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General introduction

Over the past decades the incidence of monozygotic and dizygotic twin pregnancies has increased, largely as a result of assisted reproductive technologies.[1] The number of spontaneously conceived twins has increased as well due to increased maternal age in pregnant women.[2] Dizygotic twins are more common than monozygotic twins, 70 percent of twins is dizygotic and 30 percent is monozygotic.[3] Monozygotic twinning occurs in 3.5-4 per 1000 births across the world.[4] However, the incidence of dizygotic twinning varies among countries.[5] In the United States the twin birth rate was 33.9 twins per 1000 births in 2014.[6] In low and middle income countries the average twinning rate is approximately 13.1 per 1000 births.[5]

Dizygotic twins occur from fertilization of two oocytes, resulting in two embryos with each their own placenta and their own amniotic sac, named therefore dichorionic diamniotic twinning. Monozygotic twins are identical since these twins result from fertilization of a single oocyte. The type of placentation in monozygotic twins varies and depends on the timing of cleavage of the monozygotic blastomere. Cleavage during the first three days after fertilization results in two placentas, two chorions and two amnions, thus dichorionic diamniotic twinning (such as in dizygotic twins). When cleavage occurs between the fourth to the eighth day after fertilization, monozygotic twins will share their placenta and have one chorion and two amnions, hence called monochorionic diamniotic twinning. Cleavage between the ninth till twelfth day after fertilization results in a monochorionic monoamniotic twin, where fetuses share not only their placenta but also their amniotic sac. Cleavage after the twelfth day results in conjoined twins.[4;7] Approximately 75% of monozygotic twins are monochorionic, with an overall incidence of one in 400 pregnancies.[8] Twin pregnancies are at a higher risk of perinatal and neonatal morbidity and mortality compared to singleton pregnancies.[9-11] This is partly due to the fact that twins are more likely to be born prematurely and small for gestational age.[12-15] In addition, one of the most important risk factors for the increased rate of perinatal complications in twins is due to the type of placentation. Monochorionic twins (which occur only after monozygotic twinning) are at increased risk of complications compared to dichorionic twins due to the differences in placentas. Nearly all monochorionic twins (99%) have placental vascular anastomoses connecting the blood circulation of both twins[16;17] whereas dichorionic twins have always two separate placentas without vascular connections. Only a few rare cases of dichorionic twins with placental anastomoses have been described.[18;19]

Vascular anastomoses lead to inter-twin blood transfusion, which is 'balanced' in uncomplicated monochorionic twins during pregnancy. However, vascular anastomoses may also lead to unbalanced inter-twin transfusion and play a key role in the development of severe complications such as twin-twin transfusion syndrome (TTTS) and twin anemia-polycythemia (TAPS).

TTTS occurs in approximately 9-15% of monochorionic pregnancies.[20;21] TTTS is diagnosed prenatally based on the presence of twin oligo-polyhydramnios sequence (TOPS). Oligohydramnios in the donor is defined as a cut-off at a deepest vertical pocket of amniotic fluid ≤ 2 cm and polyhydramnios in the recipient as ≥ 8 cm within the first 20 weeks of

gestation or, according to the Eurofoetus criteria, ≥ 10 cm after 20 weeks of gestation. [22;23] In 1999, Quintero et al. defined a classification which consists of 5 stages. Staging depends on bladder filling, abnormal Doppler studies, hydrops fetalis and fetal demise. [23] TTTS is associated with a high fetal and neonatal mortality rate of 73-100% if left untreated.[24] The best treatment for TTTS is fetoscopic laser coagulation of the anastomoses during pregnancy.[25]

Another complication in monochorionic twins is TAPS, first described by our research group in 2007.[26] TAPS may occur spontaneously in 3-5% of monochorionic twins or in 2-16% after laser surgery in TTTS ('post-laser TAPS').[27-31] TAPS is characterized by slow inter-twin blood transfusion resulting in large inter-twin hemoglobin differences at birth, without signs of TOPS during pregnancy. The pathogenesis is based on the presence of minuscule (<1 mm) vascular anastomoses. TAPS can be diagnosed prenatally or postnatally. Prenatal diagnosis of TAPS is based on Doppler ultrasound measurements with an increased middle cerebral artery-peak systolic velocity (MCA-PSV) > 1.5 multiples of median (MoM) in the donor, suggestive for fetal anemia and a decreased MCA-PSV (MoM < 1.0) in the recipient suggestive for polycythemia.[32] In 40-63% of cases, TAPS is diagnosed after birth.[32] Postnatal diagnosis is based on inter-twin hemoglobin difference of ≥ 8 g/dL (i.e. ≥ 5 mmol/L). In addition, to distinguish from acute peripartum TTTS, at least one of the following criteria are required: reticulocyte count ratio > 1.7 or minuscule placental anastomoses.[33]

Outline of the thesis

The Leiden University Medical Center (LUMC) is a tertiary care center and the national referral center for the treatment of complicated monochorionic twins with TTTS and TAPS. Improved antenatal management in TTTS and TAPS has led to an increase in perinatal survival. Attention is now shifting towards postnatal complications in survivors. The aim of this thesis is to evaluate the hematological and biochemical complications in twins affected by TTTS or TAPS.

- A. Hematological complications: Most previous studies reported on differences in hemoglobin values in *complicated* monochorionic twins. To compare the hematological values with *uncomplicated* twins, we analyzed hemoglobin levels in dichorionic twins and monochorionic twins without TTTS or TAPS. Since hemoglobin differences may be due to a multitude of factors, we studied the impact of various risk factors including birth order, mode of delivery and delivery time interval between the first-born and second-born twin.
- B. Biochemical complications: Only a few small studies in TTTS reported on inter-twin biochemical differences.[34;35] Knowledge on biochemical abnormalities in twins with TAPS is also sparse. We hypothesized that inter-twin blood flow through the placental anastomoses not only lead to transfer of red blood cells from one twin to the other, but also allow inter-twin transfer from nutrients and proteins, and focused mainly on differences in albumin and total protein, and renal function. Hypoalbuminemia is an independent risk factor for morbidity and mortality in neonates.[36;37] In addition, inter-twin blood flow may have an important impact on renal function due to impaired renal perfusion. To date, only a few small studies on renal function have been performed, mainly in TTTS treated with amniocentesis. [38-41]

The following chapters describe the objectives in more detail:

Chapter 2 - Literature review on hematological disorders in twins with TTTS, TAPS, acute peripartum TTTS, acute perimortem TTTS and uncomplicated monochorionic twins.

Chapter 3 - Study on hemoglobin differences in a large cohort of uncomplicated monochorionic twins in relation to birth order, mode of delivery and delivery time interval between the first-born and second-born twin.

Chapter 4 - Study on hemoglobin levels in a large cohort of dichorionic twins compared to uncomplicated monochorionic twins and in relation to birth order and mode of delivery.

Chapter 5 - Study on albumin levels in donor and recipient twins with TTTS treated conservatively or with fetoscopic laser surgery.

Chapter 6 - Study on albumin levels in donor and recipient twins with TAPS compared to a matched group of uncomplicated monochorionic twins.

Chapter 7 - Evaluation of short-term renal function in neonates with TAPS admitted to three European centers.

Chapter 8 - Study on short-term renal function in twins with TTTS treated with fetoscopic laser surgery or conservative treatment.

Chapter 9 - General discussion concerning the results of these studies and future perspectives and proposals for future studies.

Chapter 10 - Summary of the thesis.

Chapter 11 - Appendices.

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