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ARTICLE TITLE

Placental Implantation Disorders

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KEY WORDS

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SYNOPSIS

Primary disorders of placental implantation are widely recognized as having immediate consequences for the outcome of a pregnancy. These disorders have been known to clinical science for more than a century, but have been relatively rare. Recent epidemiologic obstetric data have indicated that the rise in their incidence over the last two decades has been iatrogenic in origin. In particular, the rising numbers of pregnancies resulting from *in vitro* fertilization (IVF) and the increased use of caesarean section for delivery have been associated with higher frequencies of previa implantation, accreta placentation, abnormal placental shapes and velamentous cord insertion. These disorders often occur together, and are probably due to malrotation of the blastocyst during implantation and/or its implantation into uterine scar tissue.

KEY POINTS

- The main disorders of placental implantation are associated with a high maternal and fetal morbidity and possible mortality.
- Placental implantation disorders are essentially iatrogenic, with more than 90% of cases resulting from multiple cesarean deliveries and *in vitro* fertilization.
- *In vitro* fertilization has been associated with blastocyst malrotation at implantation leading to low-lying/placenta previa and velamentous insertion of the umbilical cord.
- Caesarean scars have become the leading predisposing factor for placenta previa accreta in subsequent pregnancies.

MAIN TEXT

Introduction

Primary placental implantation disorders have been known to midwives and obstetricians for at least one hundred years. Overall, these anomalies have only been described in human pregnancies, are associated with a high risk of antenatal and perinatal complications and thus cannot be considered as an evolutionary reproductive advantage. Their etiopathology is still not completely understood but their prevalence and incidence are increased by iatrogenic factors that may have a direct or indirect impact on the functional integrity of the endometrium.

The most common of these congenital disorders, placenta previa may have been first described by Hippocrates (460-370 BC) in "*De Superfoeratione*" and "*De Morbis Mulierum*" [1]. In his apocryphal writings, he highlights the main signs: "a great flow of blood without pain occurring to the parturient before birth of the child" and "the placenta is delivered before the child", both of which have been used since in the clinical diagnosis of the condition. When undiagnosed before delivery, placenta previa is associated with high maternal and fetal mortality, and in 1878 the famous Scottish obstetrician Charles Bell described placenta praevia as "the most dreaded complication in midwifery" [2]. Not surprisingly, when radiology was developed one of its first uses in obstetric practice was the prenatal diagnosis of placenta previa [3]. With the development of ultrasound imaging, screening for placenta previa has become an essential part of the routine detailed mid-trimester fetal anomaly scan.

Other primary placental anomalies of implantation include placenta accreta spectrum (PAS), abnormal insertion of the umbilical cord and abnormal placental shape. These anomalies were first described by obstetricians during the first half of the 20th century when they were still extremely rare [4-6]. Both PAS and velamentous cord insertion (VCI) have been associated with a high risk of perinatal complications, and their incidence has risen rapidly in the last two decades with the increased use of caesarean delivery (CD) and artificial reproduction technologies (ARTs), and in

particular with in-vitro-fertilization (IVF). Thus, primary placental anomalies of implantation are a consequence of modern obstetric and reproductive practices, and are likely to become increasingly common as women delay childbearing, require reproductive assistance and enter pregnancy with medical co-morbidities. This review aims to describe and discuss current knowledge of the epidemiology and pathophysiology of primary intra-uterine placental anomalies of implantation. Placental hematomas and placenta abruptio are secondary anomalies of placentation due to the rupture of one or more spiral arteries. As their epidemiology is heterogeneous and etiopathology very different from that of placental anomalies resulting from a primary abnormal implantation process, they have not been included in the present review.

Low-lying placenta and placenta previa

Placenta previa now has a prevalence of 5 per 1000 (1 in 200) pregnancies and is due to the implantation of the placenta fully or partially in the lower uterine segment [7]. The term “placenta previa” should only be used when the placenta lies directly over the internal os of the uterine cervix. If the placental edge is < 2 cm from the internal os, but not covering it, at the 20-week detailed anatomy scan, the placenta should be labelled as “low-lying”. Additionally, the rationale for using 2cm, instead of 1.5 or 3 cm as alternatives in the literature might be considered, with the bottom line being 2 cm useful as guide to reduce risk of life-threatening bleeding intrapartum. The increase in distance between the lower placental edge and the cervix that occurs normally with advancing gestation following the development of the lower uterine segment during the third trimester of pregnancy results in resolution of a “low-lying” placenta in 90% of cases before 37 weeks [7].

Placenta previa is associated with prior CD, use of ART and maternal smoking (Table 1). With CD rates ranging between 20 and 50% in most high- and medium-income countries, a prior CD is the most common risk factor for placenta previa in subsequent pregnancies. This association has been confirmed by several systematic reviews and meta-analyses with a significant dose-response pattern

in women with multiple prior CDs [9-12]. A CD will result in major structural changes with formation of scar tissue in the lower uterine segment that are likely to modify the directionality of the physiological uterine peristaltic waves and thus the flow of intrauterine endometrial secretions. Repeat CDs are also often associated with the development of large scar defects or niches [13] which can also affect intrauterine flow, leading to more blastocysts implanting around or within the lower segment scar area.

ARTs, and in particular IVF, have also been associated with a higher incidence of placenta praevia independently of the high rate of multiple pregnancies [14-17]. A large Swedish population-based retrospective registry study analysis found that the risk of placenta previa is higher in pregnancies after blastocyst transfer compared to pregnancies after cleavage-stage replacements (adjusted OR (AOR), 2.08; 95% CI, 1.70-2.55) and to spontaneous conceptions (AOR, 6.38; 95% CI, 5.31-7.66) [35]. Overall, these findings suggest that the technique of transcervical embryo transfer, even if the catheter is inserted high within the uterine cavity, changes the physiological interaction between the blastocyst and the endometrium and/or intrauterine flows. By contrast to pregnancies after CD or resulting from ART, there have been contradictory reports regarding the incidence of placenta previa in multiple gestation pregnancies (MGP). One would assume that excessive placental volume would increase the risk of abnormal placental location; however, a national retrospective cohort study of 1,172,405 twin live births and stillbirths in the United States, from 1989 through 1998, found no increased risk in twins [18]. A recent retrospective cohort of 67,895 singleton and twin pregnancies found that dichorionic twins had an increased risk of placenta previa (AOR 1.54, 95% CI 1.15-2.06) and monochorionic twin pregnancies (RR 3.29, 95% CI 1.32-8.21) compared to singletons [19].

Maternal smoking before and during pregnancy is an independent risk factor for placenta previa [20-22]. Smoking alters the epithelial development of many organs and tissues, and in particular of the uterine endometrium. The expression of regulatory cytokines and receptivity markers, such as the C-X-C motif chemokine ligand 12 (CXCL12) and fibroblast growth factor 2 (FGF2) is

decreased in women who smoke compared to non-smokers [23]. Smoking also inhibits both recruitment of bone marrow derived stem cells to the uterus and stem cell differentiation [24], and increases the endometrial content of cadmium and lead [25]. These findings suggest that endometrial receptivity is altered in women who smoke, and could explain previa implantation in spontaneous pregnancies in primigravidae. Other risk factors that may have an impact on the site of implantation include uterine leiomyoma (AOR 2.21; 95%CI: 1.48, 2.94) [26] and endometrial thickness [21]. Compared with women with an endometrial thickness of <9 mm, women with an endometrial thickness of 9-12 mm and women with an endometrial thickness >12 mm have an AOR of 2.02 (95%CI 1.12-3.65) and of 3.74 (95% CI 1.90-7.34), respectively. The authors have suggested that the endometrium thickness could influence fundus-to-cervix uterine peristalsis, explaining the increased risk of implantation in the lower uterine segment in women with thicker endometrium [21].

Some authors have hypothesised that placentation in the lower segment of the uterus could be associated with suboptimal vascular development of both the utero-placental and the umbilico-placental circulations [27,28]. These studies were poorly controlled for the number of active smokers and medical disorders such as thrombophilia, and the women in the placenta previa group were delivered on average 3 weeks before their non-previa controls making the evaluation of placental weight and fetal birthweight inaccurate. A population-based, retrospective cohort study of singleton live births in women diagnosed with placenta previa reported a higher rate of low birth weight (LBW) due to preterm delivery, which was not significant significance when adjusted for gestational age at delivery [29]. A recent retrospective large cohort study of 724 women diagnosed prenatally with placenta previa, found no increase in the incidence of fetal growth restriction (FGR) [30]. The presence of bleeding and the type of the placenta i.e. low-lying placenta (partial previa) and placenta previa (marginal or complete) did not impact the risk of FGR. These data and our recent study showing no difference in the rate of FGR in both low-lying and placenta previa [31] suggest that implantation in the lower uterine segment does not affect the normal development of the utero-placental circulation and/or normal placental functions.

Accreta placentation

The phrase placenta accreta spectrum (PAS) was first used by Luke et al in 1966 to describe the different grades of abnormally adherent and invasive placentas [32]. These include placenta adherenta or creta when the placenta is 'adherent' but not invasive (Figure 1A); placenta increta when the villi invade into the myometrium (Figure 1B); and placenta percreta where the villi invade the full thickness of the myometrium into the serosal surface of the uterus and beyond (Figure 1C). The first large series of abnormally adherent placenta accreta was published by Irving and Hertig in 1937 [33]. They described their cases clinically as "the abnormal adherence of the afterbirth in whole or in parts to the underlying uterine wall with absence of spontaneous separation 60 min after birth", and histologically as "the complete or partial absence of the decidua basalis between the villi and the myometrium". Although, cases of invasive PAS were described earlier in the 20th century, many 21st century authors have used Irving and Hertig's definition to describe both abnormally adherent and invasive types of placentation, including a "morbidly adherent placenta", a definition that was used in the 19th century to describe placental retention [34-36]. Modern authors have also used additional clinical descriptions for PAS, including: difficult manual or piecemeal removal of the placenta; retained placental fragments requiring curettage after vaginal birth; absence of spontaneous placental separation 30 min after vaginal birth, despite active management including bimanual massage of the uterus, use of oxytocin and controlled traction of the umbilical cord; and heavy bleeding from the placental bed after placental removal during CD [37-40]. These clinical descriptions are very similar to those of placental retention, and as most modern authors of PAS do not report on clinical criteria used for the diagnosis of the condition at birth and/or on detailed histopathologic confirmation of the diagnosis, not surprisingly the prevalence of PAS varies between 1 in 100 and 1 in 10,000 births [41]. Furthermore, methodological inconsistencies between modern studies and the lack of differential diagnosis between adherent and invasive accreta placentation limits the analysis of diagnostic

criteria, outcome data and the impact of different management strategies. In an attempt to palliate for these methodological issues, which have hampered PAS epidemiology data analysis for several decades, the FIGO has recently proposed a classification and basic dataset for reporting new data [42].

Like placenta previa, the main risk factors associated with the development of PAS are prior CD and IVF procedures (Table 2), and the risks of developing PAS in subsequent pregnancies increases with the number of prior CDs. Not surprisingly, the incidence of PAS increases exponentially in women with prior CD presenting with a placenta previa [45]. The UK national case-control study [46] found that the incidence of PAS rises from 1.7 per 10,000 to 577 per 10,000 births in women presenting with a placenta previa and a prior CD (AOR 65.02; 95% CI: 16.58, 254.96). The Nordic countries population-based cohort study found that the single most important risk factor was placenta previa, which was reported in 49% of the cases (OR: 292.02, 95% CI; 196, 400) and the risk doubles in women with prior CD (OR 614; 95% CI: 372, 844). Overall 4.1% of women with one prior CD, diagnosed prenatally with placenta previa, will have a PAS and the incidence increases to 13.3% in women with $\geq$2 previous CDs [44]. IVF increases the risk for PAS between 4- to 13-fold compared to spontaneous pregnancy [46-48]. Unlike placenta previa, the risk of PAS is not affected by maternal smoking but it is also increased after minor uterine surgical procedures such as operative hysteroscopy, suction curettage, surgical termination, myomectomy and endometrial ablation [46,49]. It is also associated with uterine pathologies such as bicornuate uterus, adenomyosis and myotonic dystrophy [50].

During the last century, two opposing views of how PAS occurs have prevailed. The first and oldest concept is that there is a primary defect of the trophoblast that is abnormally invasive right from the start at the time of implantation [50]. This concept goes back to the time when CD was rarely performed and was associated with high maternal morbidity and mortality. Most women delivered at home and the main risk factors associated with accreta placentation were prior endometritis and/or placental manual delivery. Only one of the 18 cases personally treated by Irving and Hertig in 1937

occurred after a CD, and all their cases were reported as abnormally adherent with no macroscopic nor histological evidence of myometrial villous tissue invasion [33]. The second and more recent concept is that the trophoblast is normal but becomes excessively invasive secondary to implantation into an anatomically abnormal uterine bed such as from damage by a surgical scar [13,51]. This concept is supported by modern epidemiological data showing that more than 90% of women diagnosed with invasive PAS have a history of CD, and present with placenta previa [34,43,46,47].

In large and deep myometrial defects due to multiple CDs, there is often an absence of re-epithelialisation in the scar area [52]. A thin endometrial thickness is associated with low pregnancy rates after IVF irrespective of the causing factor [53], suggesting that a large scar area does not constitute an ideal environment for implantation. There is a direct association between blastocyst implantation in a caesarean scar and the development of placenta previa accreta [54-56]. Due to the high risk of complications, few caesarean scar pregnancies are managed conservatively and thus outcome data are limited to 69 cases in the international literature with only 40 progressing to the third trimester [56]. High variability in study design and poor correlation with histopathologic findings at birth, including overdiagnosis of placenta percreta due to scar dehiscence, further limit the analysis of these data. These findings suggest that a blastocyst may get trapped within a uterine scar and may implant on its border where there is sufficient decidua to allow further development and placentation. Within this context, there are similarities between ectopic pregnancies where the blastocyst implants within the epithelium of the Fallopian tube and intrauterine scar placentation.

This points to the secondary defect in PAS being the absence of the normal decidual signals that regulate placentation and affect EVT invasion and differentiation [57]. Histopathological studies have shown that EVT cells invade tubal vessels [58] but subsequent development of the placenta in the tube differs from that in the uterus in so far as invasion of the tubal tissues is unrestrained, with penetration of the trophoblast into the serosa. A recent immunohistochemical study has shown that EVT cells in tubal pregnancies show more proliferative and invasive characteristics [59] compared to their intrauterine counterparts. Similarly, in PAS the EVT cells are increased in size and number, and

the depth of their myometrial invasion is greater [60]. NK cells are absent in the non-pregnant and pregnant Fallopian tube, whereas in cases of ectopic pregnancy there are higher numbers of $CD8^+$ lymphocytes, $CD68^+$ macrophages and $CD11c^+$ dendritic cells compared to non-pregnancy [61]. Leukocyte recruitment to the endometrium during the secretory phase is affected by the presence of scar tissue [52]. In both tubal ectopic and intrauterine accreta placentation multinucleated giant cells are lower in number or totally absent [60], indicating that the EVT have not undergone their normal terminal differentiation [62]. These data suggest that accreta placentation is not due to an inherently more aggressive trophoblast, but that migration is uncontrolled due to the absence of the physiological mechanisms arising from the maternal decidual cells (including immune cells) that normally limit invasion. Hence, the result is abnormally deep placentation beyond thejunction of the decidua and chorioallantoic placenta. A key question to address, therefore, is how does decidua induce EVT to form giant cells and limit the depth of invasion?

Invasion of larger vessels in the outer myometrium as far as the uterine serosa in PAS is most certainly also determined by abnormal access rather than trophoblastic malfunction and points to the inherent ability of trophoblast to invade arteries that is also characteristic of choriocarcinoma. The EVT invasion of the tissue around and within the wall of the radial, and even the arcuate, arteries leads to their excessive dilatation and to the entry of high velocity blood flows inside the intervillous space [62]. Sub-placental hypervascularity and the presence of intra-placental lacunae are the most prominent features of invasive PAS prenatally on ultrasound [13,34,62]. The entry of abnormally high velocity blood flow into the placenta at the end of the first-trimester when the intervillous circulation is established permanently distorts the normal anatomy of the definitive placenta, in particular the architecture of the lobules and destruction of inter-lobular septae (Figure 2). The villous tissue shows no morphological changes in PAS compared to non-accreta placentas, even in the invasive areas [50,51]. Various phenotypic changes in syncytiotrophoblast in PAS villous tissue have been reported, but wide variations in study design, accreta definition, number of cases studied, type of tissue

investigated and the extent of quantification of morphological changes limits their interpretation [51]. These changes are most likely secondary to focal oxidative stress and/or mechanical shear stress within the intervillous space and the placental tissue above the invasive areas. Several authors have found that spiral artery remodelling is focally reduced [60,63,64]. The deficiency is seen more in PAS cases without local decidua, and remodelling is sometimes completely absent in the accreta area. The pathological and phenotypic changes are hard to define as the normal vascular architecture of the placental bed may be distorted in the scar area. Furthermore, these changes in remodelling of the utero-placental circulation in placenta accreta are not associated with any impact on placental or fetal growth, nor on the incidence of pre-eclampsia [31].

Abnormal insertion of the umbilical cord

The umbilical cord can be inserted centrally, eccentrically or marginally on the placental disk, and VCI refers to an umbilical cord that is inserted into the membranes [65,66]. Vasa praevia (VP) occurs when fetal vessels run through the membranes, over the cervix, and under the fetal presenting part (Figure 4). VCI is found in approximately 1% of births, and 3-4% of women with a VCI also have a vasa previa [67,68]. Conversely, 90% of women with vasa previa have VCI [65-68]. VP is relatively uncommon in the general population and has been reported to occur in 1 in 1200 to 1 in 5000 births [67]. Anomalies of the cord insertion are probably under-reported, as unlike the occurrence of a single umbilical artery cord that is systematically recorded by midwives at birth they are only recorded when associated with perinatal complications.

In twin pregnancies, the incidence of VCI of one of the umbilical cords is eight times more common than in singletons. Monochorionicity doubles the risk for VCI compared to dichorionicity [69]. IVF singleton pregnancies have a higher incidence of marginal cord insertion, VCI and VP compared to spontaneously conceived singletons [70]. There is no difference in incidence between spontaneous and IVF twins [71]. Marginal and VCI without VP have been associated with small-for-

gestational age in both singleton and twin pregnancies [72-75]. A non-central cord insertion is associated with a sparser chorionic vascular distribution which could lead to markedly reduced transport efficiency through hemodynamic effects on the feto-placental circulation [76]. The pathophysiology of abnormal cord insertion is uncertain but the higher incidence in IVF pregnancies suggest that it could be the consequence of malrotation of the blastocyst at the time of implantation [77-89]. The molecular mechanisms that control blastocyst orientation are not fully understood, but it may be relevant that as the blastocyst enlarges expression of FGFR1 becomes restricted to the trophectoderm overlying the inner cell mass [77]. This finding indicates there may be sub-populations of trophectoderm that may have different adhesive properties. Whether this differentiation is affected by ART, or whether there are changes in endometrial receptivity due to the hormonal regimens employed, is not known at present.

Abnormal placental shapes and placenta extrachorioalis

The mature placenta is often described as discoid; however, there has been considerable debate as to whether the majority are actually circular or ellipsoid [65-66]. The placenta can also be bilobate, multilobate (Figure 3) or can present with an accessory lobe, defined as succenturiate if attached to the main placenta or spuria if not. There is a strong correlation between the shape of the placenta at the end of the first trimester and that at term [78], suggesting that events during the first trimester are critical. Profound remodelling of the early placenta occurs with onset of the maternal circulation, and excessive or asymmetrical regression can lead to abnormal placental shapes and cord insertions [79]. Abnormal shapes may therefore be due to aberrant onset of the maternal circulation, which in turn may reflect local variations in the extent of extravillous trophoblast invasion across the placental bed.

Placenta extrachorialis is characterized by the transition from the villous chorion to the membranes being not at the edge of the placenta but at some distance within the fetal surface [65]. If

the transitional zone is made of a flat ring of membrane, the placenta is classified as "circummarginate" whereas if it is plicated with a raised, rolled edge it is classed as "circumvallate". Placenta extrachorialis may occur if implantation and placentation are too superficial [65].

Bilobate placenta and extrachorialis have been associated a higher incidence of anomalies of the cord insertion [80,81]. Bilobate placenta with VCI and succenturiate lobes are more commonly found in IVF pregnancies [82,83]. Succenturiate lobes of the placenta are more common in twin pregnancies compared with singletons, whereas placenta extrachorialis has the same incidence in both singletons and twins [83]. In singleton pregnancies, but not in twins, abnormally shaped placentas have been associated with a higher incidence of placental abruption, vasa previa and retained placenta [83]. Increased variability in shape has been linked to reduced placental efficiency as estimated by the ratio of fetal to placental weight [79] but there are no epidemiological data supporting this hypothesis. Circumvallate placenta has been associated with a higher incidence of preterm delivery [84], probably due to a lack of physiological elasticity of the rolled edge of membranes during formation of the lower uterine segment in the third trimester of pregnancy.

Conclusions and future research

The events taking place at the time of human implantation are not fully understood, but clearly have a profound impact on the correct formation of the placenta and on pregnancy outcome. An understanding of the factors determining where implantation occurs and how orientation of the blastocyst is regulated in normal pregnancies is critical in order to assess how these processes are perturbed in pathological cases. Equally, little is known about the molecular mechanisms restraining trophoblast invasion, but ectopic pregnancies and PAS both indicate that the decidual and maternal immune cells play a key role. The lack of pre-clinical animal models limits systematic investigation, but the recent derivation of human endometrial and trophoblast organoids [85,86] and the ability to

culture human blastocysts beyond the implantation stage [87] offer new opportunities to explore these otherwise inaccessible events.

Placenta previa and PAS should be diagnosed prior to delivery through antenatal screening in countries with well-resourced health care systems and access to specialist centres. However, they still pose considerable risks to maternal and fetal/neonatal health globally, and their incidence is rising in line with the rate of CD. Variations in placental shape and cord insertion present less of a challenge clinically, but indicate that implantation and placentation have been suboptimal. When excessive, such variations should alert health care professionals to the possibility of impaired fetal growth, vasa previa and to the risk of recurrence in subsequent pregnancies.

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Table 1. Clinical variables associated with placenta previa in large epidemiologic studies and systematic reviews.

Variables	Author (year)/type of study	Risk calculation for placenta previa
Prior CD	Ananth et al (1997)/SR&MA of 3.7 million pregnancies including 170,640 with data on the numbers of prior CDs [8].	Overall RR: 2.6 (95% CI 2.3-3.0) RR after 1 CD: 4.5 (95% CI 3.6-5.5) RR after 2 CDs: 7.4 (95% CI 7.1-7.7) RR after 3 CD: 6.5 (95% CI 6.6-11.6) RR after >3 CDs: 44.9 (95% CI 13.5-149.5)
	Getahun et al (2006)/cohort study of 187,577 singleton pregnancies [9].	RR after 1 CD: 1.5 (95% CI 1.3-1.8) RR after 2 CDs: 2.0 (95% CI 1.3-3.0)
	Marshall et al (2011)/SR&MA of 2,282,922 deliveries [10].	Summary OR: 1.48 to 3.95
	Klar et al (2014)/SR&MA of prior CDs [11].	Summary RR: 1.47 (95% CI:1.44-1.51) Summary OR: 1.62 (95% CI:1.42-1.86)
	Keag et al (2018)/SR&MA of 7,101,692 prior CDs [12].	OR: 1.74 (95% CI 1.62-1.87)
IVF	Grady et al (2012)/SR&MA of 269 single embryo transfer [14].	RR: 6.02 (95% CI 2.79-13.01)
	Ginstrom Ernstad et al (2016)/population-based study of 4,819 singleton pregnancies after blastocyst transfer [15].	aOR: 6.38 (95% CI 5.31-7.66)
	Qin et al (2016)/SR&MA of 161,370 ART conceived singleton pregnancies [16].	RR: 3.71 (95% CI 2.67-5.16)
	Karami et al (2018)/SR&MA of singleton and twin ART conceived pregnancies [17].	Singleton aOR: 2.59 (95% CI 1.70-3.48) Twins aOR: 2.91 (95% CI 1.08-4.73)
Smoking	Aliyu et al (2011)/population-based study of 1,224,133 singleton pregnancies [20].	OR: 1.34 (95% CI 1.27-1.45)
	Rombauts et al (2014)/4,537 ART conceived singleton pregnancies [21].	aOR: 2.58 (95% CI 1.07-6.24)
	Shobeiri et al (2017)/SR&MA of 9,094,443 participants [22].	OR: 1.42 (95% CI 1.30-1.54) RR: 1.27 (95% CI 1.18-1.35)

SR= systematic review; MA= meta-analysis; CD= cesarean delivery; RR= Relative risk; OR= odds ratio; aOR= adjusted odds ratio; MGP= multiple gestation pregnancy

Table 2. Clinical variables associated with PAS in large epidemiologic studies and systematic reviews.

Variables	Author (year)/type of study	Risk calculation
Prior CD	Wu et al (2005)/case-control study of 64,359 births [44].	OR after 1 CD: 2.16 (95% CI 9.0-4.86) OR after 2 or more CDs: 8.6 (95% CI 3.53-21.07).
	Silver et al (2006)/cohort study of 378,063 births and 83,754 CDs [45].	OR after 2 CDs: 17.4 (95% CI 9.0-31.4) OR after ≥ 3 CDs: 55.9 (95% CI 25.0-110.3)
	Klar et al (2014)/SR&MA of prior CDs [11].	Summary RR: 1.38 (95% CI:1.35-1.42) Summary OR: 2.19 (95% CI:1.09-4.43)
	Keag et al (2018)/SR&MA of 705,108 prior CDs [12].	OR: 2.95 (95% CI 1.32-6.60)
	Fitzpatrick et al (2012)/case-control study of 134 cases of PAS [46].	aOR: 14.41 (95% CI 5.63-36.85)
	Thurn et al (2016)/cohort-study of 605,362 births [47].	Overall OR: 8.8 (95% CI 6.1-12.6) OR after 1 CD: 6.6 (95% CI 4.4-9.8) OR after 2 CDs: 17.4 (95% CI 9.0-31.4) OR after ≥3 CDs: 55.9 (95% CI 25.0-110.3)
IVF	Fitzpatrick et al (2012)/case-control study of 134 cases of PAS [46].	aOR: 32.13 (95% CI 2.03-509.23)
	Thurn et al (2016)/cohort-study of 605,362 births [47].	OR: 3.1 (95% CI 1.6-5.8)
	Roque et al (2018)/SR&MA of fresh embryo transfer [48].	aOR: 3.51 (95% CI 2.04-6.05)
OTHER SURGERY	Fitzpatrick et al (2012)/case-control study of 134 cases of PAS [46].	aOR: 3.40 (95% CI 1.30-8.91)
	Baldwin et al (2018)/cohort-study of 380,775 births [49].	RR for 1 procedure: 1.5 (99% CI 1.1-1.9) RR for 2: 2.7 (99% CI 1.7-4.4) RR for ≥3: 5.1 (95% CI 2.7-9.6)

SR= systematic review; MA= meta-analysis; CD= cesarean delivery; RR= Relative risk; OR= odds ratio; aOR= adjusted odds ratio

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Figure legends

Figure 1. Diagrams showing the different grades of placenta previa accreta: Adherenta or Creta (PC) where placental (P) villi adhere directly to the decidua (D, dark red layer) to the myometrium (M) without interposing decidua above a prior CD scar area (arrow); Increta (PI) where the villi invade the myometrium in and around the scar area (arrow); and Percreta (PP) where the villi invade the entire myometrium and cross the uterine serosa (S, black layer). Note the presence of lacunae (L) in both placenta Increta and Percreta.

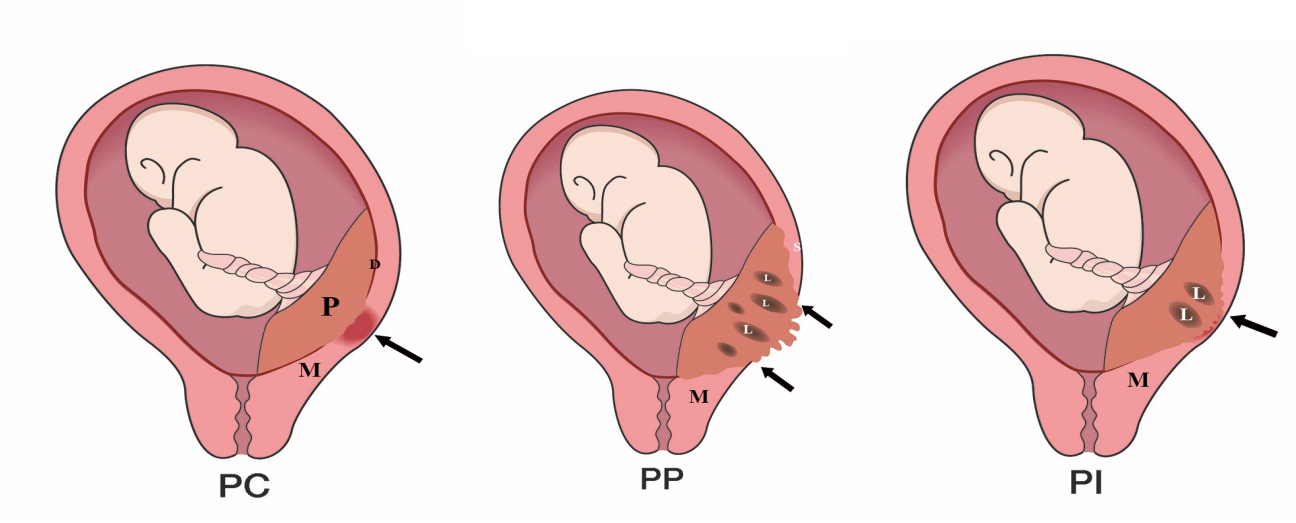

Figure 2. Diagram showing a normal placental cotyledon (left) with decidua (D) and normal myometrium (B) and an increta cotyledon (right). The increta cotyledon anatomy is distorted with villi reaching the deep myometrial circulation and the formation of a lacuna (L).

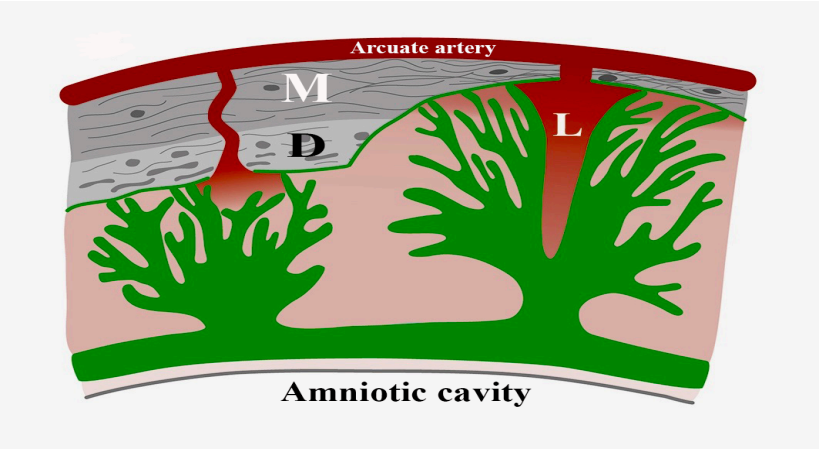

Figure 3. Trans-abdominal, longitudinal ultrasound view at 20 weeks of gestation of a fundal bilobate placenta (P) with the umbilical cord inserted at the edge of the anterior lobe. Note the presence of lakes (L) lake; AC= Amniotic cavity.

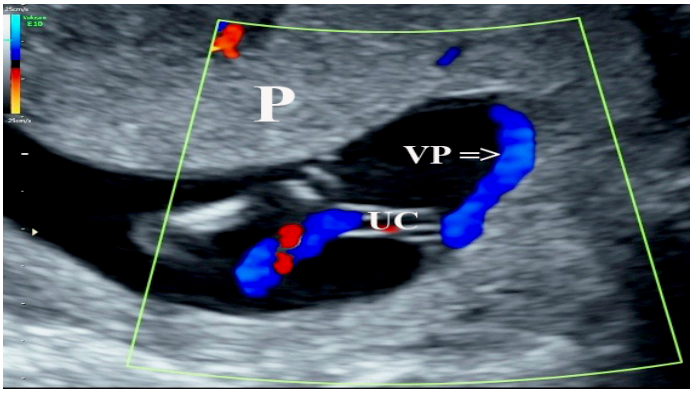

Figure 4. Trans-abdominal longitudinal ultrasound view at 13 weeks of a velamentous umbilical cord (UC) inserted outside the placenta (P) with a vasa previa (VP) connecting the cord to the placenta.