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Ultrasound studies in monochorionic twin pregnancies : results of TULIPS: Twins and ultrasound in pregnancy studies

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Chapter 1

General introduction

Introduction

Parents are often surprised, when two fetuses are spotted on ultrasound and a twin pregnancy is diagnosed. Feelings of happiness and anxiety are awakened at the same time. Twin pregnancies differ from "normal" singleton pregnancies in several ways. Maternal and fetal risks are increased, and therefore, antenatal care is intensified and should be provided by an obstetrician. Very special attention must be paid to patients pregnant with monochorionic twins. They are at risk of several complications, such as intrauterine fetal death (IUFD), intrauterine growth restriction (IUGR), discordant fetal anomalies, e.g. twin reversed arterial perfusion (TRAP) sequence, and, most severe, twin-to-twin transfusion syndrome (TTTS). TTTS is a condition in perinatal medicine that is complicated by high perinatal mortality and morbidity rates. An important tool used for monitoring monochorionic twin pregnancies is ultrasound examination.

The first description of TTTS may be found in the book of Genesis[1]. Although the twins Esau and Jacob, sons of Isaac and Rebecca, showed physical dissimilarity in adult life, suggesting dizygotic twins, Esau was born red and has therefore been labeled as the earliest example of TTTS. Placental examination after the birth of Esau and Jacob was not reported, so we will never know for sure. More recently, in 1617, a painting was made in the Netherlands: "De Wikkelkinderen" (The Swaddled Children)[2]. Two babies, obviously twins, with different facial coloring (red and white) are portrayed. The striking difference in color may be explained by monochorionicity and acute or chronic blood transfusion in the presence of a monochorionic placenta. This twin pair possibly died on the day that they were born. In the 19th century, the first scientific paper on TTTS was published by Friedrich Schatz, a German gynaecologist[3]. He was the first to study the twinning process and to speculate on the relationship between vascular anastomoses and the development of TTTS. Since 1964, more than 1000 studies on "twin-twin transfusion syndrome" have been published. This increased attention has resulted in expanded knowledge about TTTS. However, multiple aspects of TTTS are still unclear.

This chapter will focus on ultrasound examination in monochorionic twin pregnancies (Part 1) and TTTS (Part 2).

Part 1

Ultrasound examination in monochorionic twin pregnancies

Twinning

Zygosity

Twins are not rare. The incidence of spontaneous twinning in the Netherlands is approximately 1%, of which are 70% fraternal or dizygotic and 30% identical or monozygotic twins[4]. Dizygotic twins develop from two separate fertilized eggs. This type of twinning seems to be related to increased follicle-stimulating hormone concentrations in the mother. These amounts are influenced by geography, season, ethnic origin, increasing parity, and are higher in tall, heavy and older mothers[5]. The rate of dizygotic twinning has increased with the increase of induced ovulation and in vitro fertilization. Monozygotic twinning entails one zygote (fertilized egg) splitting into two separate individuals. It is not clear why monozygotic twinning occurs. The rate of monozygotic twinning has been fairly constant around the world (0.35% of pregnancies)[6]. After various forms of infertility treatment and in vitro fertilization, though, the rate of monozygotic twinning was found to be increased more than two to six times over the background rate in the general population[7-13].

Chorionicity

The terms "chorion" and "placenta" essentially have the same meaning. Dizygotic twins almost invariably have separate placentas and separate membranes (dichorionic diamniotic twins). Although both placentas can be fused and appear as one[14,15], placental circulations are separated and each fetus is supplied by its own placenta. Placentation in monozygotic twins depends on the timing of separation. In 25 to 30% of all monozygotic twins, fission of the conceptus occurs between day 0 and day 3 and results in dichorionic diamniotic twins. In 70 to 75%, fission takes place between day 4 and day 7, which results in a single placenta with two separate amnions (monochorionic diamniotic twins). Monozygotic twins with both a single placenta and a single amnion (monochorionic monoamniotic twins) are thought to originate between day 7 and day 14 (<1%). In some of these monochorionic monoamniotic pregnancies, twins are conjoined. Except for rare cases[16,17], all monochorionic pregnancies are monozygotic[6]. However, in view of the possibility of heterokaryotypic monochorionic twins (of which the exact incidence remains largely unknown), it was recently reported that dual amniocentesis was superior to chorionic villous sampling in monochorionic twin pregnancies[18].

Chorionicity, rather than zygosity, determines the outcome of twin pregnancies. Therefore, chorionicity should define the way twin pregnancies should be managed. The detection of a monochorionic placenta implies the identification of a high-risk pregnancy, as monochorionic twins are far more prone to complications than dichorionic twins. Frequent monitoring may improve the outcome, and therefore, chorionicity of every twin pregnancy must be determined

early and properly. The use of ultrasound examination has shown to be very reliable for this purpose.

Dichorionic versus monochorionic twins

First-trimester ultrasound examination

As outlined above, the identification of the chorionicity of twin pregnancies is of utmost importance for optimal antenatal care. Today, this can be done reliably by performing a first-trimester ultrasound examination. With a 100% sensitivity and 99% specificity rate, a highly accurate distinction between monochorionic and dichorionic placentation can be made before the 14th week of pregnancy[19,20]. To assess chorionicity, the intertwin membrane should be imaged at its insertion site to the placental mass. There, the presence or absence of a lambda (λ)-, "Y"- or twin peak sign should be visibly checked. When a wedge-shaped junction is observed (Figure 1), the interpretation should be the extension of chorionic tissue into the base of the intertwin membrane and therefore dichorionic. A T-shaped junction (Figure 2) should be interpreted as the fusion of two amniotic membranes without chorionic tissue and therefore considered monochorionic diamniotic. The observation of two separate placentas alone is not sufficient to diagnose dichorionicity[21]. Monochorionic placentas can, albeit rarely, be bilobate and falsely be labeled as dichorionic[22,23]. In the same way, the presence of a single placental mass alone does not prove monochorionicity. In 50% of dichorionic twin pregnancies, the two placentas are fused and appear as one[14,15].

Before 10 weeks of gestation, ultrasound examination can differentiate between monochorionic and dichorionic twin pregnancies with a high degree of accuracy. The differentiation between monochorionic diamniotic and monochorionic monoamniotic pregnancies, however, can be difficult to make before 8 weeks of gestation, as the amniotic membrane is not yet clearly visible[24,25].

Figure 1 Lambda (λ)-, "Y"- or twin peak sign

Figure 2 "T" sign

Second- and third-trimester ultrasound examination

After 14 weeks of gestation, the accuracy of chorionicity assessment decreases. After 20 weeks, the lambda sign disappears in 7% of dichorionic pregnancies[26]. Other sonographic signs are not conclusive and therefore cannot be considered reliable indicators of chorionicity. The assessment of fetal gender only helps if discordance is observed and consequently, monochorionicity can be ruled out. Moreover, although the traditional medical doctrine states that sex-discordant twins are exclusively dizygotic (and therefore dichorionic), multiple cases of sex-discordant or dizygotic monochorionic twins have recently been reported, especially after assisted reproductive technology[16,27-30]. The thickness of the intertwin membrane can be measured, but is associated with high intra- and interobserver variability[31]. Also, it does not distinguish sufficiently between the two types of twins. Although monochorionic diamniotic twins are highly unlikely to have an intertwin membrane thickness of more than 1.5 mm, the intertwin membrane thickness of dichorionic twins does not always exceed 1.5 mm. So prenatally, dichorionic twins can erroneously be classified as monochorionic diamniotic twins

Monochorionic monoamniotic twins

Less than 1% of monozygotic twins have a single amnion, which means that two fetuses share the same amniotic sac. On ultrasound, no intertwin membrane is seen and the umbilical cords are almost always entangled. Occasionally, TTTS has been described to occur in monochorionic monoamniotic twin pregnancies[32-35]. The risk of double IUFD is 10 to 25%[36,37]. Fetal sonographic surveillance should consist of ultrasound examination, at least every two weeks as in other monochorionic twins. Whether acute double IUFD from cord entanglement is in any way preventable is currently unclear[38,39].

The importance of a first-trimester scan in each twin pregnancy with clear identification and documentation of the absence or presence of a lambda (λ)-, "Y" or twin peak sign at the intertwin membrane junction cannot be emphasized enough. With today's wide availability of sonography, the failure to determine chorionicity adequately should be considered to be substandard care.

Complications

All twin pregnancies are at increased risk for obstetrical complications compared to singletons. The reason to keep underlining the significance of defining chorionicity in twin pairs, originates from the knowledge that some complications exclusively depend on chorionicity. In virtually all monochorionic twin placentas, vascular connections between the two twins

(placental anastomoses) are present[14,40-42], whereas these almost never occur in dichorionic placentas[43,44]. These anastomoses are an important cause of the high mortality and morbidity rates in monochorionic twins.

The perinatal mortality rate in monochorionic diamniotic twins is nearly twice as high as in dichorionic twins (2.8 versus 1.6%) and four times higher compared to singletons (2.8 versus 0.7%). However, the problem is even worse and underestimated by perinatal statistics, as the highest fetal loss rate is before viability, the so-called "hidden mortality", with monochorionic diamniotic twins having a sixfold higher fetal loss (12%) before 24 weeks compared to dichorionic twins and singletons (2%)[45].

Complications of monochorionic twin gestation are single IUFD, IUGR, discordant fetal anomalies, e.g. TRAP sequence, and, most severe, TTTS. The vascular connections of monochorionic twin fetuses, that are the cause of their high risk profile, have been labeled as "liaisons dangereuses"[46].

Intrauterine fetal death

Death of one twin *in utero* complicates 2.4% of twin pregnancies[47]. In uncomplicated monochorionic twins, the incidence of single IUFD has been reported to be slightly increased (2.6 to 4.6%)[48,49]. In contrast to dichorionic twins, the vascular intertwin connections in monochorionic twins put the surviving twin at substantial risks. In a recent review, the occurrence of IUFD in monochorionic twin pregnancies carried a risk of co-twin demise and neurological abnormality of 12% and 18%, respectively, compared to 4% and 1% in dichorionic pregnancies[50]. Counseling parents in the event of single IUFD can only be done adequately when chorionicity is clear.

Intrauterine growth restriction

The proportion of pregnancies with a birth weight discordance of more than 25% is similar in monochorionic (11%) and dichorionic (12%) twin pregnancies[45]. However, monochorionic twins have a fourfold risk of both being born with a birth weight below the fifth percentile compared to dichorionic twins (7.5% versus 1.7%)[45]. The risk of at least one fetus with a birth weight below the tenth percentile is 53% and 37% for monochorionic and dichorionic twins, respectively[45]. Fetal biometry should be performed regularly to detect possible growth restriction in twins. In case of IUGR, sonography can be extended with the use of Doppler waveform assessment of the umbilical arteries (UA) and middle cerebral artery (MCA) to examine placental perfusion and detect fetal brain sparing. Doppler investigation of the ductus venosus (DV) should be performed for evaluation of cardiac function. Also, the amount of amniotic fluid needs to be assessed. It should be clear that IUGR in monochorionic pregnancies compared to dichorionic pregnancies is associated with increased risk for the normally grown twin in cases of demise of the growth-restricted co-twin.

Congenital anomalies

Congenital anomalies are more common in twins. Unfortunately, most studies have not related the incidence of congenital anomalies to zygosity or chorionicity. However, it seems that malformations occur per fetus as often in dizygotic twins as in singletons (2 to 3%)[51]. In monozygotic twins, however, the incidence is suggested to be much higher, around 10%. Therefore, a detailed 20-week (or possibly earlier) anomaly scan should be performed in all monozygotic twin pregnancies. Most commonly diagnosed abnormalities include malformations such as neural tube defects, brain defects, facial clefts, cloacal and abdominal wall anomalies, and cardiac defects[52]. Although monozygotic twins are called "identical", discordance for the structural anomaly occurs in approximately 90% of monozygotic twins in which an anomaly is detected[53,54]. Two types of malformations unique to monozygotic twins are the TRAP sequence (or acardiac twin) and the conjoined twins that occur in 1 in 35 000 and 1 in 100 000 births, respectively.

Twin-to-twin transfusion syndrome

TTTS complicates about 10 to 15% of monochorionic twin pregnancies[45,55]. This represents around 1% of all twin pregnancies, and accounts for 17% of perinatal mortality[56], nearly 12% of neonatal deaths and 8.4% of infant deaths in twins[46]. TTTS is caused by imbalanced shunting of blood through the vascular anastomoses on the monochorionic placenta and does not occur in dichorionic twins. Exceptions to the rule are a few cases described in the literature of dichorionic diamniotic fused placentas with vascular anastomoses and TTTS[43,44]. TTTS is diagnosed sonographically by the detection of an oligo/polyhydramnios sequence. Left untreated, mortality rates of severe TTTS exceed 80%[57-62] and the risk of handicaps in survivors is 15 to 50%[63].

Part 2

Ultrasound examination in twin-to-twin transfusion syndrome

Twin-to-twin transfusion syndrome

Several forms of TTTS have been described: acute perimortem, acute perinatal, TRAP sequence, and chronic TTTS[64].

Acute perimortem TTTS may occur after IUFD of one twin and is due to acute exsanguination from the surviving co-twin into the low-pressure circulation of the demised twin through the placental anastomoses, eventually causing co-twin death or severe hypoxic-ischemic damage[50,65-67].

Acute perinatal TTTS has been described to occur occasionally during delivery[68,69]. Acute fetal distress during labor can result in a sudden drop in arterial pressure, precipitating acute transfusion between the twins, manifestating in a difference in hemoglobin concentration at birth between the donor (pale) and the recipient (plethoric).

The TRAP sequence, also named acardiac twinning, is the most extreme form of TTTS and occurs in 1 in 35 000 pregnancies[70]. It occurs when a large arterioarterial (AA) and venovenous (VV) anastomosis are present. The donor, or pump twin, pumps blood into its own circulation as well as directly into the, usually single, UA of the acardiac fetus that is severely malformed without a functional heart. The donor twin may die *in utero* due to high output cardiac failure.

The most common type of TTTS is the chronic form, complicating 10 to 15% of monochorionic twin pregnancies[45,55]. Chronic TTTS usually emerges in the second trimester, although first-trimester[71-73] and early third-trimester[74] cases have been described. Hypovolemia, oliguria and oligohydramnios develop in the donor twin. The recipient twin suffers from hypervolemia, polyuria and polyhydramnios, which may lead to circulatory volume overload, cardiac failure and, eventually, hydrops. The diagnosis is made sonographically by the detection of an oligo/polyhydramnios sequence[75]. This form of TTTS may lead to maternal discomfort and may cause clinical symptoms, such as premature rupture of membranes or contractions due to massive polyhydramnios.

Research studies in preparation of this thesis have been performed in pregnancies complicated by the chronic form of TTTS.

Pathophysiology

The pathophysiology of TTTS is usually explained on an angioarchitectural basis. Virtually all monochorionic placentas contain vascular anastomoses[14,40-42], whereas these almost never occur in dichorionic placentas[43,44]. Thus, intertwin transfusion is the norm in monochorionic pregnancies and a normal physiological phenomenon as long as blood flow between the fetuses is balanced. During the first half of pregnancy a random reduction in placental anastomoses takes

place, which is a progressive and unpredictable process, that may lead to unbalanced flow and subsequent development of TTTS[76].

Vascular anastomoses can be present as early as from 28 days after fertilization[6,77]. Three types of anastomoses exist: AA, VV and arteriovenous (AV). The first two types are superficial, bidirectional anastomoses lying on the surface of the chorionic plate, directly connecting chorionic vessels of the same type of both fetal circulations. AA and VV anastomoses mediate bidirectional flow, depending on the intertwin difference in blood pressure, and can compensate for the intertwin shift of blood in a rapid manner. The latter type of anastomoses is referred to as "deep", unidirectional anastomoses consisting of a chorionic artery from one twin that dips to an underlying, shared cotyledon with its venous (well-oxygenated) drainage to the other twin. Flow is facilitated in only one direction. If the blood shift through these AV anastomoses from one fetus to the other is unbalanced and insufficiently compensated by oppositely directed blood flow through superficial or other deep anastomoses, TTTS can develop.

From postnatal injection studies, it was shown that at least one unidirectional AV anasomosis is an anatomical prerequisite for the development of TTTS[42,78,79]. Placentas with TTTS have been shown to contain significantly fewer superficial anastomoses than those without TTTS[40]. Others found that only the incidence of AA anastomoses was lower in monochorionic placentas with TTTS compared to monochorionic placentas without TTTS[42]. AA anastomoses are believed to be protective against the occurrence of TTTS[42,78-80]. Denbow *et al.*[81] confirmed the *ex vivo* studies by demonstrating *in vivo* that TTTS is associated with a paucity of superficial anastomoses.

The presence of vascular anastomoses is necessary for the development of TTTS. The transfer of blood, however, fails to explain the development of TTTS completely. A supposed multifactorial origin of TTTS is supported by the fact that most TTTS cases do not show significant intertwin hemoglobin differences[82]. Moreover, erythropoietin levels are not increased in donors[83] and iron metabolism in both donors and recipients is not disturbed[84]. Thus, other mechanisms are likely to be involved as well.

Fetal hormones may play a role in the development of TTTS. In recipients, plasma endothelin-1 levels are significantly raised compared to donor twins, potentionally leading to vasoconstriction and hypertension[85-87]. Neonatally, hypertension has been documented in recipients[88-90]. Also, significantly increased levels of fetal atrial natriuric peptide and brain natriuretic peptide have been found in recipients[86,91-93]. The release of these cardiac hormones is induced by cardiac overload and stimulates fetal urine production, consequently increasing polyhydramnios and thus aggravating TTTS. In donors, the response to hypovolemia and decreased renal perfusion is the upregulation of the fetal renin-angiotensin system. In recipients, the renin-angiotensin system is downregulated. Renin-angiotensin aims at restoring euvolemia in the donor, however, the vasoconstrictive effect may diminish renal perfusion and amniotic fluid of the donor even further. Moreover, transfer of angiotensin II from donor to recipient may induce fetal hypertension and increased afterload in the recipient. This is not expected to occur in donors,

due to their hypovolemic situation[90,94-97]. The concentration of vasopressin, an antidiuretic and vasoconstrictive hormone, has also been shown to be increased in donors[98].

Until recently, the velamentous insertion of the umbilical cord was considered another potential cause of TTTS. Velamentous cord insertion has been reported to occur more often in monochorionic pregnancies affected by TTTS[99,100]. It was thought that, due to its abnormal insertion, the cord may be easily compressed, especially by the expanding sac with polyhydramnios of the recipient. This may result in decreased umbilical venous blood flow to the one twin (donor). Blood flow to the other twin (recipient) through the vascular anastomoses would then be increased, leading to the development of TTTS. However, recent studies have reported on a similar incidence of velamentous cord insertion in monochorionic twins with and without TTTS[101,102]. Therefore, velamentous cord insertion does not seem to be critical for the development of TTTS.

It is also considered that the development of TTTS is associated with a primary maldevelopment of the placenta of the donor[103]. Increased peripheral resistance in the placental circulation of the donor twin would promote the shunting of blood to the recipient, subsequently causing TTTS.

Diagnosis

Formerly, TTTS diagnosis was based on neonatal criteria: growth discordance of ≥20% associated with discordant fetal or neonatal hemoglobin concentration of ≥5 g/dl. A birth weight difference, however, is as frequently seen in monochorionic as in dichorionic twins[104]. Hemoglobin discordance of ≥5 g/dl is only present in 25% of TTTS cases[82] and hemoglobin of donor twins is not necessarily lower than in recipients[105,106]. Therefore, neither growth discordance nor hemoglobin difference can be considered mandatory features of TTTS[107].

Nowadays, TTTS is diagnosed prenatally by ultrasound examination and diagnosis is based on the combination of polyuric polyhydramnios in the recipient's sac and oliguric oligohydramnios in the donor's sac[108,109]. Quintero *et al.*[110] developed a staging system to determine the severity of this oligo/polyhydramnios sequence in the second trimester. Quintero Stage 1 is defined as an oligo/polyhydramnios sequence with the deepest vertical pocket (DVP) of amniotic fluid of the donor and recipient being ≤2 cm and ≥8 cm, respectively. The possible development into more progressive stages includes nonvisualization of bladder filling in the donor (Stage 2), critically abnormal Doppler studies including absent/reversed end-diastolic flow (AREDF) in the UA, reversed flow in the DV, or pulsatile umbilical venous flow (Stage 3), hydrops (Stage 4), and fetal demise of either twin (Stage 5) (Table 1).

Several studies have shown that disease severity at presentation is one of the determinants of fetal outcome[111-113]. Progression to a higher stage is associated with a poorer prognosis[114]. Therefore, early diagnosis of TTTS is very important. The best way to achieve this has not yet

Table 1 Staging of twin-to-twin transfusion syndrome by Quintero *et al.*[110]

Stage	Oligo/polyhydramnios*	Absent bladder filling in donor	Critically abnormal Doppler studies**	Hydrops	Intrauterine fetal demise
1	+	-	-	-	-
2	+	+	-	-	-
3	+	+	+	-	-
4	+	+	+	+	-
5	+	+	+	+	+

*Polyhydramnios: deepest vertical pocket (DVP) $\geq$ 8cm, oligohydramnios: DVP $\leq$ 2cm.

**Absent/reversed end-diastolic flow in the umbilical artery, reversed flow in the ductus venosus or pulsatile flow in the umbilical vein.

been established. In most institutions, a policy of at least biweekly ultrasound examination is used[75,107,115].

Prediction

Several studies have focused on the identification of sonographic markers early in pregnancy that could forecast the development of TTTS (Table 2).

Sebire *et al.*[116] found that pregnancies with increased nuchal translucency in the first trimester are at increased risk of developing TTTS (positive likelihood ratio of 3.5). Increased nuchal translucency is related to chromosomal defects, cardiac malformations, and a great variety of genetic syndromes. The pathophysiology of increased nuchal translucency thickness includes cardiac dysfunction, venous dysfunction in the head and neck, alteration in the extracellular matrix, lymphatic vessel hypoplasia, anemia, hypoproteinemia, and congenital infection[117,118]. In monochorionic twins, it is suggested that the recipients' hypervolemia causes heart failure with subsequent accumulation of fluid behind the neck in the first trimester, subsequently followed by the development of TTTS in the second trimester of pregnancy[116].

Matias *et al.*[119,120] proposed a role for the combination of increased nuchal translucency and abnormal DV flow patterns in anticipating TTTS. The association of increased nuchal translucency and abnormal flow in the DV in monochorionic twins is suggested to be an early manifestation of hemodynamic imbalance between the donor and the recipient twin.

Table 2 Early sonographic predictors of twin-to-twin transfusion syndrome in monochorionic twin pregnancies

	Sensitivity	**Specificity**	**Odds ratio**
Nuchal translucency thickness >95th percentile[116]	28%	90%	3.4
Abnormal ductus venosus A-wave[119,120]	100%	96-100%	-
Folding of the intertwin membrane[116]	91%	78%	38.3
Absence of arterioarterial anastomosis[81,121]	76-92%	71-74%	8.6-27.5

Another suggested TTTS predictor is folding of the intertwin membrane in the early second trimester[116]. This sonographic marker is thought to occur due to oligohydramnios in the sac of the donor, and is also associated with an increased risk of future TTTS (positive likelihood ratio of 4.2).

The absence of sonographically detectable AA anastomoses has been found to be more common in pregnancies with TTTS[81]. Detection of an AA anastomosis was associated with reduction in risk of developing TTTS (negative likelihood ratio of 9)[121]. Moreover, in those few pregnancies that developed TTTS in the presence of an AA anastomosis, chances of double fetal survival were substantially increased[122]. AA anastomoses are to be recognized from a bidirectional spectral Doppler pattern, first described by Erskine *et al.*[123] and later by others[124,125]. The sensitivity of visualizing an AA anastomosis sonographically is 75 to 85% with a specificity of 97 to 100%[81,121]. The detection rate is higher with anterior placentas and large diameter AA anastomoses. Visualizing an AA anastomosis is possible from as early as 11 weeks onwards, however at 20 weeks only 64% of AA anastomoses are generally diagnosed[81]. Therefore, the major limitation of prenatal detection of an AA anastomosis in early pregnancy is the uncertainty whether it is really absent or that it is simply not yet detected.

Unfortunately, the use of these TTTS predictors is insufficient in predicting reliably which pregnancies will develop TTTS eventually and which pregnancies will not. Therefore, frequent ultrasound examinations during gestation remain always recommended in monochorionic twin pregnancies. However, detection of one or more of these markers should alert obstetricians and should be a reason for intensifying sonographic surveillance.

Ultrasound examination

TTTS should be distinguished from monochorionic twins with severe growth discordance. The growth-restricted twin may mimic the donor presenting with oligohydramnios, a small bladder and abnormal flow in the UA. The lack of polyhydramnios in the other sac, however, rules out the diagnosis of TTTS[126].

The finding of polyhydramnios without visualization of an intertwin membrane may lead to the false diagnosis of a monoamniotic twin pregnancy. Although TTTS can occur in monoamniotic pregnacies[32-35], it is more likely that, in cases of polyhydramnios with supposed absence of the interwin membrane, the donor twin has anhydramnios with its amniotic membrane tightly wrapped around its body. This is called the “stuck” twin phenomenon (Figure 3). In most cases, the donor is fixed to the uterine wall. A variant of this classic stuck twin occurs when the donor twin with severe oligohydramnios is enveloped by dividing membranes and connected to the uterine wall by a laminar stalk of these membranes, the so-called “cocoon-sign”[127] or intrauterine sling[128]. It may appear “unstuck” and free floating in the recipient’s sac with polyhydramnios, and can therefore be misdiagnosed as being surrounded by a normal

Figure 3 "Stuck" twin at 18+1 weeks of gestation

amount of amniotic fluid. Other fetal causes of stuck twins, not associated with TTTS, have been cytomegalovirus infection[129], glomerulocystic disease[130], Russell-Silver syndrome[131], and agenesis of the DV[132].

Doppler studies

Since 1985, several papers on Doppler studies in TTTS have been published. Most of these were only case reports or small series and TTTS diagnosis was often based on neonatal criteria. In some papers, there was no comment on the presence or absence of TTTS at all. Results were conflicting, probably as a consequence of differences in criteria for TTTS and differences between gestational age of the study groups. In 1995, Hecher *et al.*[133,134] were the first to publish a detailed study on arterial and venous Doppler in TTTS diagnosed by the presence of polyhydramnios and a stuck twin in mid-gestation. One of the important findings was the AREDF in the UA of donors. It was concluded that alterations in the donor's circulation were consistent with decreased venous return due to hypovolemia and increased cardiac afterload due to increased placental resistance rather than with anemia and hypoxemia. Reversed flow in the DV during atrial contraction and pulsatile umbilical venous flow were found more often in recipients compared to donors. Tricuspid regurgitation (TR) was only diagnosed in recipients. They stated that the recipient's circulation showed the characteristics of congestive heart failure due to hypervolemia. Since then, several other important studies on fetal Doppler measurements in TTTS before and after laser treatment have been published.

Doppler in TTTS

In donors complicated by TTTS, EDF in the UA has been reported to be absent or reversed in 14 to 47%[135-137]. Pathologic Doppler findings in the UA of donors do not necessarily only reflect high placental resistance and unequal placental sharing but might also be attributed to fetal hypotension due to hypovolemia, which may be corrected by laser therapy. Pulsatile umbilical venous flow has been shown to be present in 4% of donors[137]. Absent or reversed flow during

atrial contraction in the DV has been reported to be present in 2 to 16% of donor twins[135-137]. Less than 2% of donors have been diagnosed with TR before laser treatment[136,137].

In recipients complicated by TTTS, EDF in the UA has been reported to be absent or reversed in 1 to 6%[135-137]. AREDF in the UA of recipients may be due to placental compression caused by massive polyhydramnios. Pulsatile umbilical venous flow has been shown to be present in 28% of recipients[137]. Absent or reversed flow during atrial contraction in the DV has been reported to be present in 28 to 37% of recipient twins[135-137]. Thirty-four to 36% of recipients have been diagnosed with TR before laser treatment[136,137].

Intertwin differences in umbilical vein (UV) flow have also been reported. UV flow has been found to be remarkably lower in donors compared to recipients before laser therapy[136,138]. The UV flow ratio before laser treatment between recipient and donor was found to be 3.3[63].

AREDF in the UA of the donor and reversed flow in the DV of the recipient have been identified as risk factors for the demise of these twins after laser treatment[122,137,139].

Doppler after fetoscopic laser coagulation

Laser coagulation of placental anastomoses is targeted at interrupting fetal intertwin transfusion. The supposed hypo- and hypervolemic state of donor and recipient, respectively, should be restored to a euvolemic state. Several studies have been performed to investigate fetal adaptation to the new hemodynamic situation after fetoscopic laser therapy.

In donors, positive EDF in the UA has been shown to reappear in 30 to 53% within a few days after fetoscopic laser treatment[135-137]. The UA pulsatility index (PI) has been reported to decrease significantly after laser therapy[135,136]. These findings are compatible with a change in the hemodynamic situation and an increase in the blood volume and blood pressure of the donor after laser therapy.

UV flow in donors has been shown to increase significantly after treatment and the difference with recipients has been noted to become non-significant[136,138]. This indicates an increased venous return in donor fetuses after treatment, suggestive of a cessation of the unbalanced blood flow exchange between monochorionic twins after fetoscopic laser therapy. This supposed increase in preload may put donor fetuses at risk for transient heart failure. Pulsatile UV flow has been reported to be found in 5% of donors[137]. It has also been shown that 6 to 41% of donor twins show absence or reversal of blood flow during atrial contraction in the DV after laser therapy. DV pulsatility index for veins (PIV) has been shown to increase significantly[135-137]. TR has been found in 6 to 38% of donors[136,137]. Moreover, Gratacos *et al.*[140] reported that 25% of donor fetuses showed hydropic signs within a few days after laser treatment. In all except one fetus, hydrops was mild or moderate and transient, and none of these donors died *in utero*. This phenomenon had no demonstrable impact on neonatal survival or increased risk of neurological damage, and was supposed to reflect the transient hypervolemic state of the donor after laser therapy[140]. Zikulnig *et al.*[135] also reported skin edema in donor fetuses after laser therapy.

In recipients, reappearance of forward flow during atrial contraction has been recorded in 24 to 80% and significantly decreased DV PIV has been found after fetoscopic laser treatment, indicative of fetal cardiac function improvement[135-137]. Pulsatile UV flow and TR have been shown to be still present in 22% and 34% of recipients, respectively[137].

Echocardiography

Discordant hemodynamics may result in cardiac dysfunction. Prenatal cardiac failure has been reported to occur in 55 to 100% of recipient twins[141-146] and can be transient, progressive or persistent beyond the neonatal period. The cardiac involvement of recipient twins may be of varying severity. However, a predominance of hemodynamic alterations affecting the right side of the fetal heart with eventually right ventricular outflow tract obstruction (RVOTO) has been described[52,141-149]. Cardiac changes further include cardiomegaly, ventricular hypertrophy, and tricuspid and mitral valve regurgitation[141-152]. Donors show no or little cardiac pathology in the absence of structural heart abnormalities[52,142,143,150,153]. In the only study on congenital heart disease after laser therapy so far, 55% of recipients showed signs of congestive heart failure before laser therapy. Congenital heart disease was recorded in almost 14% of surviving recipients. No correlation was found between findings before laser therapy and the development of structural heart disease after birth, as the incidence of postnatal congenital heart disease in fetuses with and without abnormal cardiac findings before laser coagulation were comparable ($p=0.66$)[146].

Whereas the exact cause of cardiac dysfunction observed in TTTS is uncertain, at least three etiologic factors may play a role. Firstly, primary cardiac pathology (e.g. congenital cardiomyopathy) has been suggested as a cause. This has been described to occur due to hypercontractility during fetal life[154] and in fetuses of insulin dependent diabetic mothers[155]. In TTTS, however, a hemodynamic component is more likely to play a role than a primary heart defect. Secondly, increased preload has been linked to the increased incidence of cardiac failure. The placental vascular anastomoses lead to blood volume overload and high cardiac output, which has been acknowledged to be compensated by right ventricular hypertrophy[52,86,156]. This hypothesis incorporates prenatal echocardiographic features of ventricular hypertrophy, tricuspid regurgitation and pulsatile venous flow. Furthermore, cardiac hormones like atrial and brain natriuretic peptides are released due to hypervolemia and levels of these hormones are increased in recipients[86]. Thirdly, the alternate hypothesis proposes that cardiac dysfunction is the result of raised afterload due to increased systemic resistance *in utero*[86]. High resistance to UA flow in the monochorionic placenta could lead to increased arterial pressure in the systemic circulation of the recipient twin, high pressure in the ductus arteriosus, and obstructed outflow to the right ventricle resulting in the development of congestive heart failure (as shown by TR) as well as chronically diminished flow through the pulmonary valve leading to RVOTO[157]. This theory is supported by the finding of neonatal hypertension in the recipient[88] and might

explain the predominance of abnormalities involving the right ventricle. High pressure in the circulation may also be mediated by vasoconstrictive substances such as endothelin-1[85] or renin-angiotensin[97].

Therapy and outcome

Conservative treatment in severe TTTS is associated with survival rates of less than 20%[57-62], although more recently an overall survival rate of 37% was reported[158]. As delivery is not an option before 25 weeks of gestation, the focus of most studies has been on different types of treatment in pregnancy during the period before viability is reached.

Since 1980, several methods to treat TTTS have been described. Maternal medical treatment with digoxin to treat cardiac failure in the recipient[159,160], administration of indomethacin to reduce polyhydramnios[161], and drawing blood from the hypervolemic recipient[162] have not been proven to be effective enough to be incorporated in current treatment options. Another type of treatment is septostomy. By intentionally perforating the intertwin membrane, the amniotic fluid in the donor's and recipient's sac should become evenly distributed[163]. Perinatal survival was shown to be comparable to serial amniodrainage and it is a less invasive method[164]. In a mathematic model for chronic TTTS, however, septostomy is not expected to have significant therapeutic efficacy[165]. A treatment option in TTTS cases in which one of the fetuses is already irreversibly damaged or likely to die, is selective feticide. Occlusion of the umbilical cord through ligation or bipolar coagulation allows the other twin to survive with, presumably, protection from neurological complications associated with co-twin death in the presence of patent anastomoses[166]. This option obviously is associated with a maximum of 50% of fetal survival.

The most commonly used treatment options for TTTS in the last decade have been amniodrainage and fetoscopic laser coagulation of the communicating placental vessels.

Amniodrainage

Since 1985, serial amnioreduction has been performed as a symptomatic treatment for polyhydramnios in the recipient's sac[167,168]. In order to relieve symptoms caused by the massive polyhydramnios and to allow prolongation of pregnancy by reducing the risk of preterm labor and premature rupture of membranes, excessive amniotic fluid is repeatedly removed by amniocentesis. Uteroplacental perfusion likely improves as the intrauterine pressure is reduced, which is shown by amelioration in uterine blood flow[169] and normalization of UA flow[170]. In a study performed by Hecher *et al.*[171], a single amniodrainage was sufficient to cure TTTS in 20% of the cases, probably because a new equilibrium developed. Also, prolonged intervals between reductions due to less reaccumulation of amniotic fluid have been described[60,167]. Furthermore, the increased transfusion from the donor to the recipient that is enhanced by compression

of the placenta through polyhydramnios, will be decreased if intra-amniotic pressure drops after amnioreduction. For whatever reason, amnioreduction appears to prolong pregnancy and improve overall perinatal survival rate to 51 to 68%[158,171-173]. An important drawback is that the risk of neurological damage is 15 to 26%[89,158,172,173]. Rodeck *et al.*[174] recently suggested that radical amnioreduction performed after 24 weeks of gestation might cause a shift of blood from the fetus to the placenta, which could explain some of the severe neurological outcomes. Serial amnioreduction is widely available and easily performed by most obstetricians. Procedure-related complications (5 to 15% per amnioreduction[111,172]) include fetal death within 48 hours, miscarriage, rupture of membranes, premature labor, infection, and abruptio placentae[75,153,175].

Fetoscopic laser coagulation of the vascular anastomoses

In 1990, fetoscopic laser coagulation of the vascular anastomoses on the placental surface as a causal treatment for TTTS was introduced by De Lia[176] and is always combined with a single amniodrainage at the end of the procedure. Initially, all placental vessels, both anastomotic and non-anastomotic, crossing the intertwin septum were ablated[177,178]. This non-selective approach resulted in high procedure-related fetal loss, particularly of the donor, as a result of devitalization of normal cotyledons[178]. Since 1996, a technique of selective coagulation of all anastomoses visualized along the vascular equator has been used[171,179-182]. The aim is to separate the monochorionic placenta into two distinct fetoplacental circulations, sparing the normal cotyledons. Perinatal survival increases to 57 to 70%[113,181-184]. The risk of long-term neurological damage in survivors is 6 to 17%[185-188]. Complications of fetoscopic laser therapy in the first week after the operation include miscarriage (12%), premature rupture of membranes (7%), placental abruption (1.7%), single IUFD (13 to 33%) and double IUFD (3 to 22%)[189,190]. Late complications are preterm premature rupture of membranes before 32 weeks (17%), recurrence of TTTS (14%), isolated marked discordant hemoglobin levels (13%), and double IUFD (1%)[190]. Maternal complications have been described only rarely. It is suggested that, due to the relatively low caseload, laser operations should be performed by fetal specialists trained in endoscopy and placental vascular anatomy only, otherwise the procedure may do more harm than good[191].

The only randomized controlled trial to date reported significantly higher perinatal survival rates and improved neurological outcome in TTTS survivors after fetoscopic laser surgery compared to serial amnioreduction[113]. The overall survival in the laser group compared to the amnioreduction group was 57% versus 41%. At the age of six months, major neurological sequelae were found in 19% of the amnioreduction group versus 7% in the laser group. Since this study, fetoscopic laser therapy is considered the treatment of first choice for TTTS by many obstetricians. Some consider a stage-based treatment of chronic TTTS, with amnioreduction in pregnancies with amniotic fluid imbalance only and fetoscopic laser surgery in pregnancies

with fetuses with cardiovascular dysfunction, a more appropriate approach[112]. The study by Senat *et al.*[113] showed, however, that laser therapy was beneficial for fetuses in all Quintero stages and concluded that the choice of treatment should not be influenced by staging. This was confirmed by recent studies of Huber *et al.*[192] and Middeldorp *et al.*[184] that also showed laser therapy to be a more effective therapeutic option in the early stages of severe TTTS.

The most recent studies report two survivors in 36 to 58% of treated pregnancies[113,181-184], of whom 6 to 17% are neurologically impaired[185-188]. It is suggested that results of laser treatment may not be improving due to limitations such as donor placental insufficiency, pre-existing stretch effects on membranous integrity and cervical competence. Also, technical limitations of laser treatment may be a factor. Persistence, recurrence or even reversal of TTTS may occur due to incomplete ablation or recanalization of anastomoses[190,193-196]. It was shown that more than half of monochorionic placentas contain additional deep anastomoses that are not visible by endoscopy[197,198]. Although it was recently published that deep-hidden anastomoses are unlikely to occur with clinical consequences[198], they have been suggested to be involved in lesser degrees of intertwin transfusion[193].

Neonatal outcome after laser therapy

Prematurity is a well recognized risk factor for adverse neonatal outcome in twins as well as in singletons[199,200]. The median age of babies born after laser therapy is 31 to 34 weeks[113,181-184], which consequently has a major impact on their neonatal morbidity rates.

Cardiovascular complications

Congenital heart disease occurs more frequently in monochorionic twins complicated by TTTS (5.4 to 13.7%), especially in recipients[52,146,201], than in the general population (0.56%)[202]. In a recent study that reported on the incidence of congenital heart disease in monochorionic twins after laser therapy (median age at follow up 21.5 months), it was concluded that 87% of survivors had a normal cardiac ultrasound examination[146]. Congenital heart disease occurred in 11.2% of surviving twins and in 13.7% of recipients. Donors showed atrial septal defects in 7.9% of cases. RVOTO developed only in recipients (7.8%). RVOTO may be serious enough to warrant valvotomy in infancy[52,141]. In our clinic, the incidence of congenital heart disease in TTTS survivors treated with laser therapy was 5.4%. In recipients, it was 7.9%. RVOTO only occurred in recipients and the incidence was 4%[201].

The hostile *in utero* environment in TTTS may also result in fetal vascular remodeling causing increased vascular stiffness and raised cardiac afterload in the surviving donor, which has been

associated with adult onset of cardiovascular disease such as hypertension and ischemic heart disease[203,204].

Neurological complications

Neurological complications are due partly to antenatally acquired lesions and partly to prematurity. Both donor and recipient twins are at risk. In the literature, only a few studies have been published on long-term neurodevelopmental outcome after laser coagulation of placental anastomoses for TTTS. The incidence of major neurological complications in these studies was 6 to 11%[185-187]. In our clinic, the incidence of neurodevelopmental impairment in TTTS survivors after laser treatment was 17%, including cerebral palsy (7%), mental developmental delay (8%), psychomotor developmental delay (10%), and deafness (1%)[188].

Other complications

Up to 30% of donors have been reported to be complicated by renal failure and/or renal tubular dysgenesis due to chronic volume depletion and renal hypoperfusion in utero[150,150,153,205]. Complete recovery of adequate renal function is usually reported[173]. Despite severe alteration of renal function before fetoscopic laser treatment (anuria/polyuria) no long-term impairment of renal function could be detected after laser therapy (median age at evaluation 3 years and 1 month)[206]. In our clinic, one donor twin presented after birth with transient renal failure. Chronic renal failure was diagnosed in none of the survivors.

Ischemic limb injury has been anecdotically described in recipient twins and may be due to polycythemia-hyperviscosity syndrome[207]. In our clinic, we had one survivor (recipient) whose right hand and forearm were suspected prenatally to be necrotic, which was confirmed after birth.

Conclusion

Most twin pregnancies have an uneventful course, although twins are at greater risk than singletons. Therefore, prenatal care should particularly focus on complications that are known to happen more often in twin pregnancies. A useful tool for monitoring is ultrasound examination. As monochorionicity is the prerequisite for TTTS and other complications, early demonstration of chorionicity is vital. If monochorionic twinning has been diagnosed, close sonographic surveillance is highly relevant.

For several reasons, TTTS currently presents a great therapeutic challenge in fetal medicine. TTTS affects two babies, both of whom are structurally normal. If left untreated, they are at great risk to die *in utero* or survive with handicaps. The basis of TTTS is in the placenta and can

be effectively treated with fetoscopic laser coagulation of the vascular anastomoses. However, with currently used therapeutic methods, perinatal mortality and morbidity rates remain high. The outcome is better if TTTS is treated in the early stages and before fetal damage has occurred. Therefore, increasing attention should be paid to early diagnosis of TTTS.

The aims of this thesis were to evaluate the use of ultrasound and Doppler in prenatal management of monochorionic twin pregnancies and to study the effects of TTTS and fetoscopic laser therapy on fetal hemodynamics.

Outline of the thesis

Leiden University Medical Center (LUMC) is a tertiary medical center in the Netherlands and serves as the national referral center for fetal therapy. Since August 2000, monochorionic twin pregnancies complicated by TTTS have been treated with fetoscopic laser coagulation of placental anastomoses. Since then, several studies on monochorionic twins with and without TTTS were started. **TULIPS**, **T**wins and **UL**trasound **I**n **P**regnancy **S**tudies, was one of these projects. The aims of this study were: 1) to evaluate serial ultrasound examinations combined with patient instructions in achieving timely detection of TTTS in a cohort of monochorionic diamniotic twin pregnancies, and 2) to study the effects of TTTS and fetoscopic laser therapy on fetal hemodynamics of monochorionic twins.

The studies of this thesis, described in detail in the following chapters, are summarized below.

In **chapter 2** we report on the occurrence of bipartite monochorionic twin placentas.

In **chapter 3** we present a case of TTTS at 11 weeks of gestation.

In **chapter 4** we describe the value of serial ultrasound examinations together with patient instructions to report the onset of symptoms in achieving timely detection of TTTS in a cohort of monochorionic diamniotic twin pregnancies, and we evaluate sonographic TTTS predictors.

Chapter 5 investigates fetal hemodynamics in monochorionic twins with TTTS before and after fetoscopic laser therapy, focusing on the renal and cerebral blood flow.

In **chapter 6** we study the influence of fetoscopic laser therapy on fetal cardiac size in monochorionic twins complicated by TTTS.

Chapter 7 compares the cardiac output between monochorionic twins complicated by TTTS and treated with laser coagulation of the placental vessels (donors and recipients), a control group of monochorionic twins without TTTS, and a control group of singletons.

Chapter 8 contains the general discussion concerning all studies of the thesis.

Recommendations for clinical practice are provided in **chapter 9**.

Chapter 10 summarizes the results of the presented studies.

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