Selective fetal growth restriction in identical twins: from womb to adolescence

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General introduction and outline of thesis

General introduction

Twinning on the rise

Worldwide, more twins are being born now than ever before. Approximately 12 out of every 1000 deliveries is a twin pair, with even higher rates in North America, Europe and Africa ranging from 15 to 30 twins per 1000 deliveries, resulting in roughly 1.6 million twin pairs globally each year[1]. This is a threefold increase compared to the 1980s and numbers keep rising steadily[1]. The surge in twinning rates is highly relevant for present day health care as twin pregnancies are at greater risk of adverse perinatal outcome, including obstetric complications, prematurity and mortality, and therefore require additional antenatal care[2-4]. This is particularly so for monochorionic (MC) twin pregnancies.

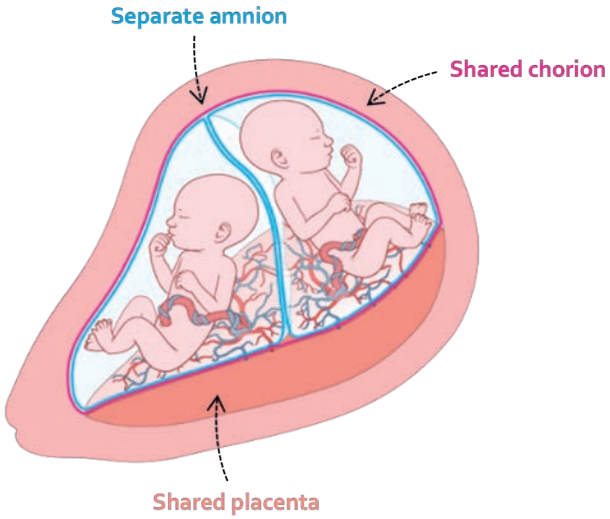

Figure 1. A schematic representation of a MC diamniotic twin pregnancy. Both the placenta, an organ that develops in utero during pregnancy and supplies oxygen and nutrients to the fetus through the umbilical cord, and the chorion, the outermost membrane surrounding the fetus, are shared between the twins. The amnion, the innermost membrane surrounding the fetus filled with amniotic fluid, can either be separate (diamniotic) or shared (monoamniotic) (illustration © Amanda Gautier).

	Uncomplicated monochorionic diamniotic twins	**Twin-twin transfusion syndrome**	**Twin anemia polycythemia sequence**	**Selective fetal growth restriction**
Clinical characteristics	Twins share the placenta equally and intertwin transfusion is balanced.	*Pathophysiology:* Unbalanced transfusion through large vascular anastomoses *Presentation:* Oligohydramnios in donor and polyhydramnios in recipient	*Pathophysiology:* Chronic unbalanced transfusion through miniscule vascular anastomoses *Presentation:* Anemia in donor and polycythemia in recipient	*Pathophysiology:* Unequal placental sharing *Presentation:* Large intertwin growth discrepancy with one twin being growth-restricted
Placenta				

Figure 2. An overview of the pathophysiology and clinical presentation of MC twin complications (top-left illustrations © Amanda Gautier).

Monochorionic twins

Of all twins, approximately two-thirds are dizygotic, that is originating from the fertilization of two separate egg cells. One-third is monozygotic, originating from the fertilization of a single egg cell. All fraternal twins are dichorionic, meaning that they each have their own placenta. Identical twins can also be dichorionic, but the majority of identical twins is MC and thereby shares a single placenta. On the surface of this shared placenta there are vascular connections allowing for intertwin blood flow[5] (Figure 1). This shared placenta can give rise to a spectrum of complications, either due to unbalanced intertwin transfusion through the vascular connections or due to unequal sharing of the placenta (Figure 2). These complications are not mutually exclusive and can overlap during the course of a pregnancy. They also elevate the risk of perinatal morbidity and mortality even higher for MC twins when compared to dichorionic twins[6]. Over the past decades, great progress has been made in understanding, management and outcome of conditions pertaining to unbalanced feto-fetal transfusion. Now, another distinct entity with substantial rates of adverse outcomes is increasingly recognized within the MC twin complications: selective fetal growth restriction (sFGR).

Figure 3. sFGR is characterized by a large intertwin growth discrepancy during pregnancy. The children in the picture were born at a gestational age of 32 weeks with birth weights of approximately 750 grams and 1750 grams (birth weight discordance of nearly 60%). (illustration ©Amanda Gautier).

Selective fetal growth restriction

Isolated sFGR occurs in up to 10-15% of MC twin pregnancies and is characterized by a large intertwin growth discrepancy in which one twin is growth-restricted[7,8] (Figure 3-

5). A large birth weight discordance (BWD) ensues, of which cut-offs vary between 20-25% in literature. sFGR is generally thought to be caused by unequal placental sharing, resulting in discordant access to oxygen and nutrients *in utero* leading (Figure 4)[9]. In 2007 Gratacós et al. proposed an antenatal classification system for sFGR based on the umbilical artery Doppler flow in the smaller twin[9]. Three types can be distinguished: Type I is characterized by positive end-diastolic flow (pEDF), Type II by persistent absent or reversed end-diastolic flow (A/REDF) and Type III by intermittent absent or reversed end-diastolic flow (iA/REDF) (Figure 6).

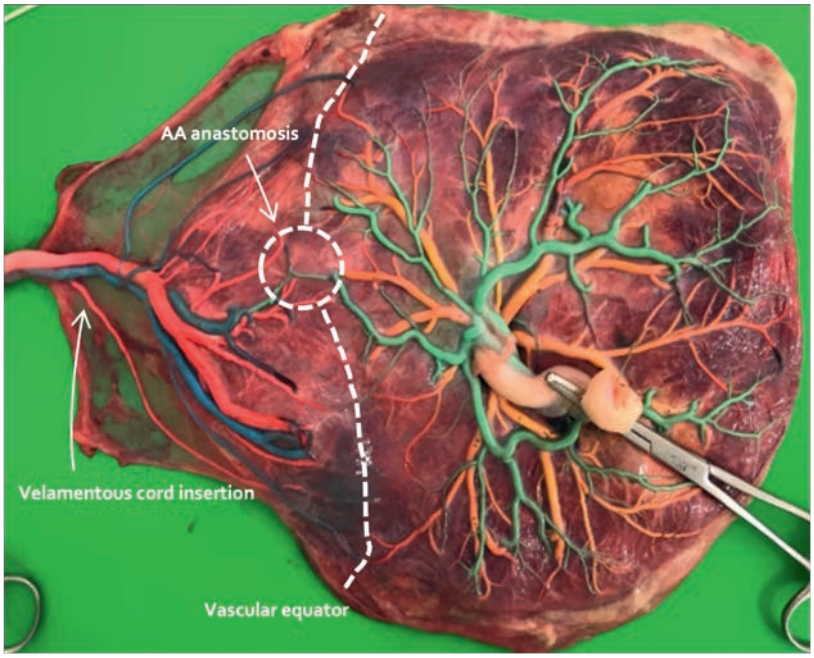

Figure 4. A MC twin placenta after sFGR, with unequal sharing in which the firstborn twin (blue/pink) had 20% of the placenta and the second born twin (green/yellow) 80%, amounting to a placental share discordance of 75%. These twins were born at a gestational age of 28 weeks, with 800 grams for the firstborn twin and 1500 grams for the second-born twin (birth weight discordance of nearly 50%). The firstborn twin has a velamentous cord insertion and the diameter of the arterio-arterial (AA) anastomosis (blue-green dye connection) was 1.3 mm.

From unequal sharing to long-term outcome

Despite the marked surge in published studies on sFGR over the past decade, many questions remain unanswered to date. This impedes proper parent counseling and short- and long-term risk assessment for MC twins with sFGR. The studies in this thesis aimed to fill this gap in knowledge to improve care for this vulnerable patient population.

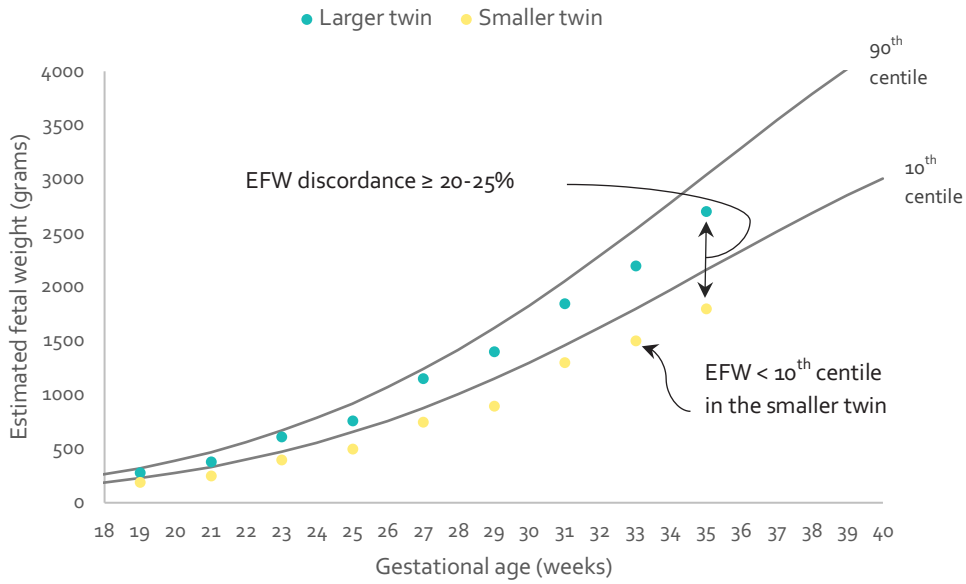

Figure 5. Selective fetal growth restriction is generally diagnosed based on an estimated fetal weight (EFW) discordance ≥ 20-25% in combination with one twin being growth-restricted, i.e., with an EFW < 10th centile. Fetal growth in MC twin pregnancies is measured every other week and EFW is calculated based on head circumference, abdominal circumference, and femur length.

Firstly, placental angioarchitecture in relation to the Gratacós classification is not yet fully understood, even though this classification has been widely used since its introduction. This in turn essentially hampers the formation of adequate antenatal management strategies. We have therefore performed two placental studies using color dye injection. The first study evaluated the placental characteristics of each Gratacós type, including the presence and diameter of bidirectional anastomoses (Chapter 1). The second study assessed if blood flow through the large bidirectional anastomoses can compensate for unequal placental sharing (Chapter 2).

Secondly, MC twins with sFGR are still complicated by high rates of (iatrogenic) prematurity and its sequelae, especially in type II and type III. We performed a systematic literature review to illustrate this international heterogeneity in timing of delivery of MC twins with sFGR (Chapter 3). In addition, available literature on perinatal outcomes after sFGR reports on an inconsistent variety of outcome parameters, chiefly concentrating on mortality and cerebral injury. Within-twin pair comparisons are scarce, resulting in an incomplete assessment of the size (smaller or larger twin) specific risks that clinicians should be wary of after birth. Hence, we

performed three studies on the short-term outcomes of MC twins with sFGR, focusing on respiratory outcomes (Chapter 4), cardiac structure (Chapter 5) and brain growth (Chapter 6) respectively.

Lastly, current research is primarily focused on perinatal outcome and should increasingly be shifted towards long-term outcome as well, in view of the importance for a child's daily functioning. We bundled available studies on long-term neurodevelopmental outcome after sFGR in a systematic literature review (Chapter 7). Additionally, we set up a large cohort study to investigate the long-term neurodevelopmental outcome (Chapter 8), social-emotional development (Chapter 9) and growth patterns (Chapter 10) after sFGR, called the LEMON study (Long-term Effects of selective fetal growth restriction in MONochorionic twins).

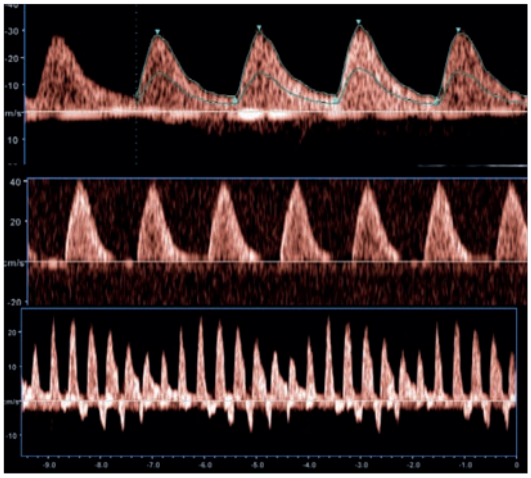

Figure 6. The Gratacós classification based on the Doppler flow pattern in the UA of the smaller twin.

A natural experiment

Lifelong cardiovascular and neurodevelopmental risk may be partially set before birth. FGR, low birth weight and preterm birth are associated with dyslipidemia, adiposity, type 2 diabetes, cardiovascular parameters and neurodevelopmental disorders[10-12]. The common denominator of these factors is that they represent an adverse intrauterine environment, resulting in greater long-term health risk. Epigenetic mechanisms are widely perceived to be a strong candidate to explain the mediation of prenatal adversity in later health[13]. Despite promising findings, it can be argued that the field still has to deliver robust mechanistic insight of the relationship between

unfavorable intrauterine circumstances and long-term health outcomes. This may be achieved by using a study population of MC twins with sFGR, in which a growth-restricted twin can be compared to an appropriately-grown, genetically identical co-twin with the same obstetrical and familial factors. Therefore, we have set up the Twinlife study (Twin Longitudinal Investigation of FEtal discordance), to longitudinally follow these twins from womb to adolescence. The results presented in this thesis will therefore not only be of immediate relevance to MC twins, but the impact may extend to the general population of singletons experiencing severe pregnancy complications such as fetal growth restriction.

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Aim and outline of this thesis

The aim of this thesis is to investigate sFGR in MC twins from womb to adolescence, to provide essential information on pathophysiology and clinical outcomes in this vulnerable patient population while simultaneously exploring the early origins of disease in this unique natural experiment in identical twins with discordant fetal growth.

Part I focuses on the placental mechanisms behind sFGR, including unequal sharing and patterns of vascular anastomoses that are associated with the antenatal classification system. *Part II* focuses on the short-term outcomes by highlighting the international discussion on optimal timing of delivery and evaluating early respiratory, cardiovascular and neurological outcomes. *Part III* focuses on the long-term health outcomes throughout childhood. Lastly, *Part IV* consist of a summary and general discussion of the results presented in this thesis.

General introduction and outline of this thesis.

Part I: From unequal placental sharing to a discordant intrauterine environment

Chapter 1: Placental characteristics in monochorionic twins with selective fetal growth restriction in relation to umbilical artery Doppler classification.
Placenta. 2018 Nov;71:1-5.

Chapter 2: Impact of placental sharing and large bidirectional anastomoses on birth weight discordance in monochorionic twins: a retrospective cohort study in 449 cases.
American Journal of Obstetrics and Gynecology. 2022 Nov 1;227(5):755.E1-755.E10.

Part II: From fetus to newborn

Chapter 3: Gestational age at birth and outcome in monochorionic twins with different types of selective fetal growth restriction: a systematic literature review.
Prenatal Diagnosis. 2022 Aug;42(9):1094-1110.

Chapter 4: Respiratory distress syndrome and bronchopulmonary dysplasia after fetal growth restriction: lessons from a natural experiment in identical twins.
EClinicalMedicine. 2021 Jan 29;32:100725.

Chapter 5: Early structural cardiovascular changes after adverse intrauterine circumstances in identical twins.
Submitted to Archives of Disease in Childhood – Fetal & Neonatal Edition. 2022 Sep.

Chapter 6: Changes in structural brain development after selective fetal growth restriction in monochorionic twins.
Ultrasound in Obstetrics and Gynecology. 2022 Jun;59(6):747-755.

Part III: From infant to adolescent

Chapter 7: The impact of selective fetal growth restriction or birth weight discordance on long-term neurodevelopment in monochorionic twins: a systematic literature review.
Journal of Clinical Medicine. 2019 Jun 28;8(7):944.

Chapter 8: Long-term effects of selective fetal growth restriction (LEMON): a cohort study of neurodevelopmental outcome in growth discordant identical twins in the Netherlands.
The Lancet Child and Adolescent Health. 2022 Sep;6(9):624-632.

Chapter 9: Insecure attachment and internalizing behavior problems in birth weight discordant identical twins.
Early Human Development. 2022 Nov;174:105679.

Chapter 10: Fetal growth restriction inhibits childhood growth despite catch-up: in discordant identical twins.
Under revision in Pediatrics. 2022 Sep.

Part IV: Summary and discussion

Summary and general discussion

Nederlandse samenvatting

Appendices

Abbreviations

List of publications

Curriculum Vitae

Dankwoord