Prenatal diagnosis and management of vasa previa in twin pregnancies: A case series and systematic review

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Condensation: Management strategies in twin pregnancies presenting with vasa praevia should be tailored on the basis of chorionicity and changes in cervical length.

Short title: Management of vasa previa in twins

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Abstract

Background: Twin pregnancies are at higher risks of velamentous cord insertion (VCI) and vasa previa (VP). In-vitro fertilization (IVF) is an additional direct risk factor of abnormal cord insertion and thus the incidence of VP is likely to increase over the next decades.

Objective: Our aim was to evaluate the specific challenges associated with the prenatal diagnosis and management of VP in twins.

Study design: We searched our database for twin pregnancies diagnosed with VP and managed antenatally using measurements of cervical length (CL) and performed a systematic review of articles which correlated prenatal diagnosis of VP in twins and pregnancy outcome. **Data sources:** PubMed and MEDLINE were searched for article published between the first prenatal ultrasound description of VP in 1987 and 20 October 2016 using medical subject heading (MeSH) terms, keywords and their combination including “vasa previa”, “velamentous insertion of the cord”, “velamentous vessel”, “membranous umbilical vessels”, “twin pregnancy”, “multiple pregnancy”, “placenta previa” “In vitro fertilization pregnancy”, “succenturiate lobe”, “low-lying placenta” and “bilobate placenta” as related to “sonography”, “ultrasound diagnosis”, “prenatal diagnosis” and “colour Doppler”. **Study eligibility criteria:** The primary eligibility criteria were articles which correlated prenatal ultrasound imaging of VP and pregnancy outcome. The secondary outcome was the use of CL in the management of twin pregnancies diagnosed antenatally with VP. **Study appraisal and synthesis methods:** The final selection included 3 case

report series, 9 retrospective cohort studies and 1 retrospective case-control study of VP diagnosed prenatally and confirmed at birth in twin pregnancies.

Results: The search of our databases identified six cases of dichorionic-diamniotic (DCDA) twins and 1 case of monochorionic-diamniotic (MCDA) twins diagnosed prenatally with VP between 22 and 29 weeks and managed using CL. Two cases were delivered by emergency because of rapid changes in CL in one and bleeding on placenta praevia in the other at 33 weeks and 30 weeks, respectively. The systematic review identified data on 56 cases. The incidence of twin pregnancies diagnosed antenatally with VP in the cohort and case-control studies was 11.0%. Data on chorionicity was available in only 34 cases and CL measurements were used by only the authors of two case reports and four cohort studies. VCI was the most common additional ultrasound findings in twins presenting with VP in both our series and the systematic review.

Conclusions: VP is associated with specific prenatal and obstetric complications with different outcomes in singletons compared to twins. Data on the diagnosis and management of VP in twin pregnancies are limited but there is enough evidence to warrant guidelines for targeted screening. To enable the development of efficient management protocols tailored to the need of individual cases, future studies of the screening, diagnosis and management of VP should be prospective and multicentric with detailed data on twins including chorionicity and use of CL.

Introduction

A vasa previa (VP) describes an aberrant chorionic vessel directly connected to the umbilical cord circulation but running between the amniotic and the chorionic layers of the placental free membranes below the fetal presenting part.[1] VP are classically separated into 2 different categories: type I which describes vessels that connect a velamentous cord to the main placental mass and type II which describes vessels running between one or more accessory lobes of the placenta.[1] The classic presentation of undiagnosed VP in labour is the presence of painless vaginal bleeding. This occurs mainly when the cervix is effaced and dilated and the membranes rupture spontaneously or are ruptured artificially. It can lead to rapid fetal exsanguination and death[1-5] and the perinatal mortality of undiagnosed VP has been reported to be as high as 60%.[6]

The incidence of VP has been reported to range between in 1 in 1200 to 1 in 5000 pregnancies but the condition may have been under-reported.[1-5] A recent systematic review of 10 cohort studies found that the incidence of VP is 0.6 per 1000 pregnancies.[7] Approximately 90% of women presenting with a VP also have a velamentous cord insertion (VCI) and 3-4% of women presenting with a VCI have a VP.[8] Unlike the single umbilical artery cord which is routinely recorded by midwives at birth, these cord anomalies are only recorded when associated with perinatal complications and the placental is examined by a pathologist.

The pathophysiology of VP and VCI is uncertain but it has been linked to an abnormal development of the definitive placenta. Both cord anomalies are more common in bilobated placenta, succenturiate or accessory placenta and

low-lying placenta.[1-8] VCI and VP type I are also more common in twin pregnancies and monochorionicity doubles the risk for VCI compared to dichorinicity.[11,12] Maternal smoking has been recently reported as a risk factor for VCI and thus potentially of VP.[13] Assisted reproduction technology (ART) and in vitro fertilization (IVF) in particular is associated with a higher incidence of abnormally shaped placenta, placenta previa and cord insertion outside the placental chorionic plate.[7,14] It has been hypothesized these placental and cord anomalies could be due to the inadequate orientation of the IVF blastocyst at the time of implantation or to a higher incidence of vanishing twins in IVF than in spontaneous twins.[10,14-18] The incidence of VP has been reported to be as high as one in 300 pregnancies conceived after ART.[7,14] These data suggest that the incidence of VP in both singleton and multiple pregnancy gestations is likely to increase in the next decade with the increase use of ART worldwide.

Recent national guidelines, expert reviews and decision analysis study on the management of VP have recommended delivery of all women presenting with VP between 34-36 weeks of gestation but none provide with a specific algorithm for twins.[3-6,8,19] Twin pregnancies are associated with specific obstetric complications and in particular with a higher incidence of premature delivery.[20] Like singletons, twins presenting with VP have very poor outcomes when antenatal diagnosis is not made before the onset of labour.[21] Previous studies and reviews have not identified twin pregnancies diagnosed with VP during pregnancy as requiring a different management strategy. We present a case series and a systematic review of the literature of twin pregnancies diagnosed prenatally with VP. Our aim is to evaluate the role of ultrasound

imaging in optimizing the management of individual cases of twins diagnosed antenatally with VP and in supporting the development of the corresponding clinical guidelines.

Material and Methods

Case series

The location of the placental insertion of the umbilical cord is included in our routine mid-trimester transabdominal fetal detailed anatomy ultrasound protocol in targeted cases i.e. in cases of low-lying placenta, bilobate placenta, succenturiate lobed placenta, multiple pregnancies and IVF conceptions. When a VCI is identified on transabominal ultrasound, a transvaginal scan (TVS) is performed to exclude a VP. Our units have collaborated on the use of cervical length (CL) in the management of twin pregnancies[22,23] and are using similar protocols based on national and international guidelines for the prenatal diagnosis of VP. Asymptomatic women presenting with VP are followed-up every 2 weeks, from 26-28 weeks until delivery, for fetal growth and wellbeing and with TVS for CL and VP position. The timing of delivery is scheduled according to changes in CL and/or clinical symptoms (mainly uterine contractions and/or vaginal bleeding), following a course of corticosteroids. When the CL remains stable with normal fetal development and there are no clinical symptoms delivery is planned at around 36 weeks.

Systematic review information sources and search strategy

The search protocol was designed a priori and registered on PROSPERO

(#50164). We performed an electronic search of the literature in PubMed and MEDLINE and selected relevant studies that have been published between the first prenatal ultrasound description of VP by Gianopoulos *et al.*[24] in 1987 and 20 October 2016. The search was achieved using medical subject heading (MeSH) terms, keywords and their combination including “vasa previa”, “velamentous insertion of the cord”, “velamentous vessel”, “membranous umbilical vessels”, “twin pregnancy”, “multiple pregnancy”, “placenta previa” “In vitro fertilization pregnancy”, “succenturiate lobe”, “low-lying placenta” and “bilobate placenta” as related to “sonography”, “ultrasound diagnosis”, “prenatal diagnosis” and “colour Doppler”.

We included all cohort studies and case reports that described the prenatal diagnosis of VP in women presenting with a twin pregnancy (Figure 1).

Systematic review eligibility criteria

The primary eligibility criteria were articles which correlated prenatal ultrasound imaging of VP and pregnancy outcome. The secondary outcome was the use of CL in the management of twin pregnancies diagnosed antenatally with VP. Two authors (EJ and RM) independently assessed inclusion criteria, data extraction and analysis.

Systematic review study selection

The initial database search provided 44 reports and cross-referencing provided an additional two reports, making a total of 43 records after removal of three duplicates (Figure 1). Out of the 43 records screened, 13 did not included data on prenatal ultrasound imaging of VP and were therefore excluded. After the second selection, letters with no description of the case, commentaries and

reviews were excluded. A further six reports where antenatal ultrasound was performed but cases of VP were only diagnosed at delivery were further excluded leaving 13 reports for the final analysis.

Statistical analysis

Numerical data from the case series and systematic review were analysed using the StatGraphic data analysis and statistical software package (Manugistics, Rockville, MD).

Results

Case series

The search of our databases identified seven sets of twins diagnosed prenatally with VP, followed-up using our standard protocol and confirmed at birth by detailed pathologic examination. Table 1 presents the clinical data and outcome of these cases. There were six cases of dichorionic-diamniotic (DCDA) twins and 1 case of monochorionic-diamniotic (MCDA) twins (case 7). Five DCDA cases were conceived following IVF. The mean (SD) gestational at time of diagnosis was 26+5 (3+1) weeks. In five cases, a VCI was detected on transabdominal ultrasound at the mid-trimester examination or during a fetal growth scan follow-up. In the other two cases, the diagnosis of VP was made at the time of the first CL measurement. In five cases, the CL remained >25 mm and the patients were managed conservatively without hospitalization. In one case, the CL was found to be 10 mm at 32+6 weeks (case 5) and an emergency CS performed the next day because of vaginal bleeding. One case was complicated by placenta previa accreta (case 6) for which an emergency

caesarean delivery was performed at 30+3 weeks because of major vaginal bleeding. In the case of MCDA twins (case 7), the cord of the presenting twin (fetus 1) was inserted half-way between the lower placental edge and the cervix. On TVS, there was a large VP above the internal os with non-pulsatile flow on Doppler imaging (Figures 2 A & B). This venous VP could be traced back to the area of the VCI with colour mapping. No VP arteries were found. The CL was stable on follow-up scans and there was no ultrasound evidence of twin-to-twin transfusion syndrome (TTTS) but a 20% discrepancy in estimated fetal weight was noted from 32+4 weeks and an elective caesarean delivery was performed at 35+1 weeks. The mean (SD) gestational at the time of delivery was 34.2 (2.1) weeks.

Systematic review report characteristics

We found data on 56 cases of VP diagnosed prenatally in twin pregnancies, confirmed at birth and included in 3 case report series,[25-27] 9 retrospective cohort studies[6,17,28-34] and 1 retrospective case-control study[35] (Table 2). The incidence of twin pregnancies diagnosed with VP on ultrasound during pregnancy for which ultrasound data and post-natal confirmation was available in the cohort and case-control studies was 11.0% (48 cases of twins for 438 pregnancies diagnosed with VP).

Systematic review synthesis of results

Out of the 34 cases for which data on chorionicity were available, there were 19 DCDA and 15 MCDA twin pregnancies. In one case report, the diagnosis of VP was made at the time of laser photocoagulation of communicating anastomoses in a MCDA twin pregnancy complicated by twin-twin transfusion syndrome

(TTTS).[27] The authors of two case reports[26,27] and of four cohorts[31-34] described the use of CL measurements in their management of twin pregnancies presenting with VP on antenatal ultrasound.

Only two authors of cohort studies included perinatal data on individual twin pregnancies that were diagnosed by ultrasound antenatally.[29,31] Detailed measurements of CL were only provided in two cases in a cohort series[31] and in one case report.[27] Table 3 displays the baseline perinatal characteristics of 12 cases of VP diagnosed antenatally and verified by clinical documentation at birth and/or a pathology report. In seven cases, there was information on additional ultrasound findings including a low-lying placenta and VCI in three cases[25,26] and VCI alone in two cases.[17,28] The mean (SD) gestational at the time of diagnosis was 23+6 (7+1) weeks. Information on the mode of delivery was available in eight cases including five elective and three emergency caesarean sections, two for premature rupture of the membranes[27,28] and one for preeclampsia.[17] The mean (SD) gestational at time of delivery was 32+6 (3+5) weeks. The neonatal outcome of the corresponding 24 fetuses including two stillbirths and two neonatal deaths.[29,31]

Discussion

Main findings

Our review indicates a total incidence of 11.0% of twin pregnancies in cohort studies on the prenatal diagnosis of VP. Our case series and systematic review confirm that like for singletons, the outcome for twin fetuses and neonates is

excellent when the VP is diagnosed antenatally. Determination of chorionicity and serial measurements of CL can provide individualised management pathways for twin pregnancies with VP and in particular in the timing of delivery or the need for emergent caesarean section before a planned delivery around 36 weeks.

Comparison with existing literature

A 97% survival rate has been reported in cases of VP diagnosis prenatally compared to only 44% when the diagnosis was made during delivery.[6] A recent systematic review of ultrasound in the diagnosis of VP including two prospective and six retrospective cohort studies out of which six had a poor methodology found prenatal detection rates ranging between 53% (10/19) to 100% for a total of 442,633 women, including 138 cases of VP.[36] Four out of the eight studies used TVS for primary assessment, while the remaining four studies used transabdominal ultrasound and only used TVS when a VP was suspected on the transabdominal scan. The gestational age at the time of diagnosis was reported in five studies and ranged from 18+0 to 26+6 weeks. The data of twin pregnancies were not analyzed separately by the authors. The accuracy of ultrasound at 9-13 weeks' gestation in screening for VP was evaluated prospectively in case-control study.[37] However, the definitive placenta is only fully formed by 10-11 weeks of gestation[1] making it difficult in many cases to predict the final position of the umbilical cord and to identify placental morphologic anomalies in particular in twins. The performance of ultrasound in screening for and diagnosing VP considered more efficient at around mid-

gestation[3-5,36] and the mean gestational age at diagnosis in twins, in our series and in the literature, was 26+5 and 23+6 weeks, respectively.

Cases of VP in both singletons and twins described in the literature present a pulsatile flow velocity waveforms indicative of an arterial previa vessel.[3-5,6,31] One of our case (case 7) presented with venous VP and the arteries were not visible on TVS color mapping (Figure 2B). We found no similar case described in the international literature. A venous VP could be easily mistaken for “free loop” of cord[3] and thus in particular in this case it may be useful to trace the route of the vessel to the VIC and to demonstrate that it does not “move” with changing maternal position and/or between ultrasound examinations.

Several studies have suggested that the majority of cases of VP can be suspected prenatally by routinely evaluating the placental cord insertion in pregnancies with low-lying placenta and the placental morphology.[4,6-8, 29,38] The incidence of succenturiate lobes and other morphological placental anomalies is higher in twin pregnancies.[1,11,39,40] A VCI of one of the umbilical cords is eight times more common in twins than in singletons. [39] The odd ratio for VP in pregnancies presenting with a bilobated placenta or with succenturiate lobe has been evaluated to be 22.11 in twin pregnancies.[39] Five of the seven cases of our series (Table 1) and five out of the eight cases described in details in the literature (Table 3) presented with a VCI. One cases in our series and three in the literature also presented a low-lying placenta or placenta previa. Thus, the placental cord insertion should be documented at the second trimester scan in all twin pregnancies.

The largest study to date on the perinatal outcome of VP is based on a retrospective multicentric cohort of 155 women with VP diagnosed at the mid-trimester scan and it included 50 (32.3%) cases associated with a bilobated or succenturiate lobed placentas and 95 (61%) with low-lying placenta.[6] Only seven cases (4.5%) were twin pregnancies and the authors provided with no data on chorionicity and individual outcome. Overall only half of the cohort studies that are included in the present review provide detailed data on chorionicity (Table 2). Similarly, to singleton pregnancies, a ruptured VP in the presenting twin of a DC pair will lead to acute hemorrhage in the corresponding twin. By contrast, in MC twins, the acute hemorrhage in the presenting twin may also lead to acute blood shift and rapid exsanguination in the co-twin due to the presence of inter-twin placental vascular anastomoses. Van Steenis *et al.* reported recently a case of double fatal outcome in MC twins and reviewed similar cases published in the international literature since the first case reports in 1939.[41] Including their case, there were three other recent cases reported in the last five years in the international literature but surprisingly none were diagnosed prenatally[42-44] and were, therefore, not included in the present review.

Clinical implications

The ultimate management goal of confirmed VP prenatally is to deliver before labor and in particular before the rupture of membranes while minimizing the impact of iatrogenic prematurity. There is no consensus about the time of delivery in cases of confirmed VP and the currently low prevalence of prenatal

diagnosis of this condition precludes any prospective trials to evaluate the ideal timing. Data from a decision analysis study comparing 11 strategies for delivery timing in a patient with VP found that delivery between 34 and 36 weeks balances the risk of premature rupture of the membranes and subsequent fetal hemorrhage and death versus the risks of prematurity.[19] This study did not differentiate between singleton and twin pregnancies. A cost-utility analysis based on a decision-analytic model comparing relevant strategies and life-long outcomes for mother and infant has shown that screening all twin pregnancies for VP with transvaginal ultrasound is cost-effective and has incremental cost-effectiveness ratio of $5488 per quality-adjusted life-years gained.[45] We suggest that in twins diagnosed with VP with uncomplicated antenatal course, to minimize the impact of prematurity the optimal timing for scheduled caesarean delivery is 36 weeks.

A recent systematic review and meta-analysis of the association between placental implantation abnormalities including placenta previa, placenta accreta, VP, and VIC and preterm delivery in singleton gestations has found a perinatal death rate risk ratio of 4.52 (95% CI, 2.77-7.39) for VP.[2] The associated complications of prematurity are, in many cases, the result of iatrogenic preterm birth in an effort to prevent stillbirth. Antenatal hospitalization to allow for closer surveillance for signs of labor in a unit with appropriate neonatal facilities has also been proposed for all pregnancies presenting with VP from 30-32 weeks of gestation[3-5,31] but the evidence is weak and based on low-quality evidence.[4] No specific data are available for twins pregnancies diagnosed with VP.

Twin pregnancies are at higher risks of preterm delivery and a recent retrospective cohort study of 441 women with twin pregnancies has found that integration of serial measurements of CL using a stepwise algorithm in asymptomatic women with twin gestations can improve the detection of women at risk of preterm birth.[46] Women with VP in a MC twin pregnancy also require a regular follow-up to assess the risks of TTTS and thus determining the twin chorionicity is pivotal in the management of these high-risk pregnancies.

Strengths and weaknesses

This study provides data supporting the need to screen for VP in twin pregnancies in particular those resulting from IVF. A recent systematic review and meta-analysis has found no clear evidence of benefit from planned caesarean section for term twin pregnancies with leading cephalic presentation[47] and thus for women opting for a vaginal birth it is essential to have exclude a VP antenatally. Our data also support the determination of chorionicity and use of transvaginal sonographic assessment of CL to evaluate the individual risk of premature delivery in twins presenting with VP. Overall our study is the first to highlights the need to incorporate these parameters in local protocols and national guidelines in the perinatal management of twins. The weakness of the study is its retrospective nature and the lack of specific details on twins in most cohort series. In twins diagnosed with VP antenatally in the literature, information on chorionicity was available in only 34 out of 56 (60.7%) cases and CL measurements used by only six authors out of 13 thus limiting the number of cases available for analysis.

Conclusions

VP is associated with specific prenatal and obstetric complications with different outcomes in singletons compared to twins. It is important to make the diagnosis in the second trimester to allow preventative measures to be taken and avoid subsequent perinatal complications. There is enough evidence to warrant guidelines for targeted screening with TVS and colour Doppler in twin pregnancies to rule out VP, as the relative obstetric risk is significantly higher than in singletons. In twin pregnancies, the ultrasound follow-up should also be tailored according to chorionicity, changes in cervical length and clinical symptoms. Outpatient management is possible if there is no evidence of cervical shortening on TVS and there are no symptoms of bleeding or preterm uterine activity. Multicentric prospective VP screening studies with detailed data on twins including their chorionicity are required to develop more efficient management protocols tailored to the need of individual cases.

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Figure legends

Fig 1: Flow diagram showing the selection of reports included in the review.

Fig 2: Transvaginal ultrasound scans: A) showing a large VP (arrow) above the internal os of the cervix (Cx) on color mapping; B) with non-pulsatile flow on Doppler imaging (arrow). Consent was obtained from the patient for the use of these images.

Table 1. Prenatal ultrasound data and outcome of 7 cases of twin pregnancies diagnosed with VP

Case No.	GA at diagnosis (wks + days)	Other US findings	Chorionicity-amnionicity	CL (mm) at last TVS (GA wks + days)	GA at delivery (wks + days)	Outcome Mode of delivery Fetal sex & weight (g)
1	28+2	None	DCDA	30 (32+3)	36+1	ElCS M2810/M2850
2	29+1	None	DCDA	33 (32+5)	34+0	ElCS F2026/F2030
3	29+2	VCI & SUA x2	DCDA	38 (34+2)	35+0	ElCS M2040/M2240
4	22+0	VCI	DCDA	34 (35+5)	36+2	ElCS F2270/M2370
5	29+2	VCI	DCDA	10 (32+6)	33+0	EmCS M1720/F1730
6	25+4	VCI & PP	DCDA	30 (28+2)	30+3	EmCS F1240/M1240
7	23+2	VCI	MCDA	30 (34+0)	35+1	ElCS F2910/F2400

VCI = velamentous cord insertion; PP = placenta previa; SUA = single umbilical artery; DCDA = dichorionic-diamniotic; MCDA = monochorionic-diamniotic; ElCS = elective caesarean section; EmCS = emergency caesarean section; F = female; M = male.

Table 2. Characteristics of the 13 reports included in the review

Author (year)	Type of study	No. of cases of VP diagnosed antenatally and confirmed at birth	No. of twin pregnancies with VP	Chorionicity
Raga *et al.*[25] (1995)	Case report	2	1	DCDA
Nomiyama *et al.*[28] (1998)	Cohort study of VCI (n=6)	2	1	DCDA
Lee *et al.*[29] (2000)	Cohort study of VP	18	2	N/A
Francois *et al.*[35] (2003)	Case-control study of VP	13	1	N/A
Oyelese *et al.*[6] (2004)	Multicenter cohort study of VP	155	7	N/A
Baulies *et al.*[17] (2007)	Cohort study of VP	9	2	2 DCDA
Ghandi *et al.*[26] 2008	Case report	3	3	3 DCDA
Chmait *et al.*[27] (2010)	Case report	2	1	MCDA
Smorgick *et al.*[30] (2010)	Cohort study of VP	19	3	3 DCDA
Bronsteen *et al.*[31] (2013)	Cohort study of VP	56	7	N/A
Rebarber *et al.*[32] (2014)	Cohort study of VP	29	5	3 DCDA 2 MCDA
Swank *et al.*[33] (2016)	Multicenter cohort study of VP	47	5	N/A
Catanzarite *et al.*[34] (2016)	Cohort study of VP	92	18	6 DCDA 12 MCDA

VCI = velamentous cord insertion; VP= vasa previa; DCDA= dichorionic-diamniotic; MCDA = monochorionic-diamniotic; N/A= not available.

Table 3. Baseline perinatal characteristics of 12 VP cases included in the review

Author (year)	GA at diagnosis (wks)	Other US findings	Chorionicity-amnionicity	CL (mm) at last TVS (wks)	GA at delivery (wks +days)	Outcome Mode of delivery Fetal sex & weight (g)
Raga *et al.*[25] (1995)	34	VCI&LLP	DCDA	N/A	38	ElCS M2810/F?
Nomiyama *et al.*[28] (1998)	18	VCI	DCDA	N/A	31	EmCS F2026/F2030
Lee *et al.*[29] (2000)	N/A N/A	N/A N/A	N/A N/A	N/A N/A	N/A 27+1	1 Stillbirth 1 post-natal death
Baulies *et al.*[17] (2007)	35 21	None VCI	DCDA DCDA	N/A N/A	36 34	EmCS F3050/M2210 ElCS F1669/M1990
Ghandi *et al.*[26] (2008)	29 18 19	None VCI&LLP VCI&LLP	DCDA DCDA DCDA	N/A N/A N/A	34 34 35	ElCS ElCS ElCS
Chmait *et al.*[27] (2010)	22	TTTS	MCDA	11 (30+5)	34+3	EmCS F2656/1240
Bronsteen *et al.*[31] (2013)	N/A N/A	N/A N/A	N/A N/A	25 (24) 15 (28)	27 31	1 post-natal death Stillbirth

GA = Gestational age; wks = weeks; VCI = velamentous cord insertion; LLP = low-lying placenta; SUA = single umbilical artery; DCDA = dichorionic-diamniotic; MCDA = monochorionic-diamniotic; TTTS = twin-twin transfusion syndrome; ElCS = elective caesarean section; EmCS = emergency caesarean section; F = female; M = male; N/A = not available

Figure 1 Flow Chart

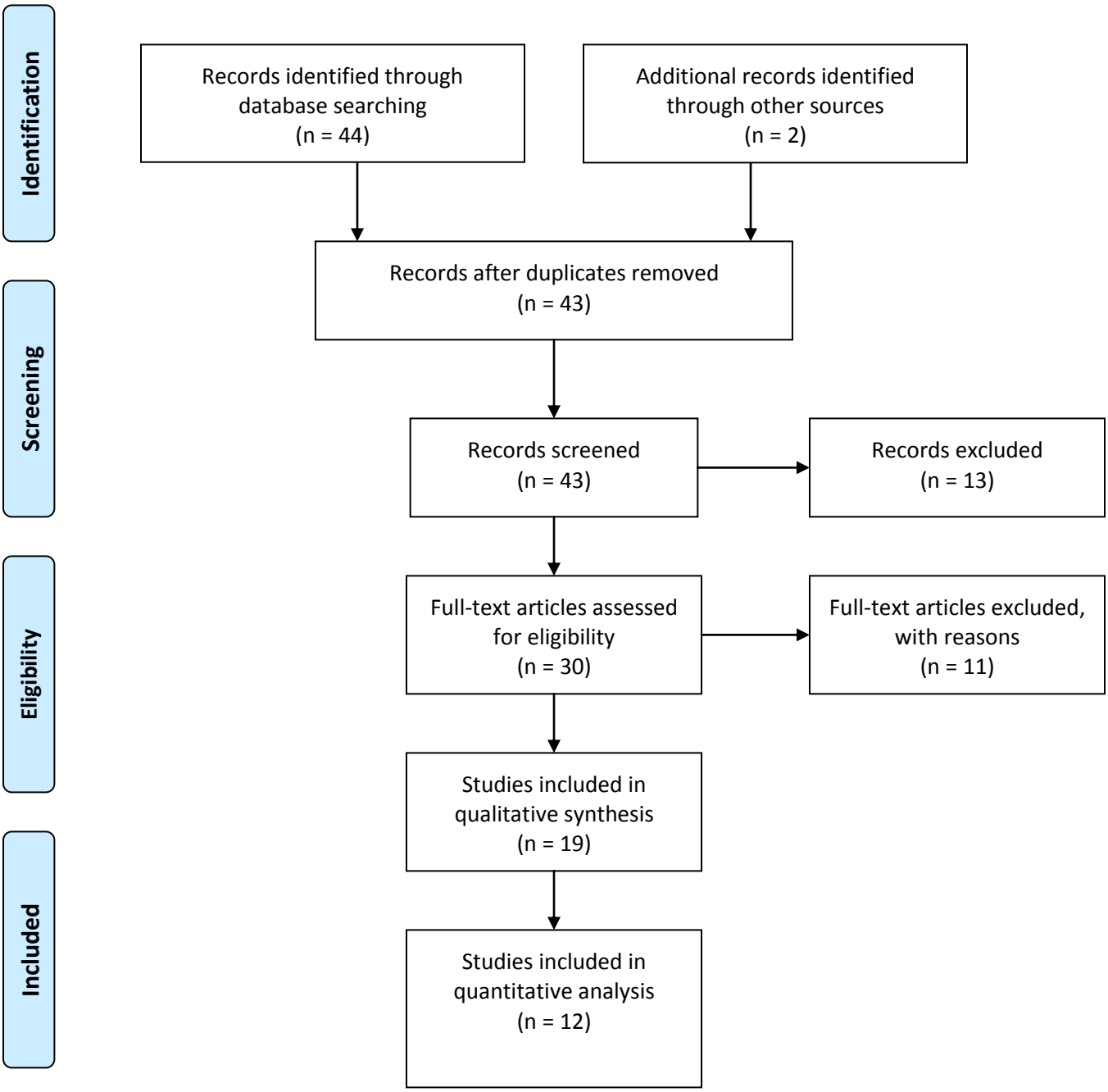

Figure 2A US

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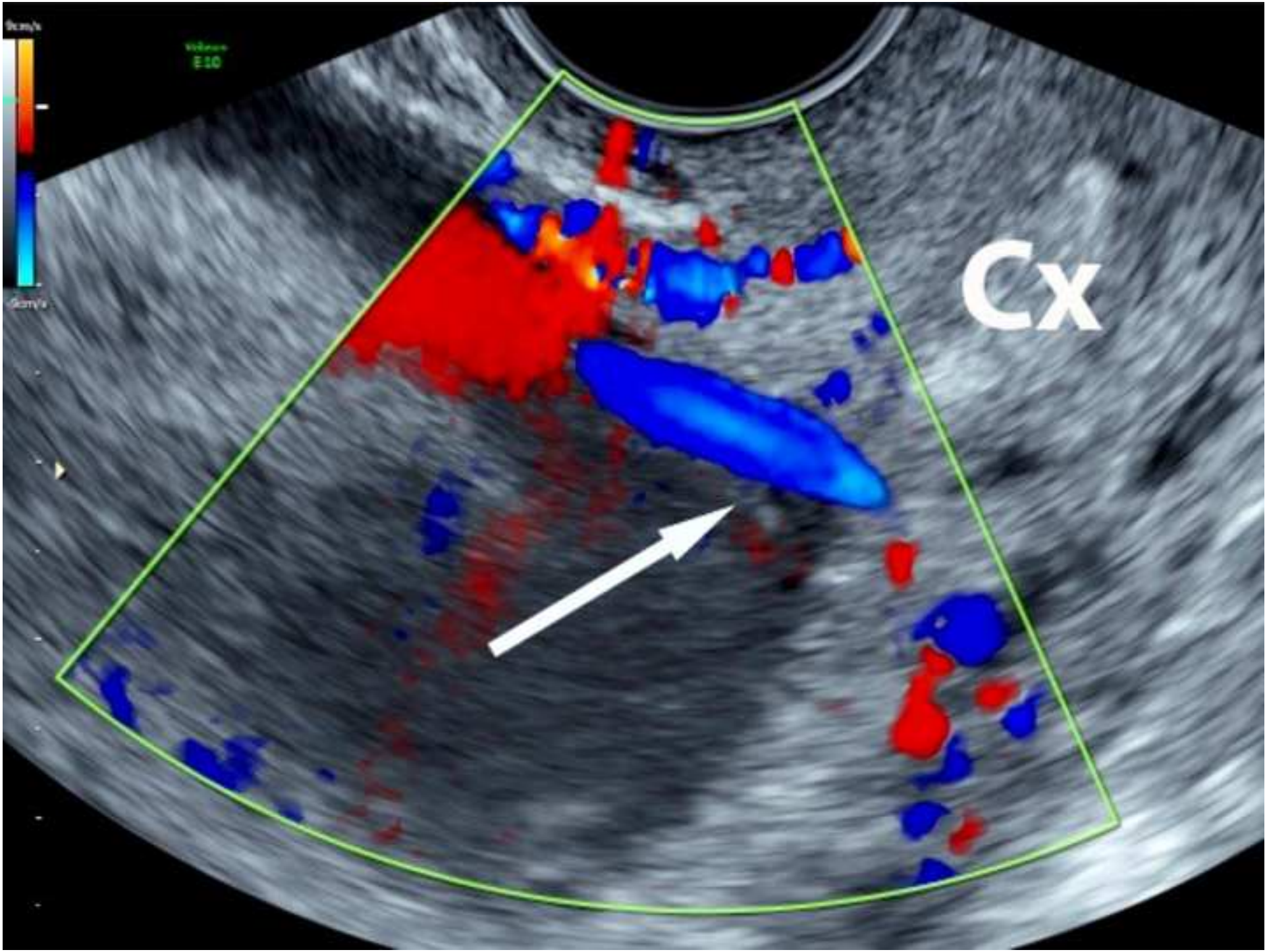

Figure 2B US

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