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Placental characteristics and complications in monochorionic twin pregnancies

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Part IV

Summary, General Discussion and Future Perspectives

Summary

Monochorionic (MC) pregnancies account for around one third of all twin gestations, but contribute disproportionately to the occurrence of adverse perinatal outcomes. Increasing body of evidence shows that perinatal outcomes in MC twins are strongly associated with the complications resulting from the unique angioarchitecture in MC placentas, in particular the placental vascular anastomoses. Due to the extensive application of prenatal ultrasound examination, an increasing number and types of complication dedicated for MC twins are being diagnosed. Delineation of the placental characteristics classified by specific complications may shed light on the pathophysiology of various complications in MC twins. One of the great successes in fetal therapy is the introduction of fetoscopic laser coagulation of vascular anastomoses for the treatment of twin–twin transfusion syndrome (TTTS). The investigation on postoperative complications in TTTS placentas is crucial for the further improvement of fetoscopic laser surgery and improvement of perinatal outcome. Since 2002, all MC placentas delivered at the Leiden University Medical Center (LUMC) are consecutively being examined and injected with colored dye. This large database of MC placentas (n=940 in 2016) allows detailed investigation of the pathogenesis and clinical outcome of these rare diseases.

Monochorionic Placentas: analysis and characteristics

In *Chapter 2* we compared the prevalence of vascular anastomoses and evaluated the sharing discordance in 134 MC placentas and 124 dichorionic (DC) placentas. This study demonstrates that vascular anastomoses are present in 99% (133/134) MC placentas and 0% DC placentas ($p < .01$). Placental share discordance between MC twins is significantly larger compared to DC twins, 19.8 (interquartile range (IQR) 8.1-33.3) and 10.8 (IQR 6.2-

19.0), respectively (p<.01). Vascular anastomoses–associated complications occurred in 16% (22/134) MC twins. Our findings show that vascular anastomoses are almost ubiquitous in MC placentas, but non-existent in DC placentas. In addition, unequal placental sharing appears to be more common in MC than in DC placentas. However, our data should be interpreted with care due to the referral nature of our center. Since twin pregnancies referred to our centers usually underwent complications related to the vascular anastomoses, the findings on MC twins in this study may be overestimated.

The aim of the study described in *Chapter 3* was to estimate the prevalence, number, size and localization of the anastomoses using color dye injection in MC placentas with complications (selective intrauterine growth restriction (sIUGR), n = 46; TTTS placentas, n = 47; spontaneous twin anemia–polycythemia (TAPS), n=16) compared to 126 uncomplicated MC placentas. The prevalence of arterio-arterial (AA) anastomoses in uncomplicated MC, sIUGR, TTTS and TAPS placentas was 96%, 98%, 47% and 19%, respectively. Median number of anastomoses in uncomplicated MC, sIUGR, TTTS and TAPS placentas was 8 (IQR: 4-12), 8 (IQR: 5-14), 7 (IQR: 5-11) and 4 (IQR: 3-5), respectively. We concluded that the prevalence, size, number and localization of the various types of vascular anastomoses differ between uncomplicated MC, sIUGR, TTTS and TAPS placentas. However, the ex vivo nature of this study should be taken into account when extrapolating our in vitro findings to the in vivo situation such as visualization of vascular anastomoses during fetoscopy.

In *Chapter 4* based on the measurements in 369 MC placentas, a reference range for the distance between cord insertions was generated to determine the cut–off value of proximate cord insertions (PCI). Additionally, the prevalence and angio-architecture of MC placentas with PCI was further evaluated. The 5th centile of the established reference range

was adopted to define PCI and was calculated by the equation : 0.027 × gestational age (weeks) +2.91 (cm), yielding a range from 3.3 to 4 cm throughout gestation. Accordingly, 18 of the 369 (5%) MC placentas fulfilled the definition criteria for PCI. The prevalence of arterio-arterial (AA) and veno-venous (VV) anastomoses in MC placentas with and without PCI was respectively 100% (18/18) versus 80% (281/351) (P=.12) and 56% (10/18) versus 26% (91/351) (P=.01). Based on our analysis, we propose that the use of a fixed cut-off set at 4 cm might be easier to use in daily practice instead of a gestational-age-dependent equation.

Placental characteristics in relation to specific complications

The objective of the multicenter study described in *Chapter 5* was to evaluate the prevalence of veno-venous (VV) anastomoses in a large cohort of 106 monochorionic (MC) twin placentas with twin–twin transfusion syndrome (TTTS) compared to a control group of 308 MC placentas without TTTS. The prevalence of VV anastomoses was significantly higher in the TTTS group than in the non-TTTS group, 36% (38/106) and 25% (78/308), respectively (p=.04; odds ratio (OR) 1.65; 95% confidence interval (CI): 1.03–2.64). In the subgroup of MC placentas without AA anastomoses, the prevalence of VV anastomoses in the TTTS group and non-TTTS group was 32% (18/57) and 8% (2/25), respectively (p=.03; OR: 5.31; 95% CI: 1.13–24.98). Our results suggest that the VV anastomoses may play a role in the development of TTTS, in particular in the absence of AA anastomoses.

Previous observational studies noted a discordance between birth weight and individual placental share in TAPS. The purpose of the study in *Chapter 6* was to investigate if fetal growth in monochorionic (MC) twins with TAPS is determined by placental share or by the net inter-twin blood transfusion. We analyzed 20 TAPS cases and 250 uncomplicated MC

twins and found that birth weight share in the TAPS group was positively correlated with hemoglobin (Hb) levels share at birth (P<0.01) but not with placental share (P=0.54). In contrast, in the group of uncomplicated MC twins, birth weight share was strongly correlated with placental share (P<0.01) but not with Hb levels share (P=0.14). Our findings suggest that fetal growth in MC twins with TAPS is determined primarily by the net inter-twin blood transfusion instead of placental share and a relatively larger placental share may enable the survival of the anemic twin in TAPS.

In *Chapter 7* we report the prevalence of proximate cord insertions and associated clinical consequences in TTTS treated with fetoscopic laser surgery (FLS). The prevalence of proximate cord insertions in TTTS placentas was 2% (4/252). Residual anastomoses were detected in all placentas with proximate cord insertions (100%, 4/4) compared to 27% (66/248)(P<.01) in TTTS placentas without proximate cord insertions. Our findings suggest that fetoscopic laser coagulation in TTTS cases with proximate cord insertions is challenging due to technical difficulties in visualizing the vascular equator and results in an increased risk of incomplete laser treatment.

Histologic chorioamnionitis and early–onset sepsis in TTTS after laser surgery

The frequency of intrauterine inflammation and associated consequences in TTTS managed with fetoscopic laser surgery is presented in *Chapter 8*. In this case–control study performed at our center from 2013 to 2014, we included all TTTS pregnancies managed with fetoscopic laser surgery (n=62) and compared to a control group of monochorionic (MC) twin pregnancies not treated with fetoscopic laser surgery (n=64). The incidence of histologic chorioamnionitis was 13% (8/62) in the laser group versus 5% (3/64) in controls (odds ratios (OR) 3.0, 95% confidence interval (CI) .8-11.9, *P*=.12). Funisitis occurred in 8% (10/124) in

the laser group versus 0% in controls (OR 11.1, 95% CI 1.3-96.9, *P*=.03). Histologic chorioamnionitis following fetoscopic laser surgery was associated with shorter laser-to-delivery interval (*P*<.01) and lower gestational age at birth (*P*<.01). These findings suggest TTTS cases managed with FLS are at increased risk of funisitis.

In *Chapter 9* we compared the rate of early–onset neonatal sepsis (EOS) in a cohort of all consecutive TTTS cases treated with laser surgery compared to a cohort of uncomplicated monochorionic twins delivered at our center. The rate of proven or suspected EOS in the TTTS group and no-TTTS group was 16% (68/208) and 10% (55/271), respectively (relative ratio (RR) 1.74, 95% confidence interval (CI) 1.19-2.55). Multivariate analysis showed that EOS in the TTTS group was independently associated with lower gestational age at birth (odds ratio (OR) 0.75, 95% CI 0.63-0.88), earlier study period (OR 2.25, 95% CI 1.08-4.67) and PPROM (OR 2.47, 95% CI 1.28-4.75). In conclusion, The rate of EOS in the TTTS group is low, but increased compared to the no-TTTS group. EOS in TTTS is independently associated with premature delivery, earlier laser period and PPROM. Our findings suggest that neonates with TTTS after laser surgery are at increased risk of EOS.