Review

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The Umbilical Cord and Complications of Twin Gestations

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Abstract

The rate of twin pregnancies has increased over the last decades, largely because of the ongoing development of assisted reproductive technology and increased maternal age at childbearing. Twins have a higher risk of adverse outcomes during pregnancy and the perinatal period. The prevalence of umbilical cord abnormalities is higher for twin pregnancies compared with singleton pregnancies. Some of these abnormalities are nonspecific to twinning and can also be found in singleton gestations (such as velamentous cord insertion, vasa previa, and single umbilical artery). Other abnormalities are associated with monochorionic twins, such as umbilical cord entanglement, and umbilical proximate cord insertion. Most of these abnormalities can be detected by ultrasound evaluation. The early and accurate ultrasound diagnosis of chorionicity, amnionicity, and placental and umbilical cord characteristics is crucial if we are to predict the risk of complications and to determine the best management for twin pregnancies. Histopathological examination of the placenta and umbilical cord after delivery can help to confirm prenatal diagnosis and to provide a better understanding of the physiopathology of their abnormalities. The aim of this review was to emphasize the role that the umbilical cord plays in twin complications and to describe the management of these high-risk pregnancies.

Keywords: Pregnancy, twin; Chorionicity; Cord entanglement; Twin reversed arterial perfusion sequence; Umbilical cord; Vasa previa; Velamentous cord insertion

Introduction

Over the last few decades, the rates of twin pregnancy have increased across the world, predominantly owing to the ongoing development of assisted reproductive technology (ART) and the increased maternal age at childbearing.[1–3] The risk of maternal complications and adverse perinatal outcomes is higher for twin pregnancies when compared with singletons.[4] Twin pregnancies are at a higher risk of spontaneous or late miscarriage, preterm birth, preeclampsia, gestational diabetes, antepartum bleeding, postpartum hemorrhage, congenital anomalies, aneuploidy, low birth weight, intrauterine growth restriction, intrauterine demise, and a low Apgar score at birth.[4–10] Adverse perinatal outcomes are also more frequent because newborns are more likely to develop respiratory disorders, necrotizing enterocolitis, brain damage, and long-term developmental morbidity, mostly related to prematurity.[11]

Chorionicity is an essential prognostic factor. Dichorionic twins can be either dizygotic or monozygotic, whereas monochorionic twins are always monozygotic. In monozygotic twins, the type of placentation will differ according to the sequence in which the zygote splits. As shown in Figure 1, splitting before day 4 postfertilization results in a dichorionic diamniotic twin pregnancy, which features the development of two embryos, two amnions, and two chorions. Two distinct placentas or a single fused placental mass may also develop. Splitting between days 4 and 8 postfertilization results in a monochorionic diamniotic twin pregnancy, leading to the development of two embryos separated by only two thin layers of amniotic membrane. Splitting between days 8 and 13 postfertilization results in a monochorionic monoamniotic (MCMA) twin pregnancy, leading to the development of two embryos in a common amniotic sac. Splitting after day 13 postfertilization results in conjoined twins.

The early and accurate ultrasound diagnosis of chorionicity, amnionicity, placental and umbilical cord characteristics is essential if we are to predict the risk of complications and to select the best management option. Chorionicity should be assessed as early as possible in multiple pregnancies because this can improve the reliability of diagnosis.[6,7,12]

The prevalence of umbilical cord abnormalities is higher for twin pregnancies.[6,7] These abnormalities can significantly affect perinatal morbidity and mortality, as they may be responsible for certain pregnancy complications. Some abnormalities are nonspecific to multiple pregnancies, including velamentous cord insertion (VCI), vasa previa (VP), and single umbilical artery (SUA). Others are related with monochorionicity, including umbilical cord entanglement and umbilical cord proximate insertion.[6] Moreover, umbilical cord abnormalities are frequently associated with twin reversed arterial perfusion (TRAP) sequence and conjoined twins.

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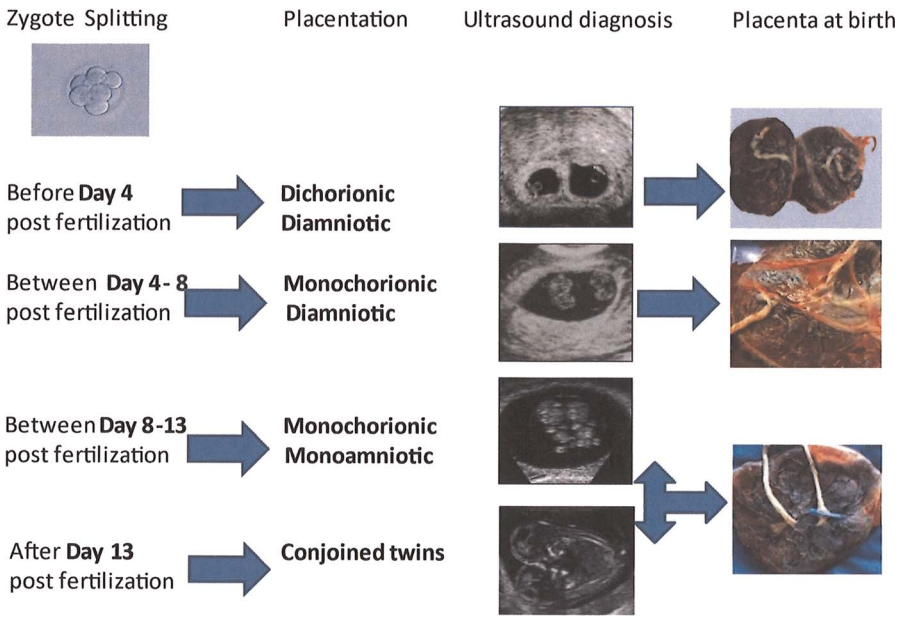

Figure 1. Ultrasound aspects of different placentation types in monozygotic twins according to the zygote splitting sequence.

The aim of this review was to highlight the importance of umbilical cord assessment in twin pregnancies as some anomalies can worsen perinatal outcomes. The presence of these anomalies should imply a close follow-up of these high-risk pregnancies.

Nonspecific cord abnormalities in twin gestations

VCI

The insertion of the umbilical cord into the placenta can be central, eccentric, marginal, or velamentous. Central and eccentric insertions represent more than 90% of such cord insertions.[13] A marginal cord is characterized by insertion on the edge of the placenta. In VCI, the umbilical vessels are located on the fetal membranes rather than in the placenta. Umbilical vessels are not protected by Wharton's jelly and have an increased risk of compression or rupture (Fig. 2).[13,14]

VCI affects around 1% of singleton pregnancies and 6% of twin pregnancies. There are several risk factors for VCI, including twin pregnancies, ART techniques, advanced maternal age, maternal chronic disease (asthma, chronic hypertension, type 1 or gestational diabetes), smoking at the beginning of pregnancy, previous pregnancy with abnormal cord insertion, and previous cesarean delivery.[14]

The prenatal ultrasound diagnosis of VCI is essential as this condition is associated with adverse perinatal outcomes such as fetal growth restriction, congenital anomalies, preterm delivery, intrauterine fetal death, low Apgar scores, transfer to a neonatal intensive care unit, placenta previa and/or bipartita, placental abruption, VP, and emergency cesarean section.[13–19]

As these conditions may be recurrent, Ebbing *et al.*[14] suggested that these cord anomalies could occur due to alterations in placental development. The growth of the placenta and the umbilical cord is influenced by environmental and maternal factors and by the characteristics of the conceptus itself.[14]

The prevalence of VCI is higher in twin pregnancies than in singleton pregnancies.[14] A VCI of one of the umbilical cords is eight-fold more frequent in twins than in singletons, with a double risk in monochorionic twins and a three-fold higher risk in twin pregnancies with fetal growth restriction.[6,13,14] Singleton pregnancies after ARTs are more often affected by abnormal cord insertion (marginal or velamentous) than spontaneous pregnancies, but this is not observed in twin pregnancies.[6,20]

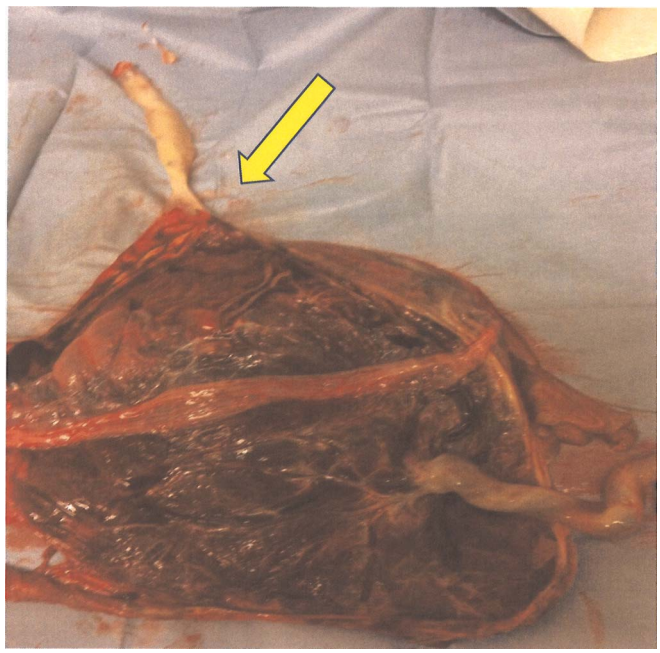

Figure 2. Velamentous cord insertion in dichorionic twin pregnancy (arrow). Obtained with the patient consent.

Some authors speculate that VCI and abnormal placental implantation may share similar developmental origins, a process also known as trophotropism, in which the placenta develops preferentially at sites for optimal uterine perfusion.[14,19,21]

VCI in monochorionic twins is a risk factor for selective fetal growth restriction and birth-weight discordance; this is because VCI is more prone to compression and blood flow reduction toward the fetus.[22–24]

The link between VCI and twin-to-twin transfusion syndrome (TTTS) is less clear. Although some studies report an association between VCI and TTTS,[25–29] this remains controversial.[23,24,30–34] Kalafat *et al.*[32] reported a significant correlation between VCI and birth-weight discordance in twins, particularly in monochorionic twins. VCI in monochorionic twins was also associated with the development of selective fetal growth restriction and severe birth-weight discordance but not with TTTS. This specific complication of monochorionic twin pregnancies is more the consequence of unbalanced intertwin blood transfusion through placental vascular anastomoses than VCI.[32] In our institution, the rate of TTTS in monochorionic pregnancies was similar when compared between a VCI group and a normal cord insertion group (S. Omar Moussa, MD, unpublished data, April 2017).

Costa-Castro *et al.*[34] reported an association between VCI and an increased risk of small for gestational age, severe birth weight discordance (>25%), and intrauterine fetal demise in monochorionic twins but not in dichorionic twins. These results confirmed those of the Evaluation of Sonographic Predictors of Restricted Growth in Twins(ESPRiT) study in which no correlation was found between umbilical cord insertion and growth discordance in dichorionic twin pregnancies.[23]

VP

VP is an aberrant chorionic vessel connected to the umbilical cord circulation but crossing the internal os of the cervix below the fetal presenting part (Fig. 3).[35,36] The prevalence of VP is approximately one in every 2500 deliveries.[37,38] The risk factors for VP include ART, multiple pregnancies, VCI, SUA, and placental abnormalities such as low-lying or previa placenta, bilobate, succenturiate, or accessory placenta.[35–37]

VP is a life-threatening condition when antenatal diagnosis is not performed before the onset of labor, thus leading to a high rate of fetal or neonatal death. VP is characterized by painless vaginal bleeding due to rupture of the vessels at spontaneous or artificial rupture of membranes. This can lead to fetal death by acute exsanguination.[35]

In dichorionic twins, as in singleton pregnancies, this complication concerns only one twin. However, in monochorionic twins, VP rupture may have severe consequences for the cotwin with exsanguination via intertwin placental vascular anastomoses; there is also a risk of double fetal deaths.[35]

The prenatal diagnosis of VP by ultrasound is critical for fetal prognosis and can be easily performed by transvaginal examination of the cervix using color Doppler. An umbilical vessel crossing the internal os of the cervix can be visualized even after manual mobilization of the uterus.[37] Oyelese *et al.*[39] previously reported a 97% survival rate when VP was diagnosed prenatally compared with only 44% when the diagnosis was made at the time of the delivery.

The incidence of VP is higher in twin pregnancies than in singletons, as placental abnormalities and VCI are more frequent in twins.[40] Cipriano *et al.*[41] reported that screening all twin pregnancies for VP with a transvaginal ultrasound is a cost-effective measure and can evaluate cervical length and, consequently, the risk of preterm birth; however, this technique could also exclude an abnormal placental insertion or a VP.

For twin pregnancies, serial measurements of cervical length in asymptomatic women can detect the risk of preterm birth.[42] A cervical length of >25 mm is the threshold for conservative management in asymptomatic women with twins. Jauniaux *et al.*[35] suggested that a cervical length of ≥30 mm could be a better limit to allow for conservative management in women with twins and VP.

The management of VP aims to deliver the patient before the onset of labor, particularly before the rupture of membranes.[35] Outpatient management is possible if there is no cervical shortening on transvaginal scans, no bleeding and no preterm labor. The administration of antenatal corticosteroid should be offered from 28 to 32 weeks of gestation. For all pregnancies diagnosed prenatally with VP, it is recommended to perform an elective cesarean section between 34 and 36 weeks of gestation in a tertiary center.[35,43,44] However, there are no specific guidelines relating to the optimal timing of delivery for twin pregnancies with VP.

SUA

SUA is the most common congenital abnormality affecting the umbilical cord and is present in 4% to 11% of twin pregnancies.[45] The incidence of SUA is similar in dichorionic and monochorionic twins.[46] The pathogenesis of SUA is complex and is likely to be linked to genetic and/or environmental factors. Antoniou *et al.*[47] studied the contributions of genetic and environmental determinants on umbilical cord morphology in more than 10,000 twins and concluded that these factors play a substantial role in the development of SUA and other related anomalies of the cord.[47]

Twin fetuses with SUA are at an increased risk for growth restriction and preterm delivery <28 weeks when compared with control twin fetuses.[6,48] The presence of SUA indicates a greater risk for deficient growth; therefore, such patients need to be followed-up closely.

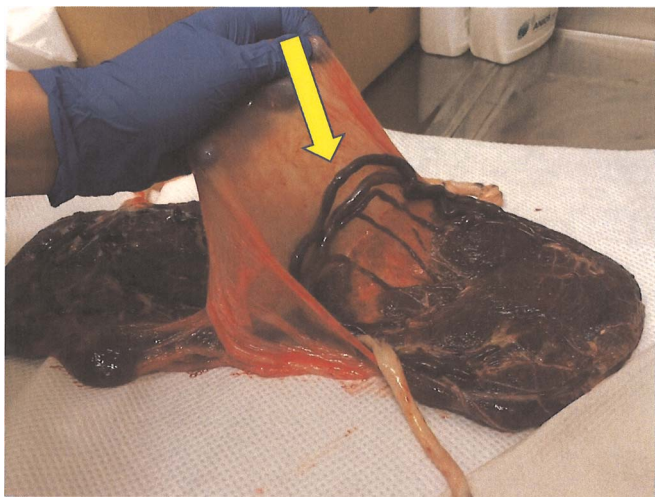

Figure 3. Vasa previa and velamentous cord insertion in twin pregnancy. Obtained with the patient consent.

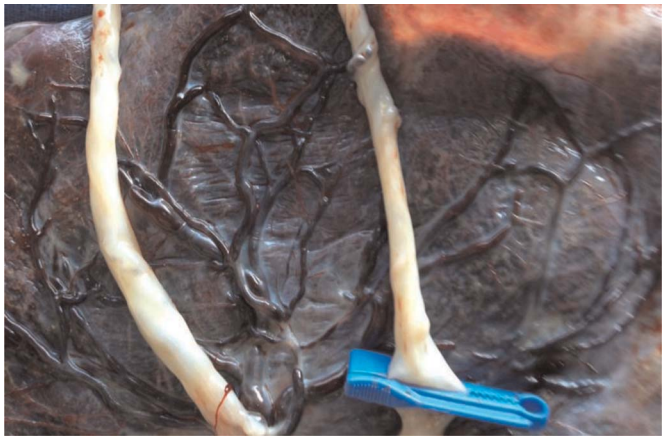

Figure 4. Umbilical proximate cord insertion in a monoamniotic twin pregnancy. Obtained with the patient consent.

Klatt *et al.*[46] reported that, in twin gestations compared with singletons, the sonographic cross-sectional area of the single artery shows a failure of adaptive dilatation that is usually seen in singletons with SUA. This phenomenon could, at least in part, explain the fact that twins with SUA have a higher rate of SGA than singletons.[46] Klatt *et al.*[46] reported that, compared with dichorionic twins with SUA, monochorionic twins more commonly experienced weight discordance of >20%; however, this was not statistically significant.

Umbilical cord abnormalities related to monochorionic twin gestations

Umbilical proximate cord insertion (PCI)

The literature describes fetal outcomes for marginal or VCI, but not for PCI. PCI corresponds to a specific abnormal umbilical cord insertion in monochorionic twins and is characterized by close cord insertion sites (Fig. 4).

Zhao *et al.*[49] established a reference range for the distance between umbilical cord insertions across gestational age. In monochorionic placentas, the distance between the insertion of the cords can vary from 4 to 25 cm at term. PCI is defined as a distance between the cord insertions that is lower than the 5th centile. The cutoff value for PCI ranged slightly during gestation, from 3.3 to 4 cm. PCI is rare in monochorionic diamniotic placentas (0%–4%) but is common in MCMA placentas (53%),[49,50] and can arise from the delayed splitting of the inner cell mass into monoamniotic twins (around 8–12 days after fertilization). PCI is a causal factor underlying cord entanglement in monoamniotic twin pregnancies.[49]

Zhao *et al.*[49] previously reported a correlation between PCI in monochorionic placentas and an increased prevalence of arterio-arterial and/or venovenous anastomoses. The higher rate of venovenous anastomoses associated with PCI is a well-known factor underlying adverse fetal outcomes such as TTTS and perinatal mortality.[6,51]

In monochorionic pregnancies complicated by TTTS, PCI may represent a technical challenge for fetoscopic laser coagulation of anastomoses because of the poor visibility of the vascular equator; thus, leading to incomplete or failure of the treatment.[6,49,52]

Umbilical cord entanglement

The prevalence of MCMA twin pregnancy is rare and accounts for approximately 1% of all monozygotic pregnancies[53] and 1/10,000 pregnancies.[54,55] Monoamniotic twins result from ovum division beyond 8 days postconception. Monoamniotic twins share a single placenta and amniotic cavity.

MCMA is associated with an increased risk of adverse pregnancy outcomes in comparison with monochorionic diamniotic or dichorionic pregnancies. The high perinatal mortality rate is due to umbilical cord entanglement, TTTS, prematurity, congenital anomalies, and growth restriction.[6,7,53–56]

Umbilical cord entanglement is a specific complication of MCMA twins, occurs in almost all MCMA pregnancies and is responsible for the increased risk of sudden dual or single fetal demise.[6,54,57,58] MCMA can be diagnosed with ultrasound early in pregnancy from 10 weeks of gestation presenting as the so-called "Y-sign" (Fig. 5).[6] Cord entanglement has also been described after spontaneous or iatrogenous septostomy in both monochorionic diamniotic and dichorionic diamniotic twins.[6,59,60]

Cord entanglement can be detected by ultrasound using two-dimensional, three-dimensional or directional color Doppler methodology.[6,61] Color flow mapping and Doppler velocimetry are associated with a positive predictive value of 89% for the diagnosis of cord entanglement (Fig. 6).[61]

The perinatal mortality of MCMA twin pregnancies is high and ranges from 10% to 40%.[57,58,62,63] However, recent data suggest a rate of about 10%, resulting from a better prenatal diagnosis, repeated fetal monitoring, and elective preterm delivery.[64]

MCMA twins need to be followed-up closely to prevent fetal morbidity and mortality associated with chronic or acute cord compression (Fig. 7).[65] Heyborne *et al.*[66] reported the improved neonatal outcomes of patients undergoing elective inpatient fetal monitoring. D'Antonio *et al.*[67] performed a meta-analysis and found that the incidence of fetal loss was 3% in pregnancies managed mainly as inpatients compared

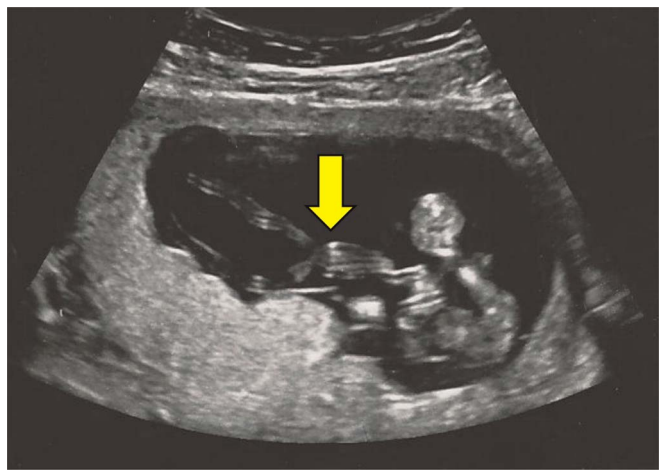

Figure 5. First-trimester ultrasound of a monochorionic-monoamniotic twin pregnancy showing a single sac and twisted umbilical cords or Y sign (arrow). Reprinted from American Journal of Obstetrics and Gynecology, Vol 213, Hubinont C, Lewi L, Bernard P, Marbaix E, Debièvre F, Jauniaux E. S91-S102, Copyright (2015), with permission from Elsevier.[6]

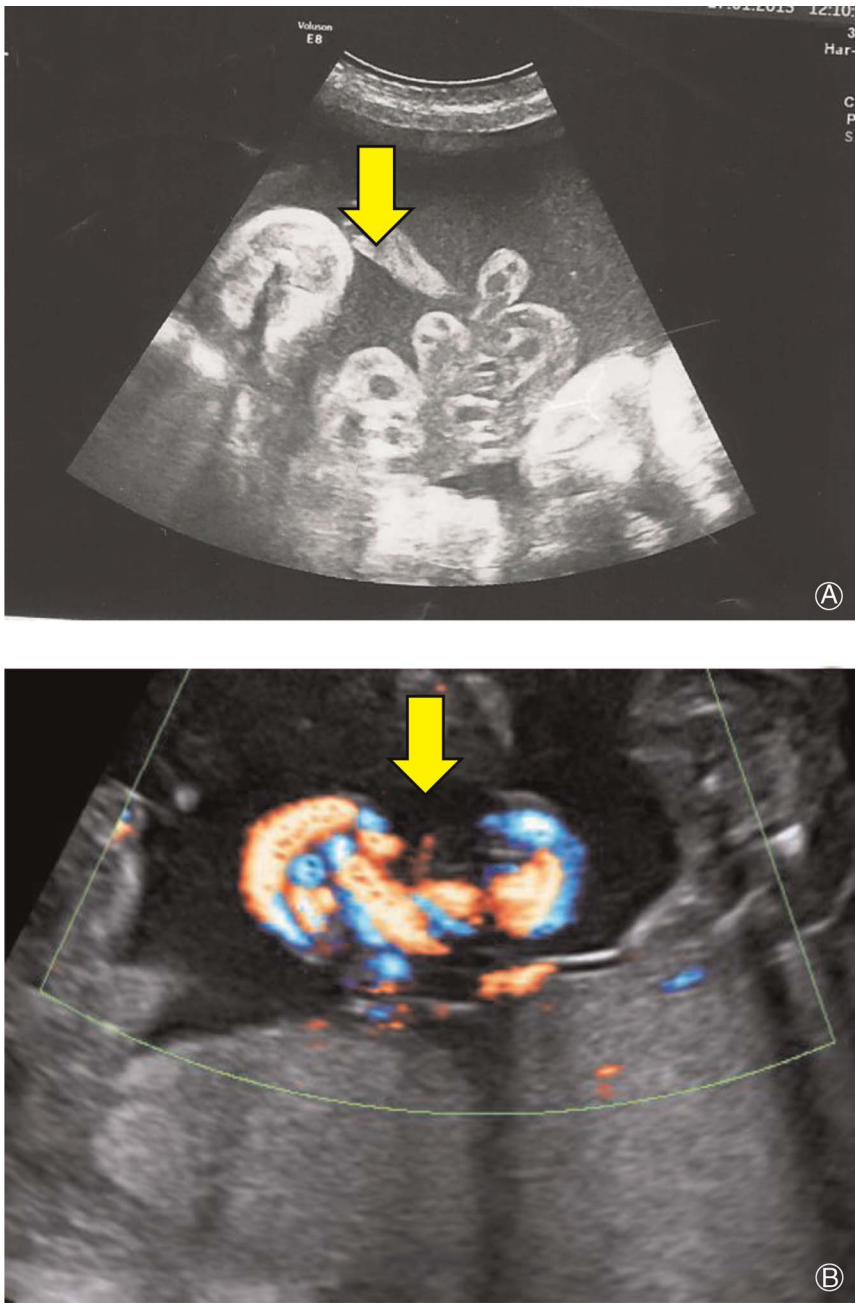

Figure 6. Ultrasound imaging of cord entanglement (arrow) in monochorionic- monoamniotic twins. A Two-dimensional ultrasound at 32 weeks. B Directional color power Doppler at 28 weeks. Reprinted from American Journal of Obstetrics and Gynecology, Vol 213, Hubinont C, Lewi L, Bernard P, Marbaix E, Debièvre F, Jauniaux E.S91-S102, Copyright (2015), with permission from Elsevier.[6]

with 7% in pregnancies followed up as outpatients. Van Mieghem *et al.*[57] reported a low risk of perinatal complications with close fetal monitoring from 26 to 28 weeks of gestation and delivery around 32 to 34 weeks of gestation, regardless of the follow-up setting. During the third term, the risk of neonatal mortality/complications is low in comparison with the risk of intrauterine death. The Monochorionic Monoamniotic (MONOMONO) study also reported that fetal monitoring is essential to achieve good outcomes in MCMA pregnancies, regardless of the surveillance setting.[64] In 2020, the Society for Maternal-Fetal Medicine(SMFM) Special Statement published a checklist for managing MCMA pregnancies that featured serial ultrasound starting from 16 weeks of gestation; every two weeks for the assessment of amniotic fluid volume and bladder filling, and every two to four weeks for the evaluation of fetal growth. A detailed fetal anatomy survey should be performed at 18 to 22 weeks of gestation (or earlier if technically feasible) and a fetal echocardiogram should be performed at 18 to 22 weeks of gestation. The choice of an inpatient or outpatient setting is dependent on the obstetrics team. Elective cesarean delivery should be performed between 32 and

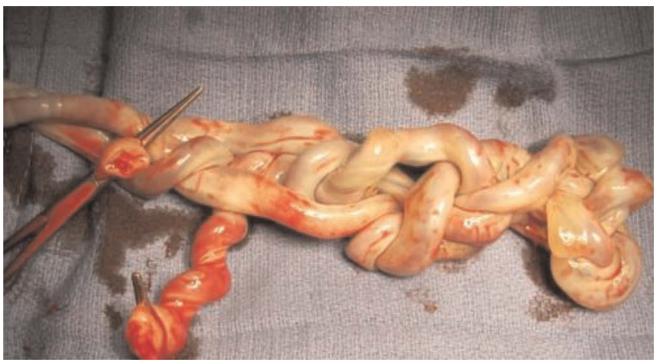

Figure 7. Cord entanglement at birth in a monoamniotic twin pregnancy. Obtained with patient consent.

34 weeks of gestation or earlier if there are complications. Antenatal corticosteroids should be provided within the seven days prior to delivery.[68]

Diseases associated with umbilical cord abnormalities

TRAP

Acardiac twinning or TRAP sequence is a specific and severe complication of monochorionic twin pregnancy. TRAP affects one in 100 monozygotic twin pregnancies and one in 35,000 pregnancies.[6,69] In a previous study, van Gemert *et al.*[70] reported that the incidence of TRAP increased from 1% to 2.6% of monozygotic twins and from 1/35,000 to 1/9500 to 11,000 pregnancies due to better ultrasound diagnosis and the development of ART.

As shown in Figures 8 and 9, in TRAP sequence, the normal (or "pump") twin should provide blood flow for itself and for the acardiac twin through an arterio-arterial anastomosis. Blood returns to the pump twin via a venovenous anastomosis. The arterial perfusion pressure of the pump twin exceeds that of the acardiac twin. This abnormal and unidirectional vascular supply results in different degrees of deficient development that affects the head, heart, and upper limb structures.[56]

The perinatal complications associated with TRAP sequence mainly relate to pump-twin congestive heart failure which is responsible for polyhydramnios and preterm birth.[6,47,69] The normal twin has a mortality rate of up to 55%.[7,69]

The best treatment for TRAP sequence is an interruption of the vascular supply to the acardiac twin with the aim of protecting the pump twin. This can occur spontaneously, but this is rare and associated with a high rate of miscarriage, intrauterine demise, or pump twin sequelae.[71,72] Because pump twin demise is difficult to predict and because there is a high spontaneous rate of loss in early pregnancy, an elective therapeutic intervention appears to be indicated in all cases of TRAP sequence rather than expective management.[73]

Several therapeutic techniques have been reported such as fetoscopic techniques (cord coagulation, cord ligation, and photocoagulation of the anastomoses) and intrafetal coagulations (radiofrequency ablation (RFA) and intrafetal laser (IFL) therapy.[74–78]

Most of these techniques can only be performed safely after 16 weeks of pregnancy, when the amnion and chorion are fused. Lewi *et al.*[71] reported a high mortality rate of 33% when TRAP was diagnosed in the first trimester and when intervention was planned at 16 to 18 weeks of gestation.

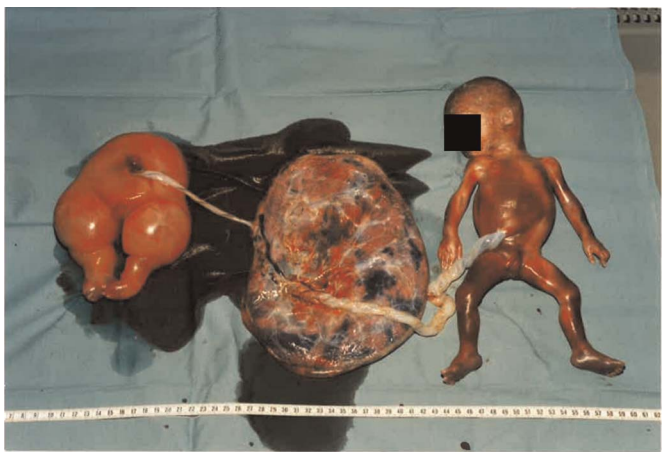

Figure 8. Twin reversed arterial perfusion sequence with a pump twin (right) and an acardiac twin (left) with a two vessels cord at 23 weeks of gestation. Obtained with the patient consent.

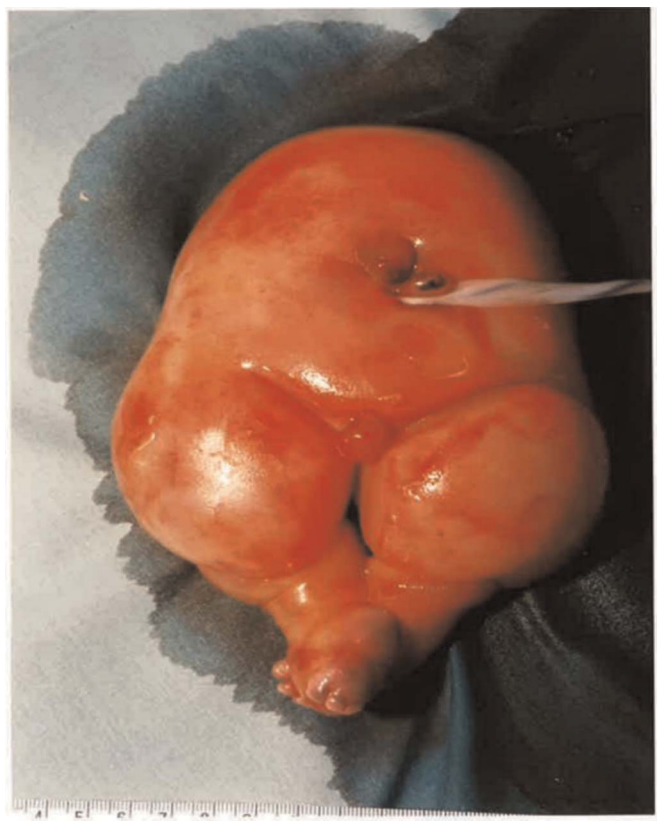

Figure 9. Acardiac twin with a two vessel cord. Obtained with patient consent.

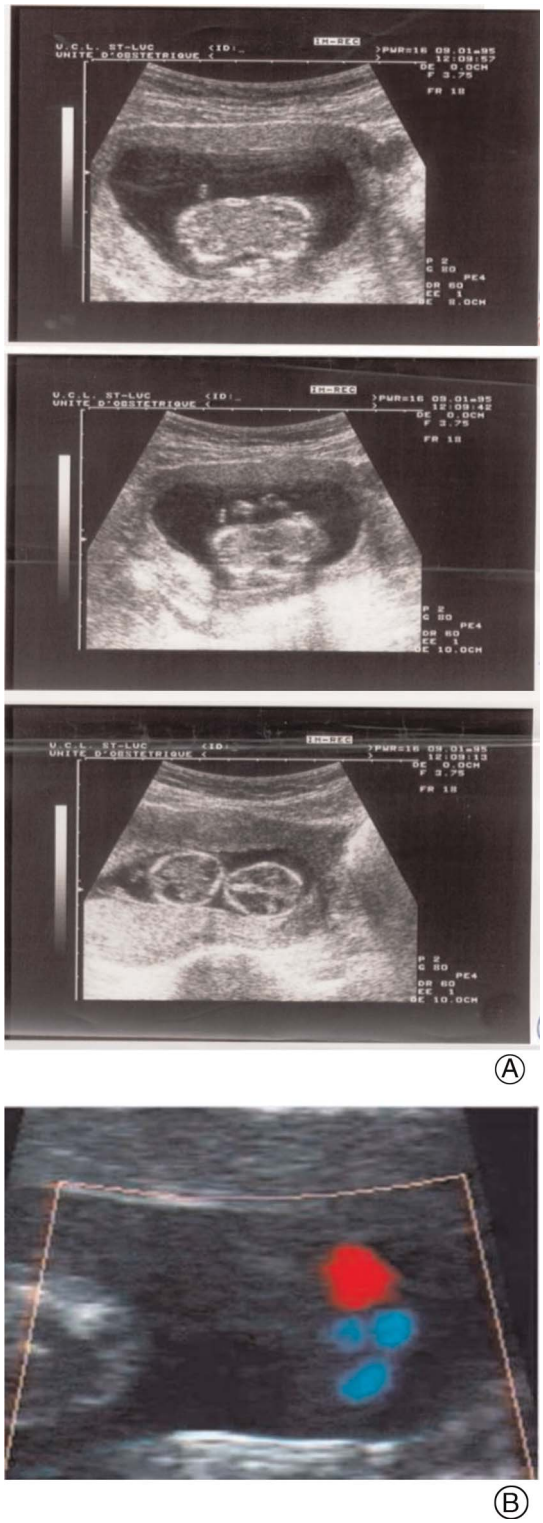

Figure 10. Ultrasound and color Doppler imaging of conjoined twins. A Thoraco-omphalopus twin. B Multivessel common cord in conjoined twins. Obtained with the patient consent.

The optimal timing of treatment is still debated, but because there is a high mortality rate during the first trimester, recent literature supports clinical intervention early in the pregnancy in order to reduce the risk of fetal demise.

Because of their invasiveness, the application of endoscopic procedures has been reduced over the last few years to such an extent that they are now no longer used. IFL and RFA of the intrafetal vessels are usually the preferred approaches.[79]

Pagani *et al.*[73] recommended elective treatment with IFL between 13 and 16 weeks of gestation. In their study, 17 TRAP pregnancies were treated with IFL; the neonatal survival rate was approximately 80%, with only 7% of preterm deliveries prior to 32 weeks of gestation. These authors noted that even if neonatal survival rate was similar between IFL and RFA, the incidence of premature preterm rupture of membranes prior to 32 weeks of gestation was significantly higher with RFA (22% *vs.* 7%, $P = 0.045$).[73] In another study, Cabassa *et al.*[76] observed an increased rate of preterm premature rupture of membranes in four out of seven patients (57%) treated with RFA at a median gestational age of 17 weeks. Chaveeva *et al.*[72] showed that the risk of pump twin death after IFL treatment was lower if the intervention was performed between 12 and 14 weeks of gestation rather than later in pregnancy. Tavares *et al.*[78] demonstrated on a cohort of 12 pregnancies an overall survival rate of 92% and a high rate of live births at term when IFL was performed prior to 14^{+3} weeks of gestation. These authors suggested that early IFL therapy does not increase fetal-loss rate in pregnancies complicated with TRAP sequenc.[78]

There are no data relating to RFA performed prior to 15 weeks of gestation. Thus, it is difficult to make a comparison between IFL and RFA. The TRAP Intervention STudy (TRAPIST), a multicenter, open-label, randomized and controlled trial, is expected to provide evidence for or against the benefit of early (12–14 weeks of gestation) *vs.* late (16–19 weeks of gestation) intervention.

Conjoined twins

Conjoined twins are a rare and complex complication of monoamniotic twinning, estimated to occur in around 1/50,000 pregnancies, but representing 1/250,000 live births, as most of cases die in utero (Fig. 10A).[80] Two theories have been put forward for the pathogenesis of conjoined twins: the "fissure theory," characterized by the incomplete splitting of the embryonic disc at about 13 to 14 days postfertilization,[7,80] and the "fusion theory," which postulates that secondary fusion may occur between two previously separate single-ovum embryonic discs.[80,81] Conjoined twins are classified according to the body point of joining. Thoracopagus (or attachment at the thoracic level) accounts for 70% of all conjoined twins.[80] Conjoined twins may be associated with a multivessel cord, which contains more than two arteries or more than one vein (Fig. 10B).[82]

Conclusion

The aim of antenatal care for twin pregnancies is to identify those at an increased risk of complications. The determination of chorionicity/amnionicity are crucial for the adequate follow-up of twin pregnancies. The evaluation of cord abnormalities by ultrasound is also essential and needs to be included in guidelines relating to the perinatal management of twin pregnancies. The improvement of ultrasound

imaging tools and clinical experience will lead to a better and earlier diagnosis of cord anomalies and subsequently, the development of an appropriate management strategy for the follow-up and delivery of these high-risk pregnancies. In all twin pregnancies, we suggest that the placenta is examined very carefully, along with the membranes and umbilical cord after delivery; it is also important to perform histopathological examination of the placenta. These tests will be useful for prenatal diagnosis and could help us to better understand the physiopathology of the adverse outcomes that occur in twins.

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Conflicts of Interest

None.

Editor Note

Corinne Hubinont is an Editorial Board member of *Maternal-Fetal Medicine*. The article was subject to the journal's standard procedures, with peer review handled independently of this editor and their research groups.

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