Chapter 1

Introduction to twin pregnancies with special attention to twin-to-twin transfusion syndrome and twin anemia-polycythemia sequence

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Zygosity and chorionicity

Twin pregnancies occur in 1-2% of all pregnancies. Two-thirds of twin pregnancies are dizygotic and one-third are monozygotic. Dizygotic twins result from the fertilization of two different egg cells by two different sperm cells. Dizygotic twins or non-identical twins have the same genetic similarities as any other two siblings would have.[1] Dizygotic pregnancies are implicitly dichorionic (DC) and diamniotic (DA) which means there are two functionally separate placentas and two individual amniotic sacs.

Monozygotic twins or identical twins develop from a single egg fertilized by a single sperm cell. The zygote divides after fertilization. In monozygotic twins, the chorionicity is determined by the time interval between fertilization and division of the zygote and can be either DC or monochorionic (MC), with a shared placenta. The time interval of the division of the zygote in MC gestations also determines whether the embryos will have individual amniotic sacs (diamniotic) or share a single amniotic sac (monoamniotic (MA)).[2] DC-DA gestations occur in 25% of monozygotic gestations, MC-DA in 75% and MC-MA in less than 1%.[3]

The mortality and morbidity of twin pregnancies is 3-7 times higher than singleton pregnancies. This is mainly owing to prematurity, fetal growth restriction and both structural and chromosomal anomalies. However, the chorionicity also affects mortality and morbidity. Mortality in MC pregnancies is twice as high as DC pregnancies and four times higher than singleton pregnancies.[4] MC gestations have unique complications as a result of their shared placenta which will be discussed in more detail as well as other complications related to possible monoamnionicity, e.g. conjoined twins and umbilical cord entanglement.[4]

Placental angioarchitecture

Placental injection studies have shown that vascular anastomoses between the fetal circulations are ubiquitous in MC placentas, but occur extremely infrequently in DC placentas.[5]

There are three types of placental anastomoses: arterio-arterial (AA), veno-venous (VV) and arterio-venous (AV) anastomoses. AA and VV anastomoses are superficial, bidirectional and have a low resistance. They form direct connections between the two fetal circulations. The direction of flow can be in either direction and is dependent on the interfetal pressure gradient/difference.[6] After placental injection studies they can be seen as direct vascular connections running on the surface of the chorionic plate. In contrast, AV anastomoses are deep, unidirectional and have a high resistance. AV anastomoses consist of an artery from one twin and the vein of the other twin that are connected by a capillary network in a shared cotyledon below the chorionic plate. They can be visualized as a supplying artery and a draining vein that pierce the chorionic plate in close proximity

to each other.[6;7] As a result of the unidirectional flow in AV-anastomoses an imbalance in the net transfusion of blood can occur.

Vascular anastomoses and complications in monochorionic gestations

Placental vascular anastomoses are the basis for the development of various complications associated with MC gestations including chronic twin-to-twin transfusion syndrome (TTTS) and twin anemia-polycythemia sequence (TAPS). TTTS and TAPS will be discussed in more detail here below. Others complications in MC gestations include acute perinatal TTTS, acute perimortem TTTS, twin reversed arterial perfusion sequence (TRAP) and selective intrauterine growth restriction (sIUGR).[8;9]

Acute perinatal TTTS is described anecdotally as acute transfusion during birth through superficial AA or VV anastomoses, however there is very little data on it. This feto-fetal transfusion is possibly caused by uterine contractions or fetal position which influence fetal blood pressure.[7;9] This is not to be confused with placento-fetal transfusion which can occur at birth after clamping the umbilical cord of the first twin. This results in the second twin receiving blood not only from its own part of the placenta, but also from the placenta share of the co-twin. Hemoglobin levels are often higher in the second twin born of MC gestations due to placenta-fetal transfusion.[10]

Acute perimortem TTTS occurs after the intrauterine death of one twin. Transfusion or exsanguination takes place from the surviving twin through placental vascular anastomoses to the low pressure circulation of the dead twin and can lead to (double) fetal demise or hypoxic-ischemic damage of the surviving twin. It is believed to occur through large diameter, bidirectional AA or VV anastomoses.[9;11]

TRAP sequence, also known as ‘acardiac twinning’, is a rare complication of MC gestations. One twin is acardiac and as the name suggests has no functional heart and may have other severe malformations. The co-twin is known as the pump twin and has no malformations. The pump twin perfuses the acardiac twin by pumping blood trough both fetal circulations. The pump twin is at risk for congestive heart failure. This extreme form of feto-fetal transfusion only occurs in 1 of 35 000 gestations and in <1% of MC gestations.[12;13]

sIUGR and/or birth weight discordance (BWD) are important complications of MC gestations. sIUGR is defined as an estimated fetal weight of one fetus below the 10th centile. BWD is defined as a discrepancy in the birth weights of more than 25%. sIUGR and BWD are strongly associated with each other and result from unequal placental sharing. The growth restricted fetus often has a small placental share and a velamentous cord insertion, while the larger fetus has a larger placental share and a para-central cord insertion.[6;14]

TWIN-TO-TWIN TRANSFUSION SYNDROME (TTTS)

Usually blood flow across placental anastomoses is balanced. However, in TTTS there is chronic and unbalanced feto-fetal transfusion from the donor-twin to the recipient-twin. Although placental anastomoses are ubiquitous in MC placentas, TTTS develops only in 9-15%.[9;15] Clinical symptoms usually occur during the second or third trimester because of severe polyhydramnios of the recipient and can include maternal discomfort, preterm prelabor rupture of membranes (PPROM), or premature labor.[3;9;16]

Placental angioarchitecture and placental characteristics

The pathophysiology of TTTS is described as resulting from a net imbalance of blood flow between the fetuses through communicating placental anastomoses. TTTS only develops in the presence of unidirectional AV-anastomoses when blood from one twin (the donor) is pumped through the artery to the shared cotyledon and then drains through a vein to the other twin (the recipient).[8;9] TTTS develops therefore in the presence of at least one AV-anastomosis, unless blood is pumped back to the donor through another AV-anastomosis in the opposite direction or through a bidirectional AA or VV anastomosis. The unbalanced blood flow causes the donor to become progressively hypovolemic, often growth restricted and oliguric, which causes oligohydramnios in the amniotic sac. In contrast the recipient becomes progressively hypervolemic and polyuric, congestive heart failure can develop as a result of the volume overload. Polyhydramnios develops in the recipient's amniotic sac.

AA anastomoses are thought to be protective against the development of TTTS. Bidirectional anastomoses can therefore theoretically compensate for unbalanced blood flow through an AV anastomosis.[3;9] A mathematical computer model showed that AA anastomoses compensate better for the hemodynamic imbalance in TTTS than contra directional AV anastomoses because of the lower resistance over AA anastomoses.[17] Previously, not much attention has been paid to the possible role VV anastomoses may have in the development of transfusion syndromes in MC gestations.

Unequal placental sharing and the incidence of velamentous cord insertions in TTTS placentas corresponds with those found in normal monochorionic placentas. In TTTS placentas, in a significant majority of cases, the donor twin has a velamentous cord insertion and a smaller placental territory.[18] Whether this has any bearing on the development of TTTS still needs to be elucidated.

Other pathophysiological mechanisms

Other pathophysiological theories have been proposed because intertwin hemoglobin differences are not always large which might disprove pathophysiological theories based solely on placental angioarchitecture, although placental anastomoses are undeniably

a prerequisite for the development of TTTS.[9] These theories include utero-placental insufficiency and activation of vasoactive and hormonal factors, including insulin-like growth factor (IGF)-II, leptin, endothelin-1 and the renin-angiotensin system.[6;9;16] When related to the expected blood pressure for birth weight, donors had a lower than expected blood pressure and recipients a higher.[19]

Diagnosis

Chorionicity is determined by antenatal ultrasound in the first trimester. Other signs of monochorionicity include a single placental mass and fetuses of the same sex. TTTS is diagnosed by twin oligo-polyhydramnios (TOPS) seen on prenatal ultrasound. It can occur at any time during the pregnancy, but is most common in the second trimester. Severe oligohydramnios or anhydramnios is defined as the deepest vertical amniotic fluid pool < 2 cm and polyhydramnios is described as the deepest amniotic fluid pool > 8cm.[3] Furthermore, signs of oligo- or anuria can be seen in the donor as a small or empty bladder and the donor may be `stuck` to the uterine wall with the amniotic membrane is tightly wrapped around it. This can be incorrectly interpreted as a MA gestation if careful attention is not paid to the reduction of movement of the fetus as is the case in a DA pregnancy with a stuck twin. Conversely, the signs of polyuria can be seen in the recipient as an extended bladder. In severe cases, Doppler investigations can show signs of congestive heart failure in the recipient as a result of hypervolemia. Sonographically, growth discrepancy may be noted with the recipient being the larger twin.

Staging: Quintero

Quintero et al. devised a staging system with which to categorize TTTS based on antenatal ultrasound criteria. Stage I is the mildest form of TTTS with oligohydramnios of the donor (deepest pocket < 2cm) with the bladder still visible and polyhydramnios of the recipient (deepest pocket > 8cm). Stage II describes a `stuck` twin and the bladder of the donor is not visible. In stage III there are severely abnormal Doppler flow patterns with absent or reverse end-diastolic flow in the umbilical artery of the donor and/or venous abnormalities in the recipient with reverse flow in the ductus venosus or pulsatile umbilical venous flow or tricuspid regurgitation. Stage IV shows fetal hydrops and stage V is described as death of one or both twins.[20]

Treatment:

The two main therapeutic options for TTTS are amniodrainage and fetoscopic laser surgery.

Serial amniodrainage is a relatively simple, symptomatic treatment and was the standard care before laser coagulation was developed.[3] Depending on the gestational age it can be used to prolong the pregnancy and postpone premature birth. It reduces

the polyhydramnios and the amniotic fluid pressure on the uterus and also improves the placental perfusion which in turn improves the condition of the fetus. The risk of complications is small, however it would seem that serial amniodrainage is only effective for MC twin gestations with mild signs of TTTS. Usually the procedure needs to be repeated a number of times as amniotic fluid reaccumulates.[6;9]

In contrast to amniodrainage, fetoscopic laser coagulation addresses the cause of TTTS by coagulating the placental anastomoses, stopping intertwin transfusion and creating two functionally separate placentas. The most frequently occurring complication is PPROM in approximately 10% of procedures, other complications occur infrequently. Fetoscopic laser coagulation is the preferred treatment before 26 weeks gestation.[9] The aim of the treatment is to completely separate the two fetal circulations, however, in our center, about a quarter to a third of lasered placentas had residual anastomoses. Most residual anastomoses were located near the edge of the placenta and were very small. However, residual anastomoses can lead to a number of complications including reversed TTTS or TAPS.[21;22]

Studies differ on whether laser coagulation improves overall survival rates, but it does reduce the risk of neurological morbidity. For this reason, laser coagulation should be considered in all TTTS cases.[6;23] The Leiden University Medical Centre (LUMC) is the national referral center in The Netherlands for complicated monochorionic gestations whe fetoscopic laser coagulation is the preferred treatment option for TTTS.

Table 1. Diagnostic criteria of TTTS and TAPS

TTTS	TAPS
Antenatal criteria Confirmed MC gestation *and* Oligohydramnios or anhydramnios in the donor with as the deepest vertical amniotic fluid pool < 2 cm *and* Polyhydramnios in the recipient with the deepest amniotic fluid pool > 8cm *and* Discordant fetal bladders with a small or empty bladder in the donor and a large bladder in the recipient	**Antenatal criteria** Confirmed MC gestation *and* Middle cerebral artery peak systolic velocity (MCA-PSV) > 1.5 multiples of the mean (MoM) in the donor *and* MCA-PSV < 1.0 MoM in the recipient **Postnatal criteria** Intertwin Hb difference > 8.0 g/dl *and* at least one of the following: • Reticulocyte count ratio > 1.7 • Placenta with only small vascular anastomoses (diameter < 1 mm)

TWIN ANEMIA-POLYCYTHEMIA SEQUENCE (TAPS)

TAPS is a form of chronic feto-fetal transfusion and is defined as a discordant hemoglobin level at birth as a result of chronic intertwin transfusion without signs of twin oligo-polyhydramnios sequence (TOPS) as seen in TTTS. It has been recently described in 2007 and can occur spontaneously or iatrogenically after laser coagulation of TTTS.

[9;24;25] Interestingly, in iatrogenic TAPS, it is usually the former TTTS recipient who becomes anemic and vice versa, the former TTTS donor who becomes polycythemic. The incidence of spontaneous TAPS has been estimated to be about 3-5%[15;26] and iatrogenic TAPS occurs in up to 2-13% of cases after laser coagulation.[27;28]

A new technique called the Solomon technique has been proposed to decrease the number of residual anastomoses. When the Solomon technique is practiced, anastomoses are identified and lasered, hereafter a line is lasered along the vascular equator. This technique shows a significant reduction in the number of post-laser TAPS cases, as well as a reduction in the recurrence of TTTS [29].

Pathophysiology

The maternal side of the placenta can be distinguished by the pale donor side and the plethoric recipient side of the placenta, as is seen in the anemic and polycythemic neonate. TAPS is caused by miniscule AV anastomoses. It is postulated that less volume and a much slower blood flow occurs in TAPS than in TTTS. This would potentially allow more time for hemodynamic compensation to take place.[9] A few additional reasons may possibly explain why inter-twin fetal transfusion in TAPS does not lead to amniotic fluid imbalance. The renin angiotensin system may play a role in achieving euvolemia and therefore the absence of oligo- and polyhydramnios. Another explanation is that TOPS had not yet developed in the progression of TTTS.[30]

Diagnosis

TAPS can be diagnosed antenatally or postnatally. Antenatally, Doppler ultrasound criteria include an increased middle cerebral artery peak systolic velocity (MCA-PSV) > 1.5 multiples of the mean (MoM) in one fetus with a simultaneous decrease in the MCA-PSV < 1 MoM in the other fetus.[27] Postnatal diagnosis of TAPS includes anemia in the donor and polycythemia in the recipient as well as reticulocytosis in the donor as a sign of chronic anemia. In 2014 diagnostic cutoff criteria were proposed with an intertwin hemoglobin difference > 8.0 g/dl and an intertwin reticulocyte count ratio donor/recipient > 1.7. The detection of minuscule AV anastomoses in placental injection is supportive of the diagnosis.[9;26]

Treatment

As with TTTS there are a number of treatment options which need to be considered, including induced labor, intrauterine transfusion (IUT) in the donor with or without partial exchange transfusion (PET) in the recipient and (repeat) laser coagulation of the vascular anastomoses.

The option of induced labor depends on the duration of gestation. The advantages of stopping the feto-fetal transfusion need to be weighed up against the disadvantages of preterm delivery.

Intrauterine transfusion is a symptomatic treatment for the anemic donor, but possibly deleterious to the recipient. However, depending on the placental angioarchitecture, one runs the risk of iatrogenically increasing the recipient's polycythemia and all risks associated with it. A computer model has shown that potentially combining this with PET in the recipient may minimize these risks. However further study is needed to verify this theory. [33]

As in the treatment of TTTS, laser coagulation remains the only causal therapy. Repeat laser coagulation in iatrogenic TAPS is technically more difficult than it is for TTTS as there is less amniotic fluid (no polyhydramnios) and the uterine wall is less tense making the visualization of anastomoses more difficult. Until recently the preference has been to avoid invasive procedures (IUT and laser coagulation) as the complications associated with preterm delivery outweigh the benefits of the procedures.[9] However, new studies indicate that laser coagulation may prolong the pregnancy, thereby improving survival and neonatal outcome.[32]

Outcome

The outcome of TAPS have not been well studied. There is only limited long-term data available. The short-term data that is available shows a low mortality and low neurological morbidity.[33;34]

PLACENTAL STUDIES IN TTTS AND TAPS

In the past two decades, major improvements in diagnosis and treatment of complicated MC pregnancies have led to improved perinatal outcome in MC twins. Placental studies with colored dye injection have played a crucial role in the understanding of the pathophysiology of the various complications and the detection of new disorders in MC twins. In addition, placental injection studies play a crucial role in the evaluation of fetoscopic laser coagulation in TTTS and TAPS. Injection studies with color dye allow accurate detection of residual anastomoses and give invaluable feedback information to the fetal surgeons in regard to the success or completeness of the laser coagulation intervention.

Placental injection studies should therefore be regarded as standard postnatal evaluation in all complicated MC twin pregnancies.

Nevertheless, various severe complications in MC twin pregnancies still pose major diagnostic and therapeutic challenges for fetal surgeons and the outcome in these complicated MC pregnancies is far from optimal. To continue improving our understanding of the

development of various complications in MC twins, routine injection of all MC placentas is of paramount importance.

The exact role of the size, number and type of anastomoses (particularly AA and VV anastomoses) in the development of TTTS and TAPS is still not fully understood. In addition, other etiological placental factors such as placental sharing and type of umbilical cord insertion also require further investigation.

The objective of our studies is to investigate several aspects of the placental angio-architecture in TTTS and TAPS cases to enhance our understanding in the development of these disorders.

OUTLINE OF THIS THESIS

PART I – Introduction

Chapter 1 – General introduction

Chapter 2 – Review on the literature on injection technique and analysis of MC twin placentas

PART II – TTTS

Chapter 3 – Study on the velamentous cord insertion in MC twins with TTTS compared to a control group of MC placentas without TTTS.

Chapter 4 – Study on arterio-arterial vascular anastomoses in MC placentas with TTTS compared to a control group of MC placentas without TTTS.

Chapter 5 – Study on veno-venous anastomoses in in MC twins with and without TTTS with special attention to the perinatal mortality.

PART III – TAPS

Chapter 6 – Study on arterio-arterial vascular anastomoses in MC placentas with spontaneous TAPS compared to a control group of MC placentas without TAPS.

Chapter 7 – Study on the placental characteristics in MC twins with spontaneous versus post-laser TAPS.

PART IV – Discussion and Summary

Chapter 8 – General discussion of the most important findings of this thesis and future perspectives.

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