**

The epidemiology of placenta accreta spectrum and of its different grades i.e. placenta accreta, increta and percreta have varied widely.<sup>26,27</sup> since the condition was first reported on ultrasound by Tabsh et al<sup>28</sup> in July 1982. The total prevalence ranges between 0.001 and 0.11 per 1000 live births.<sup>26</sup> The main factor of change in the prevalence of placenta accreta spectrum has been the exponential increase in caesarean delivery rates.<sup>2,6-8,14</sup> Although accreta placentation has been reported after many uterine surgical procedures<sup>14</sup>, it is estimated that over 90% of cases are found in women with a history of one or more prior caesarean deliveries presenting with a low-lying/placenta previa.<sup>14,29</sup> IVF has been associated with the subsequent development of accreta placentation but the association is indirect and mainly due to the increase rate of low placentation following transcervical embryo transfer.<sup>1,6,17</sup> Heterogeneity in results is due to the lack of detailed confirmation of the accreta grade at birth and variation in the criteria used for the ultrasound diagnosis of placenta previa.<sup>27</sup> Standardised clinical<sup>30</sup> and pathologic<sup>31</sup> protocols were recently proposed for the reporting of placenta accreta spectrum and grade of villous invasiveness.

The pivotal role of ultrasound imaging in accurately diagnosing accreta placentation prenatally and its potential role in the screening women at risk is highlighted in all of the recommendations of the current guidelines.<sup>6,7,8,32</sup> Based on high-quality evidence, it is recommended that pregnant women with a history of prior caesarean deliveries with an anterior low-lying or placenta previa at the routine mid-pregnancy fetal anatomical scan should be referred to a specialist unit in the diagnosis of accreta placentation. When performed by skilled operators, the pooled performance of ultrasound for the prenatal diagnosis of placenta previa accreta ranges between 88-97% for sensitivity and 90-97%

specificity.<sup>29</sup> Although authors using colour-Doppler imaging (CDI) to diagnose accreta placentation have reported the highest detection rates, grey-scale imaging alone has a sensitivity of around 90%.<sup>29</sup>

A standardized description of the ultrasonography signs associated with accreta placentation and *pro forma* reporting was proposed in 2016.<sup>32,33</sup> So far these are not yet in widespread use in the U.S. and in many other countries.<sup>7</sup> A 2017-2018 international survey of practices used in the diagnosis and management of placenta accreta spectrum disorders found that 92% of respondents routinely use grey-scale transabdominal ultrasonography to screen women at high risk.<sup>34</sup> As there is mounting evidence that placenta accreta spectrum often starts as a scar pregnancy<sup>35</sup>, it has been suggested that the screening could start at the 11-13 weeks nuchal translucency scan for high-risk women. A recent prospective study of 22604 singleton pregnancies at their 12-week nuchal translucency ultrasound examination found that 1298 (6%) presented with a combination of an anterior low-lying placenta and prior uterine surgery and were identified as high risk.<sup>36</sup> In the latter subgroup, there were 14 women who were suspected of accreta placentation; of these 13 (93%) had the diagnosis confirmed at delivery.<sup>36</sup>

Screening requires training of large numbers of non-specialist operators and the training is more complex than that required to identify women with simple placenta previa. The implementation of standardized prenatal targeted scanning protocols and training programs similar to those existing for fetal anomalies is essential to the development of a screening platform for women at high risk.<sup>37</sup> A training program using a standardised ultrasound protocol improves accuracy and inter-observer agreement among trainees after training.<sup>38</sup> The training course tested in this study is now on line on the Fetal Medicine Foundation website ([www.courses.fetalmedicine.com](http://www.courses.fetalmedicine.com) > fmf).



## **VASA PREVIA**

Vasa previa is defined the presence of one or more free umbilico-placental vessels running through the membranes across the internal os of the cervix under the fetal presenting part. The prevalence of vasa previa ranges between 1 in 1200 to 1 in 5000 pregnancies,<sup>2</sup> making it less common than both placenta previa and placenta accreta spectrum. However, the condition may be under-reported as only cases leading to perinatal complications tend to be recorded. Pregnancies conceived by ART and in particular by IVF have consistently been associated with a higher incidence of abnormal cord insertion. As cesarean deliveries increase the incidence of placenta previa<sup>2,6</sup> in subsequent pregnancies and IVF increases the risk of placental anomalies,<sup>1</sup> multiple pregnancies<sup>39,40</sup> and velamentous cord insertion,<sup>12</sup> the incidence of vasa previa is likely to increase.

When vasa praevia is diagnosed during labour, the perinatal death rate is reported as at least 60%.<sup>2,17</sup> There is moderate-quality evidence that prenatal diagnosis followed by planned caesarean delivery improves survival rates to over 95%.<sup>9-11,41</sup> A recent prospective population-based cohort Australian study found that out of 63 cases with confirmed vasa praevia at birth, there were no perinatal deaths in the 58 cases diagnosed prenatally.<sup>42</sup>

Gianopoulos et al<sup>43</sup> were the first to report on the prenatal diagnosis of vasa previa with ultrasound and the performance of ultrasound is now considered excellent.<sup>2</sup> The use of TVS combined with CDI has a sensitivity of 100% with a specificity of 99.0–99.8% when performed by specialist operators at 18-26 weeks.<sup>44</sup> The 2014 UK national screening committee concluded that there appears to be little benefit in attempting to identify cases of vasa previa in the first trimester of pregnancy due to the transformation of the primitive into the definitive placenta between 10 and 12 weeks.<sup>45</sup> Overall, prenatal diagnosis is most

effective around mid-pregnancy (18–24 weeks of gestation) but needs to be confirmed during the third trimester (30-32 weeks of gestation) in particular in cases of low-lying placenta at 18-24 weeks.<sup>8,9,11</sup> As with ultrasound screening for placenta accreta spectrum, screening and ultrasound diagnosis of vasa previa is not routinely taught during ultrasound training courses. By contrast, identification of the placental cord insertion during the mid-gestation ultrasound examination to exclude a velamentous cord insertion, which is the main risk factor for vasa previa, is easy and accurate, takes less than one minute and requires no additional scanning skills for a trained sonographer.<sup>37</sup> Due to the lack of large prospective studies, there is still limited information regarding the “safe” distance that a vasa previa needs to be from the internal os in the third trimester of pregnancy to be confident that there is no risk for vessel rupture during labor and delivery.

Around 85% of cases of vasa previa have one or more identifiable risk factors including in vitro fertilization (IVF), bilobed, succenturiate or low-lying placentas and velamentous cord insertion.<sup>12</sup> The 2014 UK national screening committee external review of the 2008 screening policy did not recommend a national screening program for vasa previa. However, they identified that targeted screening of all twins and singleton pregnancies with at least one high-risk factor for vasa previa could reduce perinatal loss rate by as many as 150 cases per year.<sup>45</sup> Nonetheless, there is currently no screening program for vasa previa in the UK.<sup>45</sup> Both the AIUM<sup>46</sup> and SMFM<sup>9</sup> recommend that the placental cord insertion site be documented when technically possible but only advise TVS screening if vasa previa is suspected on transabdominal ultrasound whereas the SOGC recommend that TVS should be considered for all women at high risk of vasa previa.<sup>10</sup>

Randomized control trials to investigate whether ultrasound screening for vasa previa decreases perinatal mortality would be ethically difficult to conduct in view of the poor

neonatal prognosis.<sup>11,45</sup> A recent decision and cost-effectiveness analysis comparing four screening strategies for prenatal screening of vasa previa in singleton pregnancies indicates that screening pregnancies conceived by IVF is the most cost-effective strategy with an incremental cost effectiveness ratio of \$29,187 / quality adjusted life years.<sup>47</sup>

## **CONCLUSIONS AND RECOMMENDATIONS**

The current screening strategy of identifying placental previa at the routine mid-pregnancy scan is well-established and considered as good clinical practice (Table 1). Screening for placenta accreta spectrum is more complex as the ultrasound diagnostic signs are not taught as part of general ultrasound training but there is strong epidemiologic evidence to support ultrasound examination by a trained operator for all women presenting with an anterior low-lying/placenta previa and prior cesarean delivery (Table 1). The development of a screening strategy is essential to reduce the maternal morbidity and mortality of placenta accreta spectrum, but it requires also the implementation of standardized clinical and pathology protocol to confirm the diagnosis at birth.

There is no current screening strategy for vasa previa but there is mounting epidemiologic evidence that screening protocols targeted at high-risk women could identify over 80% of the cases (Table 1).

We believe that there are enough data to support the adoption of universal screening for vasa previa and placenta accreta spectrum, in addition to placenta previa which already occurs. In cases with previa or low-lying anterior placenta, especially in the setting of prior caesarean delivery, the patient could be referred to a specialist with expertise in diagnosis of accreta placentation. In addition, the cord insertion on the placenta should be identified in all screening sonograms. If it is normal and in the absence of a succenturiate lobe, vasa previa

can usually be excluded. Also, CDI can be used to determine whether maternal or fetal vessels overlie the endocervical os. If cord insertion is abnormal or cannot be visualized, or if vessels overlie the os, the patient can be referred to a specialist in the diagnosis of vasa previa. This strategy adds less than one minute to a screening obstetric sonogram.

There will assuredly be false positive results with an increase in referrals to specialist units. However, the downside of false positive tests can be reduced with appropriate communication. In addition, it is important to acknowledge that such screening may fail to identify all cases of placenta accreta spectrum and vasa previa. Accordingly, our leadership organizations should make clear recommendations that both encourage increased screening and provide medic-legal protection if appropriate images are documented and vasa previa is not detected. Although not supported by clear evidence, such an approach is likely to prevent some morbidity associated with accreta placentation and vasa previa with relatively small burden and harm. Careful assessment of pros, cons and cost as well as further research will allow for refinement of the strategy in order to have the most favourable impact on maternal-child health.

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**Table 1:** General characteristics and prenatal ultrasound screening strategies for placenta and umbilical cord implantation anomalies.

<b>Anomaly</b>	<b>Prevalence (/1000 pregnancies or LB)</b>	<b>Risk factors</b>	<b>Current strategy</b>	<b>Comments</b>
Placenta previa	0.14-29.8	Prior CD IVF	Placental location at routine mid-pregnancy (18 <sup>+6</sup> –21 <sup>+6</sup> weeks) detailed fetal ultrasound examination.	The role of TVS needs to be prospectively evaluated for the follow-up of persisting placenta praevia or low-lying placenta in the 3 <sup>rd</sup> trimester and its impact on delivery outcomes.
Placenta accreta spectrum	0.001-0.11	Prior CD Uterine surgery Low-lying/Placenta previa	National guidelines strongly recommend specialist ultrasound examination for women presenting an anterior low-lying/placenta previa and prior CD.	There is a need to implement standardized prenatal targeted scanning protocols, pathologic protocols to confirm the diagnosis at birth and training programs similar to those existing for fetal anomalies.
Vasa previa	0.2-0.83	Velamentous cord insertion IVF Low-lying/Placenta previa Succenturiate/bilobate placenta	There is no universal screening for vasa previa. Targeted screening has been suggested but not implemented.	Prospective data are needed to support the implementation of standardized targeted prenatal scanning protocols.

LB= Livebirth; CD= Cesarean delivery; IVF= *in vitro* fertilization; TVS= Transvaginal sonography.

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