Prevention of stillbirths: impact of a two-stage screening for vasa previa

Weiyu Zhang[1], Samar Geris[1], Jaroslaw Beta[1], Ghada Ramadan[2], Kypros H. Nicolaides,[3] Ranjit Akolekar[1,4]

1. Fetal Medicine Unit, Medway NHS Foundation Trust, Gillingham, UK
2. Oliver Fisher Neonatal Unit, Medway NHS Foundation Trust, Gillingham, UK
3. Harris Birthright Research Centre for Fetal Medicine, Kings College Hospital, London, UK
4. Institute of Medical Sciences, Canterbury Christ Church University, Kent, UK.

Corresponding author:

Professor R Akolekar, MD, MRCOG

Institute of Medical Sciences,

Canterbury Christ Church University,

Rowan William's Court,

Chatham, Kent ME4 4UF

Email: ranjit.akolekar@canterbury.ac.uk

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CONTRIBUTION

What are the novel findings of this work?

The study has demonstrated the feasibility of introducing a two-stage screening programme for diagnosis of vasa previa based on transvaginal sonography at 20-22 weeks' gestation for those with velamentous cord insertion at the routine 11-13 weeks scan and low-lying placenta at the routine 20-22 weeks scan.

What are the clinical implications of this work?

Accurate and effective prenatal diagnosis of pregnancies with vasa previa can be achieved by a two-stage screening protocol; appropriate monitoring and delivery of such pregnancies can potentially reduce the overall rate of stillbirth by about 10%.

ABSTRACT

Objectives: To examine the feasibility and effectiveness of a two-stage ultrasound screening strategy for detection of vasa previa and estimate the potential impact of screening on prevention of stillbirth.

Methods: This was a retrospective examination of data from prospective screening for vasa previa in singleton pregnancies undertaken at the Fetal Medicine Centre at Medway Maritime Hospital, UK between 2012 and 2018. Women booked for prenatal care and delivery in our hospital had routine ultrasound examinations at 11-13 and 20-22 weeks' gestation. Those with velamentous cord insertion at the inferior part of the placenta at the first-trimester scan and those with low-lying placenta at the second-trimester scan were classified as high-risk for vasa previa and had transvaginal sonography specifically searching for vasa previa at the time of the 20-22 weeks scan. The management and outcome of cases with suspected vasa previa is described. We excluded cases of miscarriage or termination at <24 weeks' gestation.

Results: The study population of 26,830 singleton pregnancies, included 21 (0.08% or 1 in 1,278) with vasa previa. In all cases of vasa previa the diagnosis was made at the 20-22 weeks scan and confirmed by gross and histological examination of the placenta postnatally. At the 11-13 weeks scan the cord insertion was classified as central in 25,071 (93.4%) cases, marginal in 1,680 (6.3%), and velamentous in 79 (0.3%). In 16 (76.2%) of the 21 cases of vasa previa, the cord insertion at the first-trimester scan was classified as velamentous at the inferior part of the placenta, in 2 (9.5%) as marginal and in 3 (14.3%) as central. The 21 cases of vasa previa were managed on an outpatient basis with serial scans for measurement of cervical length and elective cesarean section at 34 weeks' gestation; all babies were liveborn but there was one neonatal death. In the study population there were 83 stillbirths and postnatal examination showed no evidence of vasa previa in any of the cases. On the assumption that if we had not diagnosed prenatally all 21 cases of vasa previa in our population half of these cases would have resulted in stillbirth, then the potential impact of screening is prevention of 9.6% (10/104) of stillbirths.

Conclusion: A two-stage strategy of screening for vasa previa can be incorporated into routine clinical practice and such strategy could potentially reduce the rate of stillbirth.

INTRODUCTION

Vasa previa is defined as presence of fetal blood vessels, arterial or venous, unsupported by placenta or umbilical cord in close proximity to the internal cervical os.[1-3] These vessels are at risk of rupture, in association with spontaneous or iatrogenic rupture of amniotic membranes, resulting in hemorrhagic fetal death. There is some evidence that in cases of undiagnosed vasa previa there is a high-risk of stillbirth, neonatal death and morbidity, whereas these risks can to a great extent be prevented if the condition is diagnosed prenatally.[4-10] The Society of Obstetricians and Gynaecologists of Canada recommends that if the placenta is found to be low lying at the routine second trimester ultrasound examination, further evaluation for placental cord insertion should be performed and transvaginal ultrasound may be considered in order to evaluate the internal cervical os for all women at high risk for vasa previa, including those with low or velamentous insertion of the cord, bilobate or succenturiate placenta, or for those having vaginal bleeding.[11] The Royal College of Obstetricians and Gynaecologists in the UK acknowledges that the performance of ultrasound in diagnosing vasa previa at the time of the routine fetal anomaly scan has a high diagnostic accuracy with a low false-positive rate, but concludes that there is insufficient evidence to support universal screening for vasa previa at the time of the routine midpregnancy fetal anomaly scan in the general population and that although targeted ultrasound screening of pregnancies at higher risk of vasa previa may reduce perinatal loss, the balance of benefit versus harm remains undetermined and further research in this area is required.[12]

The objectives of our study are to examine the feasibility and effectiveness of a two-stage ultrasound screening strategy for detection of vasa previa and estimate the potential impact of screening on prevention of stillbirth. In the first stage, a high-risk group is identified by first, the presence of velamentous cord insertion at the inferior part of the placenta at the 11-13 weeks scan and second, presence of low-lying placenta at the 20-22 weeks scan. In the second-stage, the high-risk group is examined by transvaginal sonography with color Doppler to diagnose or exclude vasa previa at the time of the 20-22 weeks scan.

METHODS

Study population

This was a retrospective examination of data from prospective screening for vasa previa undertaken at the Fetal Medicine Centre at Medway Maritime Hospital, UK between January 2012 to June 2018. All women booking for their pregnancy care in our hospital are offered a routine ultrasound examination at 11-13 weeks' gestation for dating of the pregnancy by measurement of fetal crown-rump length (CRL), combined screening for fetal aneuploidies, systematic examination of the fetal anatomy,[13-15] and position of umbilical cord attachment to the placenta; the latter is recorded as central, marginal or velamentous (Figure 1). A second routine scan is offered at 20-22 weeks' gestation and this includes assessment of fetal growth and anatomy, placental localisation and determination of the position of umbilical cord attachment to the placenta; the scan is carried out transabdominally, but in cases of suspected low-lying placenta the diagnosis is confirmed by transvaginal sonography.

In this study, we included all singleton pregnancies that booked in our unit for their pregnancy care prior to 14 week's gestation. We excluded cases of miscarriage or termination at <24 weeks' gestation and those that were lost to follow-up. The protocol for this study was approved by the National Research Ethics Committee (REC reference number 19/LO/0413). The study was registered with ISRCTN [ISRCTN registry number 11893931].

Screening and management of pregnancies with vasa previa

Screening for vasa previa was based on a two-stage strategy. In the first stage, a high-risk group is identified by first, the presence of velamentous cord insertion at the inferior part of the placenta at the 11-13 weeks scan and second, the presence of low-lying placenta at the 20-22 weeks scan. In the second-stage, the high-risk group is examined by transvaginal sonography with color Doppler to diagnose or exclude vasa previa at the time of the 20-22 weeks scan by identifying vessels within 5 cm of the internal os.

Pregnancies with vasa previa were managed on an out-patient basis with transvaginal ultrasound scans for measurement of cervical length and confirmation of vasa previa every two weeks till 28 weeks' gestation and every one week thereafter till delivery, which was planned at 34-35 weeks' by an elective cesarean section. Women were hospitalized if they had regular uterine contractions, short cervix <15 mm, evidence of progressive cervical shortening or polyhydramnios. In all pregnancies with vasa previa, a sticker was placed on the front of their notes to ensure that all staff were aware of the diagnosis if they presented to the labor ward with contractions or vaginal bleeding.

Outcome measures

Data regarding maternal demographic characteristics, medical history, ultrasound findings and pregnancy outcome were recorded on an electronic database (Viewpoint version 5.6; GE Healthcare, Buckinghamshire, UK). In all pregnancies with a prenatal diagnosis of vasa previa, we carried out a postnatal confirmation of the diagnosis by examination of the placenta, amniotic membranes and umbilical cord insertion (Figure 2). Similarly, gross and histological examination of the placenta and umbilical cord was carried out in all stillbirths.

The following adverse outcomes were examined: first, stillbirth; second, early preterm birth at <32 weeks' gestation; third, small for gestational age (SGA) neonates with birthweight <5th percentile;[16] fourth, elective and emergency cesarean section; fifth, post-partum hemorrhage (PPH) with estimated blood loss of >1L;[17] sixth, admission to neonatal intensive care unit (NICU) and total length of stay in the neonatal unit; seventh, hypoxic ischemic encephalopathy (HIE), diagnosed when there was abnormal neurological function with evidence of perinatal hypoxia, supported by neuroimaging evidence of acute brain injury;[18] eighth, neonatal blood transfusion; and ninth, neonatal death within one week of delivery.

Statistical analysis

Comparison of the maternal and pregnancy characteristics between those with and without vasa previa was by the χ^2-square test or Fisher's exact test for categorical variables and Mann-Whitney U-test for continuous variables, respectively. Significance was assumed at 5% and *post hoc* Bonferroni correction was used to adjust for multiple comparisons where necessary. Univariable and multivariable logistic regression analysis was used to determine which of the maternal and pregnancy characteristics had a significant contribution in prediction of vasa previa. The effect size of characteristics associated with vasa previa was expressed as odds ratio (OR) (95% confidence intervals [CI]). The performance of screening for vasa praevia was assessed by estimating detection rate (DR), false positive rate (FPR), positive and negative likelihood ratio (LR) and positive and negative predictive values (PPV and NPV, respectively). The statistical package SPSS 24.0 (IBM SPSS Statistics for Windows, Version 24.0, Armonk, NY: IBM Corp; 2016) and MedCalc Statistical Software version 18.5 (MedCalc Software, Ostend, Belgium; http://www.medcalc.org; 2018) were used for data analyses.

RESULTS

Study population

During the study period 28,526 women with singleton pregnancies were booked for delivery in our hospital. We excluded 1,696 pregnancies (5.9%), including 408 who had termination, 332 with miscarriage and 956 with missing follow-up data. The study population of 26,830 singleton pregnancies, included 22 with suspected vasa previa (Figure 3), but in one of these cases subsequent scans at 24 and 26 weeks showed that there was no vasa previa. Therefore, the incidence of vasa previa in our population was 0.08% (21/26830 or 1 in 1,278).

Maternal and pregnancy characteristics associated with vasa previa

The maternal and pregnancy characteristics in the study population are shown in Table 1. In pregnancies with, than without, vasa previa, there was a higher prevelance conceptions by *in-vitro* fertilsation, velamentous cord insertion at the 11-13 weeks scan and low-lying placenta and bilobed placenta at the 20-22 weeks scan.

Maternal and neonatal outcomes in pregnancies with vasa previa

In pregnancies with a prenatal diagnosis of vasa previa, there were no stillbirths. In pregnancies with, than without, vasa previa there was a higher prevalence of preterm birth, SGA neonates, emergency cesarean section, postpartum hemorrhage, admission to NICU, neonatal blood transfusion and neonatal death and earlier gestational age at delivery and longer length of stay in the neonatal unit. In the vasa previa group, 71% (15/21) pregnancies were delivered by elective cesarean section at a median gestational age of 34.2 (IQR 32.9-35.1) weeks; 6 women had spontaneous onset of uterine contractions and 5 (83.3%) of these had an emergency cesarean section, whereas 1 had vaginal birth at 24.9 weeks' gestation following precipitate labor. Two of the neonates from the vasa previa group required blood transfusion for anemia due to presumed hemorrhage from rupture of the vasa previa; one case had vaginal birth at 24.9 weeks and the

other emergency cesarean section for fetal distress after spontaneous labour at 34.3 weeks. In the group with elective cesarean section regression analysis demonstrated that there was a linear relationship between the serial cervical length measurements and gestational age: expected cervical length = 39.92 -0.275 x gestational age in weeks, adjusted R2=0.101 and p<0.0001 (Figure 4). This was used to determine the 5th, 50th and 95th percentiles at different gestational ages; at 22 weeks, the respective values were 29, 34 and 38 mm, whereas at 34 weeks, these values were 26, 31 and 35 mm. The serial measurements of cervical length in the five cases requiring emergency cesarean section because of spontaneous onset of labor or rupture of membranes are shown in Figure 4; in all cases onset of labor or membrane rupture were preceded by cervical shortening to below the 5^{th} percentile.

Prediction of vasa previa from maternal and pregnancy characteristics

Univariate and multivariate logistic regression analysis demonstrated that significant independent contribution to prediction of vasa previa was from conception by *in-vitro* fertilisation, velamentous cord insertion at 11-13 weeks, and bilobed placenta and low-lying placenta at 20-22 weeks (R^2=0.634; p<0.0001) but not from maternal age, weight, height, racial origin, cigarette smoking, parity or maternal diabetes (Table 3).

The performance of screening for vasa previa by *in-vitro* fertilisation, velamentous cord insertion, bilobed placenta and low-lying placenta is shown in Table 4. Velamentous cord insertion had a DR of 76%, FPR of 0.2% and a PPV of 20%; implying that about 3 in 4 pregnancies with vasa previa have velamentous insertion but only about 1 in 5 of those with velamentous cord insertion would have vasa previa. A bilobed placenta had a DR of 38%, FPR of 0.3% and a PPV of about 9% suggesting that 2 in 5 pregnancies with vasa previa have a bilobed placenta but only about 1 in 10 of those with a bilobed placenta would have vasa previa. Similarly, a low-lying placenta at the 20-22 weeks scan had a DR of 57%, but with a relatively higher FPR of 10% and a low PPV of 0.5%; implying that while 3 in 5 pregnancies with vasa previa have a low-lying placenta, only 1 in 200 of those that have a low-lying placenta would have vasa previa. Similarly, about 1 in 5

pregnancies with vasa previa conceive by *in-vitro* fertilisation but only 1 in 100 of those conceived by *in-vitro* fertilisation would have vasa previa.

Stillbirths and neonatal deaths in the study population

In the pregnancies with vasa previa there were no antenatal or intrapartum stillbirths, but there was one neonatal death attributable to vasa previa related hemorrhage in a case which presented with spontaneous preterm labor, antepartum hemorrhage and fetal bradycardia requiring an emergency cesarean section. In none of the 83 pregnancies with stillbirth there were postpartum findings suggestive of an undiagnosed vasa previa. On the assumption that if we had not diagnosed prenatally all 21 cases of vasa previa in our population half of these cases would have resulted in stillbirth, then the potential impact of screening is prevention of 9.6% (10/104) of stillbirths.

DISCUSSION

Principal findings of the study

The study has demonstrated the feasibility of introducing a two stage screening programme for diagnosis of vasa previa based on transvaginal sonography at 20-22 weeks' gestation for those with velamentous cord insertion at the routine 11-13 weeks scan and low-lying placenta at the 20-22 weeks scan. We found that first, the prevalence of vasa previa in a routinely screened population is about 1 in 1,300 pregnancies; second, risk factors for vasa previa are conception by *in vitro* fertilisation, velamentous cord insertion, bilobed placenta and a low-lying placenta; third, all pregnancies with prenatal diagnosis of vasa previa resulted in live births; and fourth, effective prenatal diagnosis of vasa previa can potentially contribute to prevention of about 10% of all stillbirths.

Comparison with other studies

Our results on perinatal survival in cases of vasa previa are consistent with those of previous studies which reported that prenatal diagnosis of vasa previa is associated with survival rates of 97-100%, compared to <50% in those that were not detected.[4-10,19,20] A multicentre study of 155 pregnancies with vasa previa, reported that perinatal survival was 97% (59/61) in those diagnosed prenatally compared to 44% (41/94) in those without prenatal diagnosis.[5]

Our findings on risk factors for vasa previa are consistent with those of a systematic review of 13 studies on 569,410 pregnancies, including 325 cases of vasa previa, which identified five risk factors, including conception by assisted reproductive techniques, bilobed placenta, second-trimester placenta previa, first-trimester cord insertion in the lower third of the uterus and velamentous cord insertion.[21]

Implications for clinical practice

The results of our study demonstrate that accurate and effective prenatal diagnosis of pregnancies with vasa previa can be achieved by a two-stage screening protocol to identify a high-risk group in need of transvaginal color Doppler assessment at 20-22 weeks' gestation. Although findings such as velamentous cord insertion, bilobed placenta and low-lying placenta are high-risk factors for vasa previa, the majority of pregnancies with these findings do not have vasa previa and therefore can be reassured after assessment at the 20-22 weeks' scan. Our findings suggest that prenatal diagnosis of vasa previa and appropriate monitoring and delivery of such pregnancies can potentially reduce the overall rate of stillbirth by about 10%.

Strengths and limitations

The main strengths of our study are first, prospective examination of a large unselected population of pregnancies attending for routine ultrasound scans at 11-13 and 20-22 weeks' gestation; and second, postnatal confirmation of all cases of suspected vasa previa and exclusion of vasa previa in all cases of stillbirth. A limitation of the study is that postnatal examination of the placenta and membranes was not carried out in all pregnancies and it is therefore possible that some cases of vasa previa in livebirths may have been undetected by prenatal ultrasound. Another limitation is that the study was confined to singleton pregnancies.

Conclusion

A two-stage strategy of screening for vasa previa can be incorporated into routine clinical practice and such strategy could potentially reduce the rate of stillbirth. The feasibility and cost-effectiveness of such strategy requires investigation in prospective multicentre studies in hospitals providing routine pregnancy care.

Conflicts of interest

No conflict of interest to report

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FIGURE LEGENDS

Figure 1. Velamentous (left) and central (right) cord insertion into the placenta at the 11-13 weeks scan.

Figure 2. Vasa previa with bilobed placenta (top) and velamentous cord insertion (bottom) demonstrated by color Doppler ultrasound images (left) and gross placental appearance (right).

Figure 3. Flow chart on two-stage screening for vasa previa.

Figure 4. Cervical length measurements in the cases of vasa previa that had an elective caesarean section and relationship with gestational age (left). On the right are the serial measurements of cervical length in the five cases requiring emergency cesarean section because of spontaneous onset of labor or rupture of membranes.

Table 1. Maternal and pregnancy characteristics in the study population.

Maternal and pregnancy characteristics	**No vasa previa (n=26,809)**	**Vasa previa (n=21)**
Maternal age in years, median (IQR)	29.0 (25.0-33.0)	32.4 (27.1-35.6)
Maternal weight in kg, median (IQR)	68.0 (59.0-80.1)	67.9 (57.9-76.5)
Maternal height in cm, median (IQR)	165 (160-169)	164 (160-169)
Racial origin		
Caucasian, n (%)	24,422 (91.1)	17 (81.0)
Afro-Caribbean, n (%)	787 (2.9)	0
South Asian, n (%)	1,161 (4.3)	3 (14.3)
East Asian, n (%)	123 (0.5)	0
Mixed, n (%)	316 (1.2)	1 (4.8)
Conception		
Spontaneous (Reference), n (%)	26,288 (98.1)	17 (81.0)
In vitro fertilisation, n (%)	354 (1.3)	4 (19.0)**
Ovulation induction drugs, n (%)	167 (0.6)	0
Cigarette smoking, n (%)	4,475 (16.7)	1 (4.8)
History of medical disorders		
Chronic hypertension, n (%)	286 (1.1)	0
Diabetes mellitus, n (%)	223 (0.8)	1 (4.8)
Nulliparous	11,117 (41.5)	13 (61.9)
Ultrasound findings at 11-13 weeks		
Velamentous cord insertion	63 (0.2)	16 (76.2)**
Marginal cord insertion	1,678 (6.3)	2 (9.5)
Central cord insertion	25,068 (93.5)	3 (14.3)
Ultrasound findings at 20-22 weeks		
Low lying placenta	2,550 (9.5)	12 (57.1)**
Bilobed placenta	86 (0.3)	8 (38.1)**

IQR = interquartile range; Significance level **p<0.01.

Table 2. Adverse outcomes in pregnancies with vasa previa compared to those without.

Outcome	No vasa previa (n=26,809)	Vasa previa (n=21)
Stillbirth, n (%)	83 (0.3)	0
Preterm birth <32 weeks, n (%)	256 (1.0)	4 (19.0)**
Small for gestational age <5th percentile, n (%)	1,641 (6.1)	4 (19.0)*
Elective cesarean section, n (%)	3,051 (11.4)	15 (71.4)**
Emergency cesarean section, n (%)	4,303 (16.1)	5 (23.8)**
Postpartum hemorrhage, n (%)	1,859 (6.9)	7 (33.3)**
Gestational age at delivery, median (IQR)	39.6 (38.6-40.5)	34.2 (32.9-35.1)**
Birth weight percentile, median (IQR)	52.9 (26.1-77.9)	40.6 (8.3-68.1)
Admission to NICU, n (%)	4,451 (16.6)	21.0 (100.0)**
Length of stay in neonatal unit in days, median (IQR)¥	4.0 (3.0-7.0)	9.0 (7.0-16.0)**
Hypoxic ischaemic encephalopathy, n (%)	60 (0.2)	0
Neonatal blood transfusion, n (%)	125 (0.5)	2 (9.5)**
Neonatal death, n (%)	12 (0.01)	1 (4.8)**

IQR = interquartile range; Significance level p * p<0.05; **p<0.01.

¥ = Calculated only for neonates admitted to the NNU

Table 3. Univariate and multivariate logistic regression analysis demonstrating the association of maternal and pregnancy characteristics with vasa previa

Maternal and pregnancy characteristics	Univariate OR (95% CI)	Multivariate OR (95% CI)
Maternal age - 30 (years)	1.07 (0.99-1.16)	-
Maternal weight - 70 (kg)	0.98 (0.96-1.01)	-
Maternal height - 164 (cm)	0.98 (0.92-1.05)	-
Racial origin		
Caucasian (Reference)	1.00	-
Afro-Caribbean	-	-
South Asian	3.71 (1.09-12.69)*	-
East Asian	-	-
Mixed	4.55 (0.60-34.25)	-
Conception		
Spontaneous (Reference)	1.00	-
In vitro fertilisation	17.47 (5.85-52.19)**	10.35 (1.69-63.32)*
Ovulation induction drugs	-	-
Cigarette smoking	0.25 (0.03-1.86)	-
History of medical disorders		
Chronic hypertension	-	-
Diabetes mellitus	5.96 (0.80-44.61)	-
Nulliparous	2.29 (0.95-5.54)	-
Ultrasound findings at 11-13 weeks		
Velamentous cord insertion	1358.53 (482.99-3821.22)**	706.55 (217.63-2293.81)**
Marginal cord insertion	2.50 (0.74-8.48)	
Ultrasound findings at 20-22 weeks		
Low lying placenta	12.68 (5.34-30.13)**	19.85 (5.81-67.78)**
Bilobed placenta	191.22 (77.29-473.07)**	39.09 (8.83-173.07)**

OR = odds ratio; CI = confidence interval; Significance level p * p<0.05; **p<0.01.

Table 4. Performance of screening for vasa previa from maternal and pregnancy characteristics

Test performance	*In vitro* fertilisation	Velamentous cord insertion	Bilobed placenta	Low-lying placenta
DR, % (95% CI)	19.05 (5.45-41.91)	76.19 (52.83-91.78)	38.10 (18.11-61.56)	57.14 (34.02-78.18)
FPR, % (95% CI)	1.32 (1.19-1.46)	0.23 (0.18-0.30)	0.32 (0.26-0.40)	9.51 (9.16-9.87)
Positive LR, (95% CI)	14.43 (5.94-35.05)	324.22 (229.96-547.12)	118.76 (66.18-213.09)	6.01 (4.14-8.72)
Negative LR, (95% CI)	0.82 (0.67-1.01)	0.24 (0.11-0.51)	0.62 (0.44-0.87)	0.47 (0.29-0.78)
PPV, % (95% CI)	1.12 (0.46-2.67)	20.25 (15.26-26.37)	8.51 (4.93-14.30)	0.47 (0.32-0.68)
NPV, % (95% CI)	99.94 (99.92-99.95)	99.98 (99.96-99.99)	99.95 (99.93-99.97)	99.96 (99.94-99.98)

DR = Detection rate; FPR = False positive rate; LR = Likelihood ratio; PPV = positive predictive value; NPV = Negative predictive value; CI = confidence interval

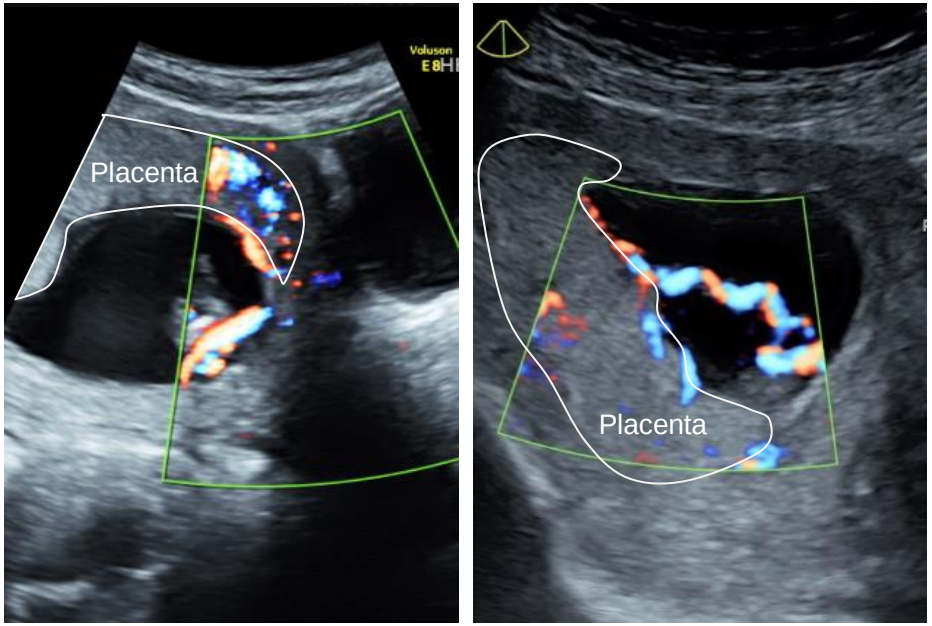

Figure 1.

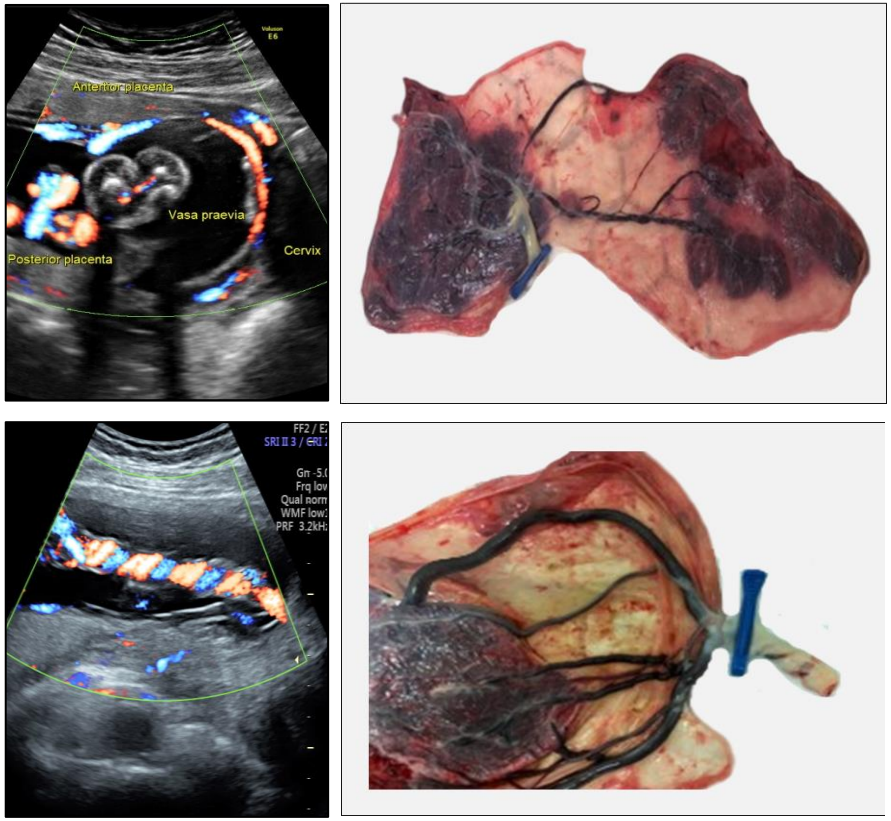

Figure 2.

Stage 1

Stage 2

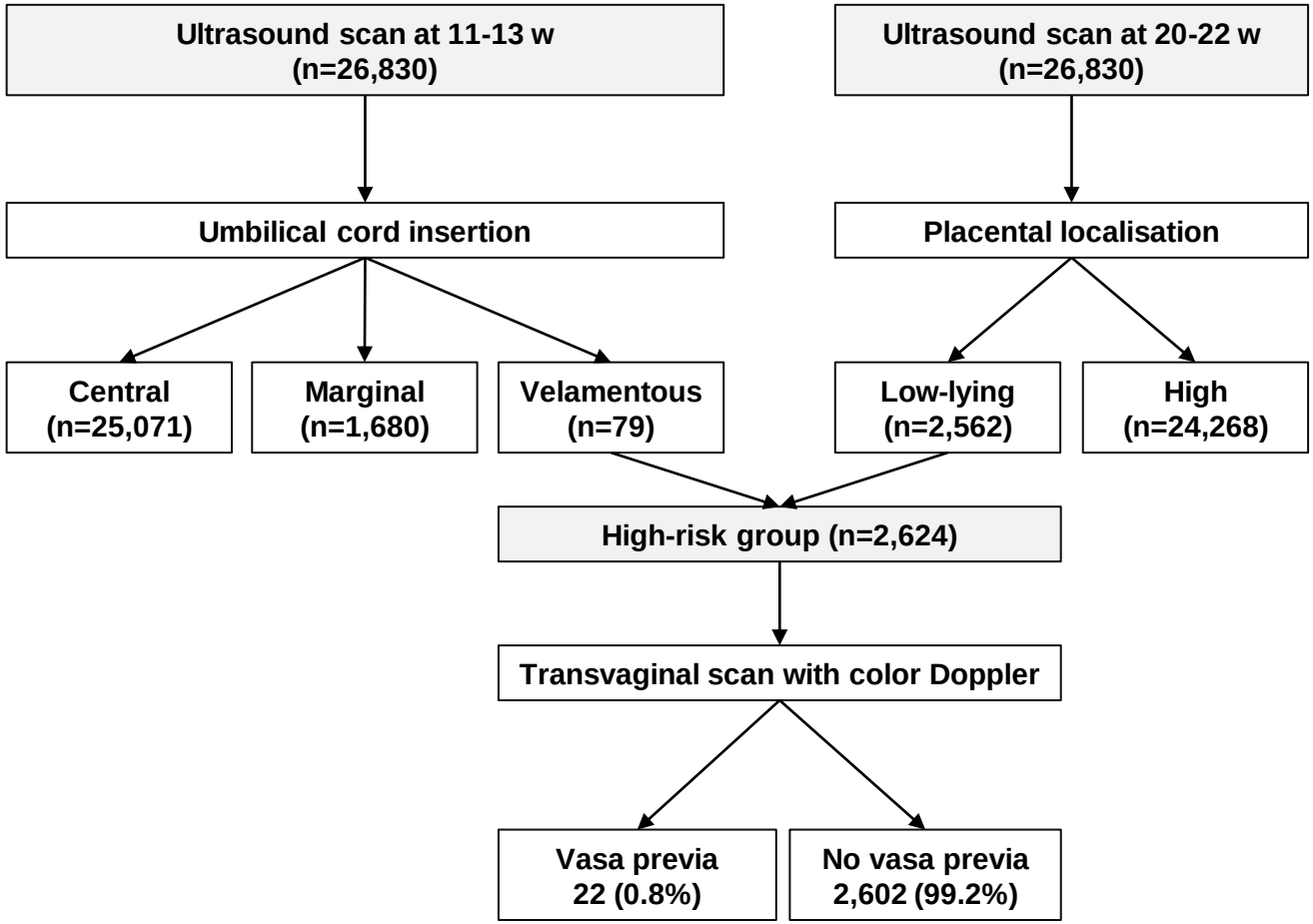

Figure 3.

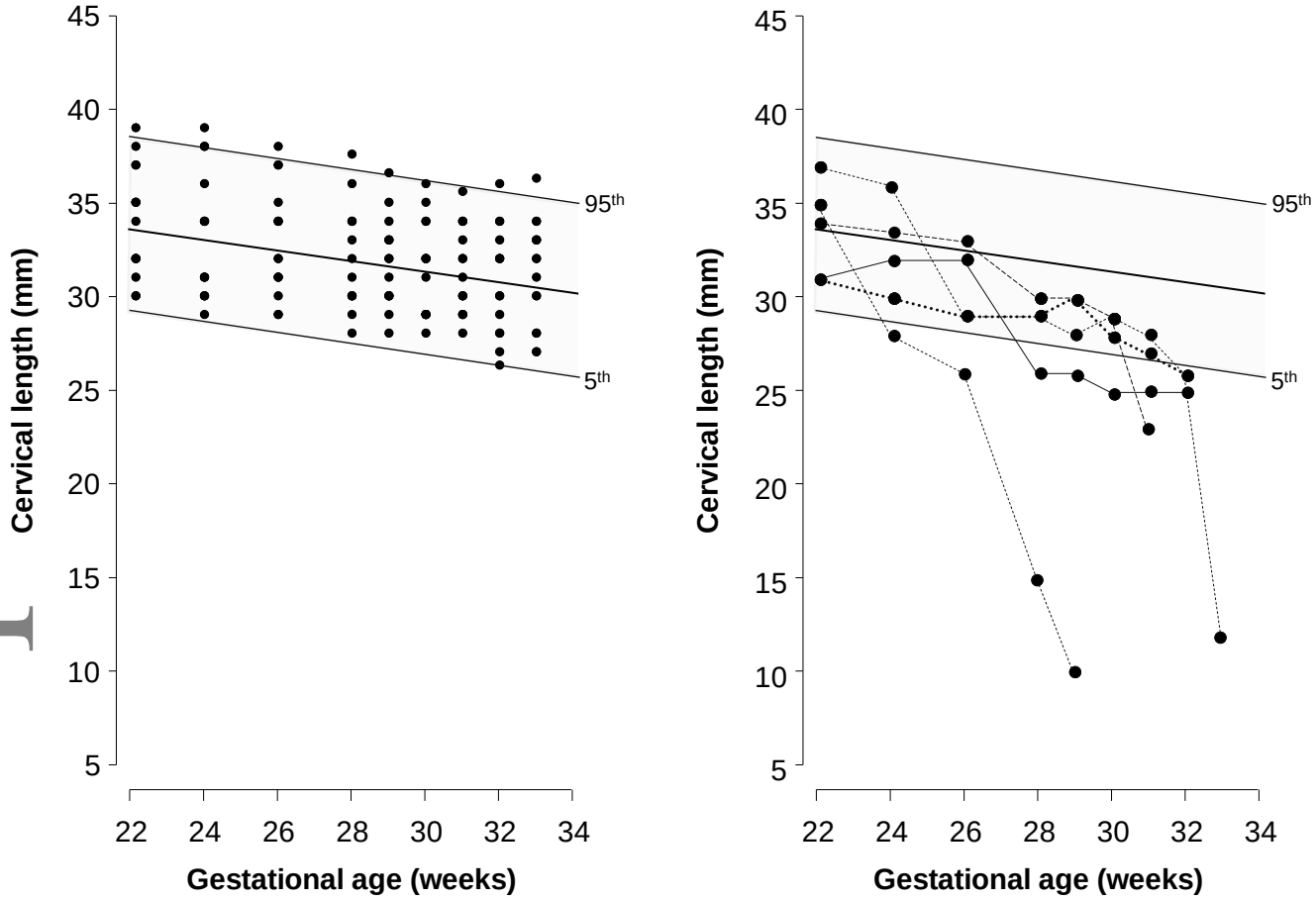

Figure 4.