Anomalies of the placenta and umbilical cord in twin gestations

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With the development of new assisted reproductive techniques (ART) in the late 1970s, multiple gestation pregnancy rates have increased markedly around the world. In the United States, the rate of twin pregnancies has stabilized at 32 per 1000 births in 2006. The latest Centers for Disease Control and Prevention report on ART surveillance indicates that 43% of ART-conceived infants in 2011 in the United States were twins.

Twinning is associated with higher incidence of perinatal risks for both mothers and fetuses compared to singleton pregnancies. The main risks are early and late miscarriage, pre-eclampsia, antepartum bleeding, postpartum hemorrhage, preterm delivery, intrauterine growth restriction (IUGR), and stillbirths. Twins are also more prone to birth asphyxia, hyaline membrane disease, respiratory disorders, seizures, and long-term developmental morbidity. Prematurity and its complications is the single most important cause of perinatal morbidity and mortality in multiple pregnancies. Overall, perinatal mortality rates are reported to be 4-fold higher for twins than for singletons. Most of these complications are directly or indirectly associated with placental or umbilical cord disorders.

Twin pregnancies are obviously at higher risks for birth defects than singleton due to the development of 2 fetuses instead of 1. Cohort studies have suggested that in vitro fertilization (IVF) could be associated with higher incidence of birth defects. However, the lack of information on the etiology of the infertility, chorionicity, maternal preexisting medical conditions, parental smoking status, and social environments in most studies hampers the interpretation of the corresponding data. A recent large Australian cohort study showed that the increased risk of birth defects associated with IVF is no longer significant after adjustment for parental factors. However, placenta previa and velamentous cord insertion (VCI) are more common in singleton IVF than in spontaneous pregnancies suggesting the incidence of placental and cord abnormalities can be influenced by the mode of conception.

Development, position, and vascular abnormalities of the placenta and the umbilical cord can impact significantly perinatal morbidity and mortality. The aim of this review is to provide an outline of these anomalies associated with the twinning process and discuss the corresponding pathophysiology and diagnostic features. Most of these pathologies can be diagnosed in utero by routine ultrasound examination and should be an integral part of prenatal investigations in twins. For a better understanding of the pathogenesis, it is essential to confirm the prenatal diagnosis with a detailed histopathological placenta examination at birth. Placental and cord pathologies are traditionally divided into primary or
congenital anomalies such as tumors and secondary anomalies such as thrombosis. For the purpose of our review, we have analyzed these anomalies according to their specific and nonspecific association with twin pregnancies.

Zygosity vs chorionicity

Zygosity and chorionicity are distinct entities. A dichorionic (DC)-diamniotic (DA) placenta can be found in both monozygotic (MZ) and dizygotic twins whereas a single or monochorionic (MC) placenta mass is mainly associated with MZ twins. Zygosity or twins classification based on a double or a single fertilization cannot be predicted in DC similar gender twins. The low incidence of MZ twinning is constant worldwide and seems independent of environmental factors. However, ART and mainly IVF increase both the incidence of MZ but also MC twins.

Zygosity is generally established postnatally using genetic tests on umbilical cord blood. Quantitative fluorescent polymerase chain reaction amplification of microsatellite markers has been performed antenatally on fetal/placental cells obtained from amniocentesis or chorionic villous sampling for scientific purposes. Noninvasive prenatal determination of twin zygosity using maternal plasma free fetal DNA sequencing similar to that used for the aneuploidy testing has recently been reported.

Independently of the conception mode, the fetal, placental, and cord anomalies risk depends mainly on the chorionicity and amnionicity in twins. Overall, perinatal mortality is around 11% in MC twins compared to 5.0% in DC twins. Monoamniotic (MA) twins are rare (1% of MZ twins) but associated with the highest morbidity and mortality rate of all different types of twinning. An early determination of chorionicity and amnionicity is therefore essential to optimize the management pathways in twin pregnancies.

The optimal window to determine chorionicity in twins with 98% accuracy is at 7-9 weeks of gestation. Accuracy may be higher for DC twins than MC twins and is related to the gestational age at which the sonographic appearance of the amniotic sac develops.

Ultrasound examination of twin pregnancies at 10-14 weeks of gestation predicts chorionicity with a high degree of accuracy using a combination of the number of placentas, lambda and T signs, and intertwin membrane thickness.

Two distinct placental masses and different fetal gender indicate DC. When only 1 placental mass is visible on ultrasound, the presence of a lambda sign at the insertion of the intertwin membranes is an accurate predictor for DC whereas T sign is the most reliable indicator of MC (Figure 1). Measurements of the intertwin membrane thickness and membrane layer count are associated with a lower sensitivity and specificity than the ultrasound features used earlier in pregnancy but can be useful to determine chorionicity during the second trimester of pregnancy when the insertion of the intertwin is less clear.

MA is determined by the absence of a dividing membrane between the amniotic sacs. MA should be suspected at 10-14 weeks in the presence of a single amniotic sac and closely inserted umbilical cords (Figure 2). The number of yolk sacs is not always an accurate sonographic sign of amnionicity.

Twin-specific anomalies of the placenta and umbilical cord

Placental vascular anastomoses

Nearly all MC placentas have vascular connections or anastomoses between the 2 umbilical-placental circulations. Postdelivery placental examination injections studies have shown that they are located either superficially on the fetal surface or more deeply inside the placental mass (Figure 3). Three different types of anastomoses have
been described: arterioarterial (AA), arteriovenous (AV), and venovenous (VV) (Figure 4).

Their role in twin’s morbidity is well established since early studies have suggested that in twin-twin transfusion syndrome (TTTS) there is an important blood flow transfer through unidirectional AV anastomoses with an insufficient compensatory counter-
transfusion.25,26,28,29

**AA anastomoses.** These anastomoses are generally superficial and bidirectional.24,27 Their frequency varies but their presence seems to be associated with a protective effect for many of the complications of MC (Figure 4). A recent case-control series has found that AA anastomoses are present in 37% of TTTS placentas compared to 91% in control non-TTTS placentas (P < .001).28 AA anastomoses are also less frequent in twin anemia-polycthemia sequence (TAPS). TAPS is a particular form of intertwin transfusion imbalance, which is characterized by a difference in hemoglobin without the amniotic fluid discordance typical for chronic TTTS.30 When AA anastomoses are present in TAPS, they have a smaller diameter than those found in placentas from control twin pregnancies (Figure 5).30,31

AA anastomoses can be demonstrated by color Doppler ultrasound imaging and are characterized by cyclic changes in systolic velocities with intermittent reversal of end-diastolic velocities.32,33 A computer model has shown that this typical waveform pattern is the result of 2 opposing pulsatile blood flow waveforms with different velocities and frequencies.32 In TTTS, the survival rate is better when AA anastomoses are present.33

AA anastomoses may also play a role in the pathophysiology of the twin reversed arterial perfusion sequence, MCMA twinning, and morbidity after intrauterine death of 1 twin.24 In the latter, AA anastomoses are associated with a higher mortality in the surviving cotwin.32 In twin fetuses presenting with discordant growth with unequally shared placentas, an increase in the AA anastomoses diameter is associated with a reduced birthweight discordance. This is attributed to a rescue blood transfer through AA anastomoses to the smaller twin.34

**AV anastomoses.** They are present in 95% of MC placentas, are unidirectional, and are located in the depth of the placenta.24,31 When they are unbalanced, AV anastomoses are responsible for the occurrence of the main complications of MC including TTTS, TAPS, and severe growth discordance (Figure 4).25-29 In TTTS, there is at least 1 unidirectional AV anastomosis and a paucity of superficial anastomoses.25,29,33 Because of their location inside the placental mass, their exact number is difficult to evaluate even under direct fetoscopic vision. This can explain some of the therapeutic failures observed with laser coagulation.24 Postfetoscopy iatrogenic TAPS may result from small (<1 mm) intra-placental AV anastomoses missed by laser coagulation.24,31,35 TAPS may be associated with a specific placental feature, a dichotomy with the placental part of the anemic twin appearing hyperechogenic on ultrasound and hyperemetic at placental examination (Figure 6).36

**VV anastomoses.** They are superficial, bidirectional, and present in only one quarter of MC placentas (Figure 4). The clinical significance of VV anastomoses is still inconclusive and controversial. Their presence in MC placenta is associated with a 2-fold increase in the risk of TTTS compared to cases with no VV.24-27 A recent study has shown that VV anastomoses are associated with TTTS and their presence is an independent risk factor for its development.37

**Angioarchitecture patterns in MCMA twins.** MCMA placentas have a higher number of AA, lower number of AV, and a similar number of VV anastomoses than MCDA placentas.24,38,39 (Figure 7). This specific vascular pattern could explain the low incidence of TTTS in MCMA twins.39 Large-diameter AA anastomoses are generally present between the 2 umbilical cord circulations in MCMA placentas. This could explain partly the high incidence of discordant congenital anomalies found in MCMA twins. Brain and cardiac anomalies may result mainly from transfusion imbalances in the placental circulation during embryogenesis but others defects may be associated with early zygotic abnormal splitting, fusion event, genetic or environmental factors.9,24,39

**Discordant growth in twins and placental function.** Twin pregnancy is a specific condition in which placental development is physically constrained. Not surprisingly, IUGR is more frequent in twins compared to singletons.1,3,40-47 Poor growth affecting both twins may reflect a general uteroplacental dysfunction whereas a discordant twin growth may be attributed to several factors such as genetic growth potential differences between cotwins, placental dysfunction confined to 1 placenta, or unequal share of the placental territory in MC placenta.40

Discordant growth between twins is defined by a birthweight difference >25% between the 2 fetuses. It occurs with a similar incidence of 10-15% in both DC and MC twins.24,34 Selective IUGR (sIUGR) is defined by an estimated fetal weight <10th centile affecting one of the twins. Recent studies have suggested that first-trimester crown-rump length evaluation could...
predict the outcome in twin pregnancies but this is controversial.45,46

The gestational age at diagnosis of the growth discordance is also important for the prognosis. An early IUGR (diagnosed <20 weeks) is associated with either unequal placental sharing or early transfusion unbalances in MC twins and with placental pathologies in DC twins.42,43,47 Twins with an early-onset discordant growth have an overall lower survival rate than those with late-onset discordant and those with concordant growth (83% vs 96% vs 99%; P < .001).43,47

**DISCORDANT FETAL GROWTH IN MC TWINS.** In MC twins, IUGR is generally due to unequal placentation sharing with a high blood flow transfusion from one twin to the other through large-diameter AV anastomoses.23,24,34,41,42 A rescue connecting vessel can protect the smaller twin. If the intertwin transfusion volume is high in this rescue vessel, the risk of major growth discordance is low.24,39-43 In case of early-onset discordant growth, the placentas are more unequally shared, having more and larger AA anastomoses compared with placentas with late-onset discordant or concordant growth.43

The severity of sIUGR can be evaluated according to placentation characteristics and blood flow in the umbilical arteries. Type I presents with unequally shared placental mass, average size AA anastomoses, and normal umbilical artery Doppler measurements. Type II is characterized by unequally shared placentas, absent or small AA anastomoses, and continuous increased resistance to blood flow in the umbilical artery (absent or reverse end-diastolic flow). Type III presents with major unequal placentation sharing, at least 1 large AA anastomose, and an intermittent increased resistance to blood flow in the umbilical artery.40-43

It has recently been found that MC twin pregnancies complicated by TTTS and sIUGR are characterized by a decreased angiogenic activity reflecting an abnormal placentation process.44

**DISCORDANT FETAL GROWTH IN DC TWINS.** The mechanisms for IUGR in most DC twins are not clearly known. Since twin fetuses share the same maternal environment during gestation, birthweight discordance is related to factors affecting growth of each individual fetus. Various hypotheses have been proposed such as genetic factors and physical interactions at implantation resulting in a less favorable placental insertion in the uterus.40 Spiral artery physiological conversion may be restricted in these areas, leading to an impaired vascular perfusion of the placenta later in pregnancy. In one case report of discordant DC twins, the morphological study of the placental-decidual interface showed the development of a rare condition, maternal floor infarcts in the smaller twin placenta responsible for uteroplacental vascular insufficiency.48

In most twin studies, there is a correlation between placentation and fetal weight. It has been suggested that the
placenta size is more responsible for growth restriction in twins than a placentation deficiency.\textsuperscript{49} As the results are not correlated with the growth discordance severity, the data interpretation is limited. Others factors could be involved for explaining growth disturbances in twins. Incomplete conversion of the uteroplacental circulation is associated with chronic ischemia reperfusion of the placental tissue and leads to intermittent perfusion of the intervillous space.\textsuperscript{49,50} The resulting oxygen fluctuation is a potent inducer of oxidative stress and apoptosis in the placenta.\textsuperscript{51,52} Trophoblastic apoptosis is increased in case of preeclampsia and miscarriages and is linked directly with oxidative stress.\textsuperscript{50,51} An excess of placental apoptosis and changes in synthesis of various trophoblastic proteins are found in discordant DC twins confirming the role of oxygenation, apoptosis, and oxidative stress in their growth disturbance.\textsuperscript{53-54}

**Umbilical cord entanglement**

This complication is specific of MCMA twinning but has also been described after spontaneous and iatrogenous septostomy in both MCDA and DCDA twins.\textsuperscript{35-58} Cord entanglement can be detected with ultrasound from 10 gestational weeks using the so-called “Y sign” (Figure 2). Cord entanglement has been associated with a high incidence of intrauterine fetal death.\textsuperscript{5,14,16,59} A regular ultrasound follow-up using 2-dimensional or if available, 3-dimensional and directional color Doppler imaging is recommended (Figure 8).\textsuperscript{17,60} However, a recent systematic review has reported an overall survival rate as high as 88.6% suggesting that ultrasound prenatal diagnosis of cord entanglement did not improve neonatal outcome.\textsuperscript{59} A small cases series has also shown that the presence of a notch in umbilical artery waveform is not associated with an adverse perinatal outcome.\textsuperscript{61} Furthermore, even in cases complicated with severe TTTS requiring laser surgery, survival rate remains at 75%,\textsuperscript{62} confirming a better perinatal outcome for MCMA pregnancies than previously reported during the procedure.\textsuperscript{64} The data on PCI have been exclusively obtained from morphological placental examination after delivery and there are no data on prenatal sonographic prognostic evaluation of PCI in the management of twins.

### Umbilical proximate cord insertion

Umbilical cord development is essential for an ultimate fetal nutrition. A retrospective study based on 11,980 twins’ umbilical cords suggests a combined influence of genetic and environmental factors on their morphological characteristics.\textsuperscript{63} One of them is the distance between the insertion of the cords in MC twins placenta ranging from 4-25 cm at delivery at term.\textsuperscript{64} A measurement <5th centile (3.3-4 cm) is found in 5% of MC twin pregnancies (Figure 7). It occurs more frequently in MCMA (53%) than in MCDA (3%) placenta. The presence of proximate cord insertion (PCI) in MC placenta is associated with a higher prevalence of AA and VV anastomoses.\textsuperscript{64} A reduced space between the 2 cord insertions is probably not pathogenic but the increased number of VV anastomoses associated with PCI is a well-established factor for adverse fetal outcomes.\textsuperscript{37} In severe TTTS, the presence of PCI has been associated with higher rates of laser therapy failures due to technical difficulties in accessing the placental equator and preventing all anastomoses from being coagulated during the procedure.\textsuperscript{64} The data on PCI have been exclusively obtained from morphological placental examination after delivery and there are no data on prenatal sonographic prognostic evaluation of PCI in the management of twins.
Intertwin septum anomalies

A disparity in fluid volume distribution between amniotic sacs creates a fold in the intertwin membranes described as the “folding sign.” It is generally associated with a discrepancy in the echogenicity of amniotic fluid. In MCDA twins, the absence of membrane folding at 15-17 weeks is associated with a low incidence (<2%) of TTTS compared to the group with the folding sign subsequently developing TTTS in 43%. This early second-trimester ultrasound sign is a good predictor of twins’ outcome.65

Surgical septostomy or accidental rupture of the intertwin membrane during fetoscopic laser photocoagulation for TTTS can increase the risks of complications such as cord entanglement.56,66-69 Septostomy can be associated with amniotic membrane flaps and induce a pseudoamniotic band syndrome in 2-3% of the cases involving the limbs or the umbilical cord and leading to amputation and intrauterine death.70 Therapeutic septostomy is controversial in TTTS but has been associated with an improvement of fetal and neonatal morbidity, also due to concomitant amniodrainage.57,71

An intertwin membrane hematoma is a rare complication of DCDA twins generally associated with the development of a subchorionic hematoma under the insertion of the membrane. On ultrasound, it appears as a hypoechogenic mass located between the intertwin membranes and should be managed as marginal placental abruption.72

Nonspecific placental and cord anomalies in twins

Complete hydatiform mole in twin gestation

A classic or complete hydatiform mole (CHM) may coexist with a normal fetus and placenta in cases of molar transformation of 1 ovum in a dizygotic twin pregnancy.73,74 This rare complication of twin gestation can be misdiagnosed during the first trimester if the molar tissue partially covers the normal placenta. An accurate detection of the CHM is possible at the end of the first trimester (Figure 9). The differential diagnosis includes mainly large cystic placenta, mesenchymal dysplasia of the placenta, and degenerating uterine fibroids. As pregnancy advances, the marked generalized swelling of the molar tissue with large hemorrhagic areas can be more easily identified and managed accordingly. Twin pregnancies including a CHM are at high risk of developing severe medical complications such as preeclampsia, IUGR, and poor perinatal outcome.74

Placental lesions

Systematic reviews have confirmed the essential role of placental pathology, mainly inflammatory and vascular lesions on the neonatal morbidity and mortality in singletons.75,76 In twins, these lesions are more frequent as the incidence of complications such as preterm labor, premature rupture of the membranes, preeclampsia, and growth restriction is increased.1,5,6 In case of chorioamnionitis, nonspecific placental anomalies such as funisitis, acute and chronic villitis, and deciduitis may be found postnatally.77 Placental vascular lesions prevalence is higher in twins than in singletons. Moreover, in MC placenta, histopathology examination
shows a higher incidence of infarctions, subchorial fibrin deposition, and abnormal villous maturation compared to DC twins (41.5% vs 32.9%; \( P = .009 \)).78,79 MC twins present also with a higher incidence of fetal vessels thrombosis compared to DC.80 Fetal vascular thrombosis is found generally in association with IUGR in MC twins and with hypertensive disorders in DC twins.80 The increased incidence of placental infarctions and thrombosis in DC twin placentas compared to MC and singletons may be associated with the higher prevalence of preclampsia in DC twin pregnancies.81 These lesions are more likely to be the consequences of abnormal placentation rather than the cause of preeclampsia.

**Placenta previa**
The overall incidence of placenta previa in twins has been reported to be 40% higher than in singletons after exclusion of confounding factors such as multigravida, advanced gestational age, and smoking.82 However, a recent retrospective study has found a similar incidence of placenta previa during the second trimester in singleton and twin pregnancies. In the vast majority of cases in both groups, the low placental location resolved spontaneously during the third trimester.82 This controversial study may be explained by the lack of knowledge about chorionicity.

Chorionicity is pivotal in evaluating the risk of placenta previa in twins and an increased risk has been found in DC twins compared with singletons and MC twins.82,83 This is probably the consequence of the presence of 2 developing placental masses in DC twins. IVF twins presents with an increased incidence of placenta previa than singleton and spontaneous twins.4,83 Determination of placental location is part of routine prenatal ultrasound examination and its diagnostic modality is transvaginal ultrasonography.

**Morbidly adherent placenta**
The incidence of placenta accreta (PA) has increased 10-fold since the early 1900s and directly correlates with the increasing cesarean delivery rate in most Western countries.84 There are limited clinical data on the diagnosis and management of PA in twin pregnancies. Three cases of deep PA (percreta) have been reported, all complicated by uterine rupture during the second trimester and requiring an emergency hysterectomy.85-87 Prenatal diagnosis by imaging followed by an adequate management by a multidisciplinary team reduces significantly both morbidity and mortality associated with PA. The specific ultrasound features including the presence of placental lacuna, absence of hypoechochogenic line between placenta and myometrium, and transmyometrial bulging of placental sinus at the myometrium and bladder interface should be detected with the same accuracy in twins.84

**Velamentous cord insertion**

A VCI of one of the umbilical cords is 8 times more common in twins than in singletons. MC doubles the risk for VCI.
and is associated with a contralateral development of the superficial angio-vasculature suggesting that early angiogenesis is dependent of umbilical cord insertion in relation to the development of the definitive placenta.93-96 The incidence of VCI, vasa previa, or marginal cord insertion is higher in ART than in spontaneously conceived singletons but similar in both types of twins.4,7,97 There is a 3-fold increase in the incidence of VCI in twins presenting with IUGR compared to normally grown twins.96

Vasa previa is a rare anomaly in both singleton and twin pregnancies but is more common in twins due to the higher incidence of VCI, bilobated placenta, and placenta previa.98,99 (Figure 10). Vasa previa in twins has been associated with a higher but unexplained risk of emergency preterm delivery compared to singletons.99

**Single umbilical artery**

In twins, the incidence of single umbilical artery (SUA) is 3 times greater than in singletons (3% vs 1%) but similar in MC and DC twins.100-102 The fact that MC twins can be discordant for SUA in MC twins indicates that environmental factors play a role for determining the occurrence of this anomaly.9,101 SUA twins are at higher risks of IUGR and preterm delivery <28 weeks. Twin pairs discordant for SUA present with higher growth discordance than those with normal umbilical cords.100-103 The sonographic cross-sectional area of the SUA does not appear to show the typical adaptive dilatation usually seen in singleton pregnancies with SUA.101 This apparent failure of umbilical artery compensatory dilatation in twins with SUA could explain partly the increased risk for IUGR in these cases. The prenatal diagnosis of SUA is pivotal for the management of twins presenting with discordant growth.

**Postpartum placental examination**

The utility of histopathological examination of the placenta and umbilical cord after delivery is directly relevant to many different aspects of perinatology from the epidemiology of specific obstetric complications76,104 to malpractice litigation.105

Morphological examination should start in the delivery room with labelling of placenta and umbilical cords, using different size or shapes of clips (Table). A complete macroscopic report should include placental weight and membranes examination, structure of intertwin membranes, site of insertion and number of vessels in each umbilical cord, and evaluation of vascular anastomoses in MC twin pregnancies.10-23,106

**TABLE**

Recommended morphologic examination of placenta in twins

| 1. Identification and labeling of cords and placenta(s) |
| 2. Examination of membranes (layers, vasa previa) |
| 3. Number of placenta(s) |
| 4. Macroscopic examination of maternal and fetal placental sides |
| 5. Insertion of umbilical cords (velamentous, proximity) |
| 6. Number of vessels in cords (single umbilical artery) |
| 7. Placental weight and fetal to placental weight ratio |
| 8. In monochorionic twins, identification of vascular anastomoses with or without injection |


**Evolution of fetal to placental weight ratio during gestation in singleton and twin pregnancies.**

Adapted from Almog et al.110

In MC twins complicated by TTTS, anastomoses can only be accurately evaluated by injection studies (Figures 3, 5, and 7) but these techniques require specific equipment and expertise. A simplified method using milk injection in cord vessels after clamping can be helpful to identify superficial vascular anastomoses (Figure 12).

**Conclusions**

Perinatal data suggest that in human beings, the high rate of complications observed in twin pregnancies is linked to specific pathophysiological changes in the placentation process. MC twins have higher rates of perinatal mortality, growth discrepancies, and IUGR of both fetuses than DC twins. This suggests that these complications could be related to specific placentation angioarchitecture of MC twinning. In MC twins, the most frequent causes for growth restriction are intertwin transfusion unbalances and unequal placental sharing. In DC twins, second- and third-trimester IUGR is generally associated with either primary abnormal cord location or uteroplacental vascular insufficiency.

Most placental and cord anomalies can be diagnosed accurately using ultrasound before delivery. Prenatal diagnosis of anomalies such as placental anastomoses, SUA, or vasa previa have a direct impact on the obstetrical management. Placental morphological examination in twins can provide essential information for evaluating perinatal outcome epidemiology. It can contribute toward a better understanding of intrauterine environment in twin pregnancies. Future research correlating antenatal findings and postnatal histopathological assessment from multiple studies into larger data sets will allow delineation of distinctive clinicopathological associations and further understanding of pathophysiology of complex placenta and cord anomalies in twins.

**REFERENCES**


