Placental characteristics and complications in monochorionic twin pregnancies

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General Discussion

A. Monochorionic Placentas: analysis and characteristics

Although all twin pregnancies are at increased risk of abnormal placentation, several types of placental anomalies are exclusive to monochorionic (MC) pregnancies such as vascular anastomoses, abnormal umbilical cord insertion and unequal placental sharing.

1. Vascular anastomoses

Vascular anastomoses are extremely rare in dichorionic (DC) twins but ubiquitous in MC twins. These anastomoses play a crucial role in the well-being of MC twins and have therefore been the subject of great interest by perinatologists in the past decades. Several injection methods have been proposed to demonstrate the presence and types of vascular anastomoses using air, milk, barium and colored dye. In our recent cohorts using colored dye, we found on average 8 to 11 vascular anastomoses per placenta (Chapter 2 and 3) whereas other studies reported a smaller number of anastomoses, on average 1 to 6 vascular anastomoses per placenta.[1-3] This disparity is likely attributable to differences in injection techniques. In particular the use of air or milk may not be appropriate to detect small size anastomoses and to distinguish between the various types of anastomoses. The difference between the three types of vascular anastomoses (arterio-arterial (AA), veno-venous (VV) and arterio-venous (AV) anastomoses) can easily be detected when using color dye injection. Small size anastomoses can only be detected through accurate and thorough injection with colored dye. Since detection of these minuscule anastomoses is one of the crucial diagnostic criteria for twin anemia-polycythemia sequence (TAPS),[4] high quality injection technique is of paramount importance for the diagnosis of TAPS (see section B.2 on TAPS).

2. Abnormal umbilical cord insertion

Another placental characteristic that is typical to MC twins is abnormal placental cord insertion, namely velamentous cord insertion (VCI). The rate of VCI per fetus is significantly higher in MC twins (35%) compared to DC twins (8%).[5] The higher frequency of VCI in MC twins may be associated with the unequal allocation of blastocyst to each twin during the twining process, leading to lower growth potential of placental mass to protect the chorionic vasculature. VCI is associated with adverse perinatal outcome in MC twins, which may be in part due to the smaller corresponding placental share.[6, 7] As a consequence of the higher prevalence of VCI, MC twins also carry an increased risk of vasa previa and concomitant increased risk of rupture of the vessels during delivery. We recently reported two cases of MC twin pregnancies with rupture of vasa previa which led to acute blood loss in one twin followed by acute exsanguination from its co-twin through the vascular anastomoses.[8, 9] Acute double exsanguination led to double fetal demise in one case and double severe perinatal asphyxia in the other case. Antenatal detection of vasa previa in MC twins is thus of paramount importance.

Another abnormal form of cord insertion which appears to be unique to MC twins is the presence of proximate cord insertions (PCIs). Interestingly, PCIs are around 18 times more likely to occur in monoamniotic (MA) placentas (53%) compared to diamniotic twins (3%) (Chapter 4), suggesting a possible association of PCIs with twining process. In addition, we found that arterio-arterial (AA) and veno-venous (VV) anastomoses were more prevalent in MC placentas with PCIs (100% and 56%, respectively) compared to MC placentas without PCIs (80% and 26%, respectively). Our findings support the theory proposed by De Paepe et al. that the interaction between both cord insertions may play a role in the formation of

angio-architecture in MC placentas.[10] A crucial step of fetoscopic laser surgery is the visualization of vascular equator.[11] However, the presence of PCIs results in difficulty in identifying the vascular equator and high risk of residual anastomoses and treatment failure of fetoscopic laser surgery (Chapter 7). Interestingly, in a recent study the authors reported successful performance of fetoscopic laser surgery in TTTS with PCIs except when the two umbilical cords have a joint part near the insertion site.[12] Noticeably, in case of PCIs fetal surgeons may consider not to coagulate the part of vascular equator between the side-by-side cord insertions to avoid damage to quite large anastomoses or umbilical cords. However, the large vascular anastomose may be obscured by the PCIs, leading to failed detection by preoperational sonography. Therefore, we agree with proposal by the authors that evaluation of the feasibility of fetoscopic laser surgery for TTTS with PCIs should be done during fetoscopy, rather than ultrasound examination.

3. Unequal placental share

In most studies, unequal placental share is empirically defined as a placental share difference of 20% or greater, yielding a rate of around 50% in MC twins. The unequal placental share in MC twins is theorized to result from the poor implantation site represented by the presence of VCI and disequilibrated cleavage of inner cell mass at twinning. MC twins with birth weight discordance of ≥20% have a 2 to 5 times likelihood of unequal placental share compared to MC twins with concordant growth, suggesting that unequal placental share is the main contributor to growth discordance, and may lead to selective intrauterine growth restriction (sIUGR).[13] In MC twins, a larger placental share usually leads to a larger birth weight, while a smaller placental share results in a smaller birth weight. However, the placental share usually does not well correspond to the birth

weight share, i.e. birth weight share/placental share ratio is significantly higher in the smaller twin compared to the larger twin in sIUGR.[14, 15] This may be explained by the more shared circulation as a result of more efficient network of vascular anastomoses with larger anastomotic size, more superficial anastomoses and shorter distance between cord insertions.[14, 16]

B. Placental characteristics in relation to specific complications: twin-twin transfusion syndrome and twin anemia-polycythemia sequence

Vascular anastomoses are the anatomical prerequisite for the net intertwin transfusion enabling the development of twin-twin transfusion syndrome (TTTS) or TAPS. Although the placental angioarchitecture in TTTS and TAPS placentas is different from uncomplicated MC twins (Chapter 5 and 6), the role of placental angioarchitecture in the pathophysiology of TTTS and TAPS is not fully understood yet. One recent hypothesis is that all chronic intertwin transfusion first results in intertwin hemoglobin discordance leading to intertwin osmotic gradient.[17] Subsequently, extraction of fluid from the donor to the recipient may ensue when large anastomoses are present (TTTS placenta) or may be limited when only minuscule anastomoses are present (TAPS placenta). Another theory is that TTTS results from fetal circulatory imbalance and its secondary effect of vasoactive hormones (renin-angiotensin system and endothelin-1), leading to large differences in amniotic fluid production and the development of oligo-polyhydramnion sequence.[18] In contrast, TAPS results mainly from slow chronic intertwin blood transfusion through the minuscule vascular anastomoses leading to differences in Hb levels without discordant amniotic fluid levels.[19]

1. TTTS placentas

Although AV anastomoses carrying unidirectional blood flow are essential for the pathogenesis of TTTS, the number and size of AV anastomoses in TTTS placentas is not different from that in uncomplicated MC placentas.[20] The main difference in the angioarchitecture of TTTS placentas is the lower prevalence of AA anastomoses (around 35%) compared to uncomplicated MC twins placentas (above 90%), suggesting a protective role of AA anastomoses against TTTS.[3, 21] In contrast to AA anastomoses, VV anastomoses occurs more frequently in TTTS placentas (around 35%) than uncomplicated placentas (about 25%).[3] In particular in the absence of AA anastomoses, the presence of VV anastomoses seems to predispose MC twins to the development of TTTS. Unlike the arterial system, the resistance in the venous circulation is low. Inter-twin pressure gradient in the venous circulation is therefore prone to being affected by external impact, such as fetal position. Theoretically, VV anastomoses may then act as AV anastomoses and carry unidirectional blood flow when the inter-twin pressure gradient in venous circulation becomes skewed to one twin. This may, in certain circumstances, lead to the development of TTTS. Given the more recent theory on the pathogenesis of TTTS as discussed above, VV anastomoses with blood flow of low resistance may facilitate the extraction of fluid from donor to recipient when the intertwin Hb difference is present.

The prevalence of VCI is similar between TTTS and uncomplicated MC twins, suggesting that there is no causal relation between development of TTTS and velamentous insertion of the umbilical cord. However, if TTTS occurs, VCI is most often detected in the donor twin.[7] The presence of VCI in TTTS may thus be related to the donor versus recipient status, but not the pathogenesis of TTTS. Velamentous insertion of the cord is associated with the magistral

pattern of chronic vasculature.[10] The few and lager chorionic arteries in the placental territory of the donor twin may tend to be affected by the heart beat and have a higher blood pressure, facilitating the blood loss from the donor to the recipient.

2. TAPS placentas

The typical angioarchitecture of TAPS placentas demonstrates few and miniscule anastomoses (diameter < 1mm), on average 4 in spontaneous TAPS placentas and 2 in post-laser TAPS placentas.[22] AA anastomoses occur strikingly less frequently in TAPS placentas (<20%) compared to uncomplicated MC placentas (above 90%),[23] allowing the accumulation of Hb difference without adequate compensation. Interestingly, most anastomoses in post-laser TAPS placentas are localized near the edge of placenta. These small anastomoses on the margin of the placenta are probably more difficult to detect and can be missed during fetoscopic laser surgery.

Another feature of TAPS placentas is the larger ratio between cord insertion distance and placental diameter compared to uncomplicated MC placentas (69% vs 63%, respectively, *P*<.05).[24] This may result in the diminution of vascular caliber along the vascular equator and smaller vascular anastomoses.

The placental share discordance in TAPS placentas is comparable to uncomplicated MC placentas.[25] However, unlike uncomplicated MC twins, the smaller twin in TAPS who is often the anemic twin usually has a larger placental share, suggesting that fetal growth in TAPS is determined primarily by the net inter-twin blood transfusion instead of placental share. Importantly, the larger placental share found in donor twins could be a result of selection bias in our study due to the inclusion of only TAPS cases with two live-born infants. We speculate that in TAPS donor twins with a significantly smaller placental share may be at

increased risk of fetal demise due to the accumulation of potential risks (chronic blood loss and smaller placental share).

C. Placental complications and associated neonatal outcomes after fetoscopic laser surgery for TTTS: histologic chorioamnionitis, funisitis and early–onset neonatal sepsis

An important aspect that had not been evaluated in detail is related to the impact of intrauterine inflammation after laser surgery for TTTS. Recent studies have shown that intrauterine inflammation are related to adverse fetal and neonatal outcomes and associated with adverse long-term neurodevelopmental outcome.[26-28]

1. **Chorioamnionitis and funisitis**

In our case-control study with histologic evaluation of placenta and umbilical cord (Chapter 8), we found an higher risk of intrauterine inflammation (13% of histologic chorioamnionitis (CA) and 8% of funisitis) in TTTS cases treated with fetoscopic laser surgery compared to previous reports based on clinical CA (0-4%).[29-39]This disparity may be attributable in part to the different definitions of intrauterine inflammation. Noticeably, around half of histologic CA occurs without clinical signs and symptoms including maternal fever, the essential criterion to diagnose clinical CA. Given that funisitis is associated with higher risk of adverse short and long-term outcome than histological CA only,[27] the more important finding in our study is the increased risk of funisitis after fetoscopic laser surgery, suggesting the necessity of postpartum histologic evaluation of the placenta and umbilical cord in TTTS cases treated with laser surgery. Although both the operational and perinatal variables were recorded and analyzed, this study however failed in identifying the risk factors for the

occurrence of histological CA after fetoscopic laser surgery. Nevertheless, our study was primarily designed and powered to display a difference in the risk of histologic CA between the study group of TTTS managed with fetoscopic laser surgery and a control group of mostly uncomplicated MC twins without fetoscopic laser surgery. Analysis of risk factor for histologic CA after fetoscopic laser surgery requires a larger study.

2. Early-onset neonatal sepsis

The clinical implication of histologic CA is the direct association with early-onset neonatal sepsis (EOS). EOS is one of the leading causes of neonatal morbidity and mortality. In our large prospective cohort study (Chapter 9), we found that the incidence of EOS after fetoscopic laser surgery was 16% (2% proven EOS and 14% suspected EOS). The rate of EOS in our cohort is substantially higher compared to the general population of MC twins reported by Lewis et al (4%).[40] This higher incidence of EOS found in our TTTS cohort may be explained by the TTTS disorder itself and the invasive nature of fetoscopic laser surgery leading to increased risk of prematurity and preterm previable rupture of membranes (PPROM). Although fetoscopic laser surgery significantly improves the clinical outcome in TTTS, perinatologists should be aware of the potential risk of intrauterine inflammation and EOS. Future studies and developments focusing on improvement of laser technique and instruments may reduce the risk of (iatrogenic) PPROM, intrauterine inflammation (infection) and EOS.

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