Twin-to-twin transfusion syndrome : from placental anastomoses to long term outcome

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Chapter 2

Twin-to-twin transfusion syndrome: from placental anastomoses to long-term neurodevelopmental outcome

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Introduction

Twin-to-twin transfusion syndrome (TTTS) is a complication of monochorionic twin gestations and is one of the most lethal conditions in perinatal medicine. TTTS is thought to result from an unbalanced net transfusion of blood between one twin, the donor, and the other twin, the recipient, via placental vascular anastomoses. In the 19th century, Friedrich Schatz, a German obstetrician, extensively studied the twinning process and was the first to speculate on the relationship between vascular anastomoses and the development of TTTS[7]. The number, size and type of these anastomoses appear to play an important role in the etiology of TTTS[8]. Despite a growing understanding of TTTS, the exact pathophysiology remains to be elucidated. Various new hypotheses question the validity of the classic concept of TTTS resulting mainly from inter-twin transfusion of blood. Recently, a staging system based on antenatal ultrasound findings has been introduced and appears to have prognostic significance[9]. Most importantly, this staging system may be used to compare various therapeutic modalities in TTTS. The two main current treatment options in TTTS are serial amnioreduction and fetoscopic laser occlusion of vascular anastomoses. Both treatments are associated with improved survival rates. The first randomized trial designed to compare the effectiveness of these two therapeutic options has recently been published and has shown that fetoscopic laser surgery is associated with less mortality and less short-term neurological morbidity than serial amnioreduction[10]. The results of other ongoing randomized trials are eagerly awaited. Despite the improvement in overall survival rates, mortality and morbidity rates remain strikingly high, especially in TTTS managed expectantly or with serial amnioreduction. A high risk of long-term neurodevelopmental disability has been reported, particularly after intrauterine fetal demise of a co-twin during the second or third trimester[11-16]. Severe cerebral damage in the surviving monochorionic twin may even occur during the first trimester[17]. In TTTS with double survival, recipient twins are at risk for life-threatening cardiovascular complications such as hypertrophic cardiomyopathy and right ventricular outflow tract obstruction[18;19], whereas donor twins are at risk for acute or chronic renal failure due to chronic renal hypoperfusion[20;21].

This review examines the various theories on the pathogenesis of TTTS, describes the diagnostic tools and criteria, discusses some of the randomized trials on the efficacy of various treatments and focuses on neonatal and pediatric morbidity associated with TTTS.

The twin-to-twin transfusion syndrome

Several forms of TTTS have been described: chronic, acute perimortem, acute perinatal and twin reversed arterial perfusion sequence[11]. The chronic form of TTTS is the most common form and complicates about 10 to 15% of monochorionic twin pregnancies[22-24]. Chronic TTTS usually becomes clinically apparent during the second or early third trimester of pregnancy. Recent reports suggest that chronic TTTS may occur even in the first trimester of pregnancy[25;26]. Clinical symptoms are due the rapid development of polyhydramnios, causing maternal discomfort, premature rupture of the membranes, or preterm labor. Chronic TTTS is then diagnosed if the oligo-poyhydramnios sequence is detected on ultrasound examination[27]. The donor twin has severe oligohydramnios due to hypovolemia and oliguria and appears tightly wrapped in his amniotic sac and "stuck" to the uterine wall despite changes in maternal position, hence referred to as the "stuck" twin. Conversely, the recipient twin has severe polyhydramnios due to hypervolemia and polyuria. In the most severe cases, the recipient may subsequently develop circulatory volume overload and fetal hydrops. Inter-twin growth discrepancy and hemoglobin discordance are often reported, but are not key criteria for the diagnosis of chronic TTTS[27-29]. Both fetuses are at risk for intrauterine fetal demise, either due to hypoxia and anemia in the donor, or cardiac failure in the recipient. Moreover, both fetuses may die as a result of preterm delivery. An acute form of TTTS, referred to as acute perimortem TTTS, occurs after intrauterine fetal demise of a co-twin and is due to acute exsanguination from the surviving twin into the low-pressure circulation of the demised co-twin through the vascular anastomoses[30-32]. Acute exsanguination often leads to co-twin death or may lead to severe hypoxic-ischemic damage in the surviving twin due to hypovolemia, hypotension and anemia, resulting in co-twin death, multicystic encephalomalacy and multi-organ damage[12-16;33].

Anecdotal reports suggest that acute TTTS may also occur during delivery[34-39]. This form of TTTS, often referred to as acute perinatal TTTS, may then lead to a difference in hemoglobin concentration at birth between the donor and the recipient twin without necessarily discordance in birth weight[40-44]. Acute shifts of blood from one twin to the other are thought to result from blood pressure differences due to uterine contractions or changes in fetal positions[36;44;45]. The donor twin has often signs of acute hemorrhagic hypovolemic shock and requires treatment with urgent blood transfusion or volume expanders[35-37]. Research data on acute perinatal TTTS is however extremely scarce. Hemoglobin differences between monochorionic twins at birth have also been shown to be related to birth order[35;38;46]. In a recent study in monochorionic twins without chronic TTTS, we reported that hemoglobin levels in second-born twins are significantly higher than in first-born twins[47]. Once the umbilical cord of the first-born twin is clamped, the second-born twin has the sole connection to the entire placenta and may not only receive blood from its own placenta but also from the placenta-share of the co-twin, through the vascular anastomoses[38;41].

The most extreme form of TTTS is acardiac twinning, which occurs in 1 out of 35 000 pregnancies[48]. Acardiac twinning, also named twin reversed arterial perfusion sequence, occurs when a large arterio-arterial and veno-venous shunt is present, causing reversed flow in the single umbilical artery of the acardiac fetus. The acardiac fetus is severely malformed without a functional heart. The donor twin is otherwise structurally normal and is referred to as the pump twin as it pumps blood both into its own circulation as well as directly into the circulation of the acardiac co-twin. The pump twin is therefore also at risk for intrauterine fetal demise due to high output cardiac failure.

Incidence

Twin gestations represent 1 to 2% of all pregnancies. Two thirds of twin gestations are dizygotic (therefore always dichorionic) and are not at risk for developing TTTS. One third of twin gestations are monozygotic and may give rise to either monochorionic or dichorionic placentation.

Chorionicity in monozygotic twinning depends upon the time interval between fertilization and cleavage of the embryo[49]. Cleavage within three days of fertilization results in a dichorionic placentation, whereas cleavage occurring within four to eight days of fertilization will lead to a monochorionic placenta[49]. Two third of monozygotic pregnancies are monochorionic. Only monochorionic twins are at risk for developing TTTS. Approximately 10 to 15% of all monochorionic twin pregnancies will eventually develop chronic TTTS[22-24]. The incidence of acute perinatal TTTS is not known.

Increased infertility treatments have led to a higher rate of multifetal gestations. Twinning rate in the United States was 31 per 1000 total live births in 2002, an increased twinning rate of 65% since 1980 and 38% since 1990[50]. To date, approximately one million children world-wide were conceived through assisted reproductive technology, with associated rates of multifetal gestations up to 50%[51;52]. Most twins born after assisted reproduction techniques are dizygotic. However, various studies have also shown a significant increase in monozygotic twinning after various forms of infertility treatment such as in vitro fertilization related techniques (in particular blastocyst transfer), ovulation induction and intracytoplasmic sperm injection, mostly due to alterations on the zona pellucida[53-56]. Monozygotic twinning is increased 2 to 6 times in babies born after in vitro fertilization[57-59]. Consequently, increased rates of multifetal gestations due to infertility treatments may theoretically also lead to increased rates of TTTS.

Pathogenesis

The presence of placental vascular anastomoses is a *conditio sine qua non* for the development of TTTS. Injection studies of twin placentas have shown that such anastomoses are almost invariably present in monochorionic twins and extremely rare in dichorionic twins[5]. Three types of anastomoses have been documented: from artery to artery, from vein to vein and from artery to vein. Arterio-venous anastomoses are unidirectional and are referred to as “deep” anastomoses since they proceed through a shared placental cotyledon, whereas arterio-arterial and veno-venous anastomoses

are bi-directional and are referred to as "superficial" since they lie on the chorionic plate (Figure 1). Injection studies of monochorionic placentas have demonstrated that arterio-arterial, arterio-venous and veno-venous anastomoses are present in 80%, 95% and 20% of monochorionic placentas, respectively [60-62].

The presence of at least one arterio-venous anastomosis has been shown to be essential for the development of chronic TTTS[26;61-63]. According to the classic pathophysiological concept, chronic TTTS is caused by net imbalance of blood flow between the twins due to arterio-venous anastomoses[7;8]. Blood from one twin (the donor) is pumped through an artery into the shared placental cotyledon and then drained through a vein into the circulation of the other twin (the recipient). Unless blood is pumped back from the recipient to the donor through oppositely directed

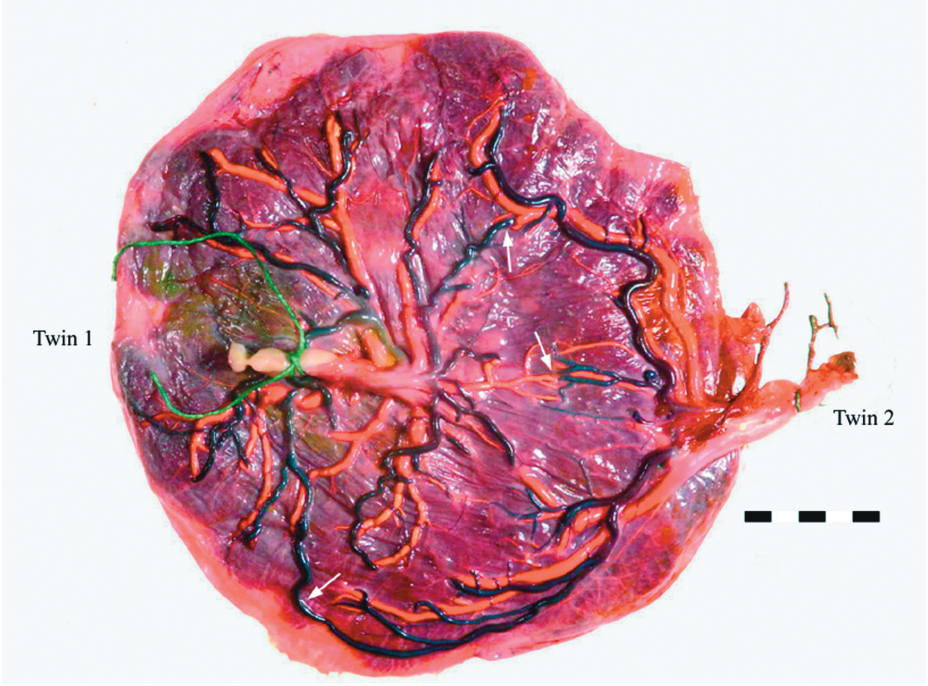

FIGURE 1 Placenta injection study with colored dye from a monochorionic twin gestation without chronic twin-to-twin transfusion syndrome delivered after 38 weeks of gestation. Arteries are injected with dark-blue dye and veins with orange dye. The arrow at the bottom of the picture indicates an arterio-arterial anastomosis. An arterio-venous anastomosis from twin 2 to twin 1 is pointed out in the center of the picture, whereas an arterio-venous anastomosis from twin 1 to twin 2 is indicated at the top of the picture. Twin 2 has a velamentous cord insertion.

deep arterio-venous anastomoses or through superficial anastosmoses, an imbalance of blood volumes occurs, gradually leading to the development of chronic TTTS. The presence of arterio-arterial anastomoses in particular is thought to give some protection against the development of chronic TTTS by compensating for the circulatory imbalance caused by the uni-directional arterio-venous anastomoses[7;8]. Various studies have demonstrated that these bi-directional arterio-arterial anastomoses occur more frequently in monochorionic placentas of twins without chronic TTTS compared to placentas of twins with chronic TTTS around 80% and 25%, respectively [26;64-67]. The antenatal detection of an arterio-arterial anastomosis with color Doppler ultrasound examination is associated with a 9-fold reduction in likelihood ratio of developing chronic TTTS[68]. This protective role of arterio-arterial anastomoses which was already proposed by Schatz in the 19th century[7], has recently also been demonstrated in a mathematical computer model of chronic TTTS[69]. Conversely, the pathogenesis of acute perimortem and acute perinatal TTTS is mainly mediated through large superficial low-resistance arterio-arterial or veno-venous anastomoses[13;29-32;44;70;71].

The validity of the traditional theory of unbalanced blood shunting from the donor to the recipient as the major factor causing the development of chronic TTTS has frequently been questioned. Several studies report the absence of differences in hemoglobin, erythropoietin and iron metabolism between donors and recipients[72-74]. However, these data are not in direct conflict with the classic pathophysiologic concept of inter-twin transfusion in TTTS and may simply reflect the inter-twin transfusion of blood components and various hormones through the vascular anastomoses. Several new hypotheses have been added to the classic pathophysiologic concept of TTTS and may also play a role in the pathogenesis of chronic TTTS (Table 1).

Significant higher concentrations of fetal atrial natriuretic peptide as well as brain natriuretic peptide have been found in recipient twins compared to donor twins[75-78]. The release of these peptides is stimulated by cardiac overload and causes increased fetal urine production, leading consequently to polyhydramnios and to the further development of chronic TTTS. The fetal renin-angiotensin system is reported to be up-regulated in donor twins due to hypovolemia and decreased renal perfusion[79-81]. Although

TABLE 1 Summary of theories on pathogenesis of chronic TTTS.

Author (year)	Pathogenesis
Schatz (1882)[7]	Donor "pumps" blood into recipient through placental vascular anastomoses
Schatz (1882)[7]	Absent compensatory arterio-arterial anastomoses
Nageotte (1989)[75]	Increased atriopeptin in recipient
Wieacker (1992)[77]	Increased atriopeptin and decreased antidiuretic hormone in recipient
Wax (1992)[92]	Compression of placental vessels of donor
Fries (1992)[89]	Compression of velamentous inserted cord of donor
Bajoria (1999)[84]	Increased endothelin concentrations in recipient
Mahieu-Caputo (2000)[80]	Up-regulation of renin-angiotensin system in donor
Bajoria (2000)[88]	Reduced amino-acids levels in donor
Sooranna (2001)[87]	Reduced leptin levels in donor
Bajoria (2001)[86]	Reduced insulin-like growth factor II levels in donor
Bajoria (2004)[82]	Increased vasopressin concentrations in donor

up-regulation of renin synthesis may be necessary to restore euvolemia in the donor, the activation of the renin-angiotensin system also leads to vasoconstriction and may further aggravate renal hypoperfusion and oligohydramnios in the donor twin. Similarly, raised concentrations of vasopressin were recently found in donor twins, suggesting that oligohydramnios may also result from the antidiuretic and vasoconstricitve activity of vasopressin[82]. Furthermore, vasoconstriction may contribute to placental dysfunction and aggravate intrauterine growth restriction in the donor. Activation of the renin-angiotensin system may also have a paradoxical effect in the recipient twin. Transfer of renin and angiotensin II through the vascular anastomoses from the donor into the hypervolemic recipient may increase the blood pressure and aggravate cardiac dysfunction in the recipient. Increased blood pressure has indeed often been reported in recipient twins after birth[12;83] and may also be due to other vasoconstrictive substances circulating in the recipient twin. Various studies have demonstrated a significantly higher concentration of endothelin-1 in recipient twins compared to donor twins[78;84;85]. Endothelin-1, a potent vasoconstrictor, may cause hypertension and therefore also aggravate cardiac dysfunction in the recipient.

Several other hormones, such as insulin-like growth factor-II and leptin may also contribute to the development of chronic TTTS. Levels of insulin-like growth factor-II and leptin, both playing a role in intrauterine growth restriction, were recently reported to be significantly lower in donor twins, suggesting that growth restriction in the donor twin might result from abnormal placental development[86;87]. Similarly, lower essential and non-essential amino acids have been reported in growth restricted donor twins suggesting that fetal undernutrition may be partly due to impaired placental transport of amino acids[88].

Velamentous cord insertion is reported to be more common in pregnancies affected by chronic TTTS compared to monochorionic gestations without chronic TTTS, and occur principally in donor twins[89-91]. It is suggested that a velamentous inserted cord may be more easily compressed resulting in reduced blood flow through the umbilical vein to one twin[89]. A vicious circle may then be established as less blood flows to one twin (the donor), more blood will flow to the other twin (the recipient) through the placental anastomoses. The consequent development of polyhydramnios in the recipient twin may then compress the umbilical vein of the donor twin even further, ultimately leading to the development of chronic TTTS. A comparable mechanism is advocated by other authors who speculated that polyhydramnios may partially compress the venous placental vessels of the donor twin, leading, through a similar vicious circle, to the development of chronic TTTS[92]. However, these theories do not explain why chronic TTTS also occurs in twins without velamentous inserted cords. Moreover, similar rates of velamentous insertion between monochorionic pregnancies with chronic TTTS compared to monochorionic pregnancies without chronic TTTS have recently been reported[93]. We are currently performing a prospective study on the rate of velamentous cord insertion and type of placental vascular anastomoses in monochorionic twins with chronic TTTS compared to monochorionic twins without chronic TTTS.

In summary, the development of TTTS is associated with a multitude of complex hormonal and hemodynamic mechanisms. More research is needed in order to determine which of these mechanisms is the most important. However, monochorionic twinning does not occur in the animal world except in humans and in armadillos[94], and animal models for studying the pathogenesis of TTTS are not available. Lack of a suitable

experimental animal model may hamper further investigations on the pathogenesis of TTTS. Nevertheless, computer modeling studies may help to further elucidate the exact etiology of TTTS and test the various hypotheses[95-101].

Diagnosis

The diagnostic criteria of TTTS have dramatically changed since the advent of prenatal ultrasonography. In the past, the definition of chronic TTTS was based on two main neonatal criteria: a birth weight discordance > 20% and a hemoglobin difference > 5 g/dL between the two infants. These traditional criteria have been abandoned because similar differences in hemoglobin and birth weight exist also in dichorionic twins and in monochorionic without chronic TTTS[44;71]. Moreover, studies with fetal blood sampling in chronic TTTS pregnancies have shown that the donor twin does not necessarily have a lower hemoglobin concentration than the recipient twin[72;102;103]. Absence of significant inter-twin hemoglobin differences may be due to compensatory increased hematopoiesis in the donor twin[103;104]. However, erythropoietin concentrations have recently been shown to be similar between donors and recipients, questioning the validity of the hypothesis on discordant hematopoiesis between twins with chronic TTTS[73].

The diagnosis of chronic TTTS is currently defined by prenatal ultrasound criteria[27;28;105;106]. Firstly, since TTTS occurs only in monochorionic twins, chorionicity must be determined through prenatal ultrasound scanning in the first (or early second) trimester of pregnancy. Ultrasound criteria for monochorionicity are the absence of a lambda-sign at the inter-twin membrane junction and the presence of a thin dividing membrane with a T-sign. Assessment of monochorionicity must imply a higher level of alertness from doctors and parents in order to detect the first clinical symptoms related to chronic TTTS, such as excessive uterine growth and premature contractions due to polyhydramnios. Prenatal diagnosis of chronic TTTS is then reached by demonstrating the characteristic oligo-polyhydramnios sequence on ultrasound. Oligohydramnios is present in the donor who is often also stuck to the uterine wall and tightly wrapped in his amniotic

sac, whereas polyhydramnios is found in the recipient. Oligohydramnios is defined as a deepest vertical amniotic fluid pool ≤ 2cm in the donor's sac, and polyhydramnios as a deepest vertical pool ≤ 8cm in the recipient's sac until 20 weeks of gestation and ≥ 10 cm after 20 weeks of gestation[105;106]. A staging system according to Quintero has recently been introduced and stratifies chronic TTTS in 5 stages based on ultrasound criteria (Table 2)[9]. This staging system allows comparison of different management strategies in chronic TTTS and is also useful in monitoring disease progression[9;12;107]. Several sonographic signs, such as increased nuchal translucency, folding of the inter-twin membrane, presence of a velamentous insertion of the umbilical cord and absence of arterio-arterial anastomoses are associated with a higher probability of the development of chronic TTTS[66;89;108]. However, accurate prediction of chronic TTTS is not yet possible and more research on the diagnostic value of early ultrasound findings is necessary. A study on early ultrasound predictors in monochorionic twins without chronic TTTS has been performed at our institution[109].

Diagnostic criteria for acute perinatal TTTS vary among studies, but usually include an hemoglobin difference > 5 g/dL at birth[34;35;38;39;44]. Most studies also rely on the absence of birth weight discordance to exclude chronic TTTS. However, birth weight discordance is not a reliable criterion to exclude chronic TTTS[27;28;44;71;93]. Moreover, rapid shifts of blood during labor can occur in any monochorionic twins with patent vascular anastomoses, with or without birth weight discordance[44]. Diagnostic

TABLE 2 *Staging classification of chronic TTTS according to Quintero[9].*

Stage	Sonographic criteria
stage I	Bladder of the donor twin still visible, Doppler studies are normal
stage II	Bladder of the donor twin not visible, Doppler studies are still normal
stage III	Doppler studies are critically abnormal*
stage IV	Ascites, pericardial effusion or pleural effusion, scalp edema, or overt hydrops are present
stage V	One or both twins are dead

** reversed flow in the ductus venosus or pulsatile umbilical venous flow in the recipient, and/or absent or reversed end-diastolic flow in the umbilical artery of the donor*

criteria of acute perinatal TTTS should therefore include an hemoglobin difference > 5 g/dL, with or without birth discordance[44]. Furthermore, diagnosis of chronic TTTS based on antenatal ultrasound examination and acute perimortem TTTS, should first be excluded.

Therapy

The intrauterine management of chronic TTTS remains a significant challenge in perinatal medicine. In severe TTTS, conservative treatment is associated with mortality rates from 73 to 100%[110-114]. Therefore, a wide variety of aggressive, sometimes even desperate treatment modalities have been attempted. Some reported treatments are not considered to be effective first-line treatments, including maternal treatment with digoxin to treat cardiac failure in the recipient[115], maternal treatment with indomethacin in order to reduce polyhydramnios[116] and fetal blood-letting from the hypervolemic recipient[117]. Other treatments are considered to be more effective, such as selective feticide by occlusion of the umbilical cord through ligation or bipolar diathermy to order to save one infant[118], inter-twin septostomy by creating a hole in the dividing membrane aiming at equilibrating the amniotic fluid between the donor's sac and the recipient's sac[119], serial amnioreduction[120] and fetoscopic laser occlusion of vascular anastomoses[121;122]. The latest two treatment options, serial amnioreduction and fetoscopic laser coagulation of vascular anastomoses, are the two main current treatment options in chronic TTTS. Although chorioamnionitis, rupture of the membranes, preterm labor and placental abruption are potential risks associated with these procedures, both treatments are widely reported to be associated with improved outcome. The aim of serial amnioreduction is to prevent uterine stretch and preterm labor by reducing the intrauterine pressure. Usually, repeated drainage procedures of the recipient's sac are needed as amniotic fluid re-accumulates leading to a relapse of polyhydramnios. The major advantage of treatment with amnioreduction is that it is widely available. Overall perinatal survival rates in case series treated with serial amnioreduction are reported to range from 47 to 80%[12;123-130]. However, serial amnioreduction does not treat the underlying pathology and is therefore mainly a symptomatic treatment.

Fetoscopic laser coagulation of vascular anastomoses was first described by De Lia *et al* in 1990[121]. The aim of fetoscopic laser surgery is to occlude the anastomosing vessels along the vascular equator of the chorionic plate in order to interrupt the inter-twin transfusion of blood, as shown in Figure 2. After fetoscopic laser coagulation of the anastomoses, the amniotic sac of the recipient is drained a single time to reduce the polyhydramnios. Fetoscopic laser surgery is therefore a combination of a symptomatic and a causal treatment. Overall perinatal survival rates in case series treated with fetoscopic laser coagulation of vascular anastomoses vary from 48 to 71%[9;121-124;131-137]. The true efficacy of the various treatments can only be assessed with prospective, randomized controlled trials designed not only to establish the survival rate but also the long-term neurodevelopmental sequelae. Assessment of the stage of chronic TTTS before treatment is crucial to be able to compare various

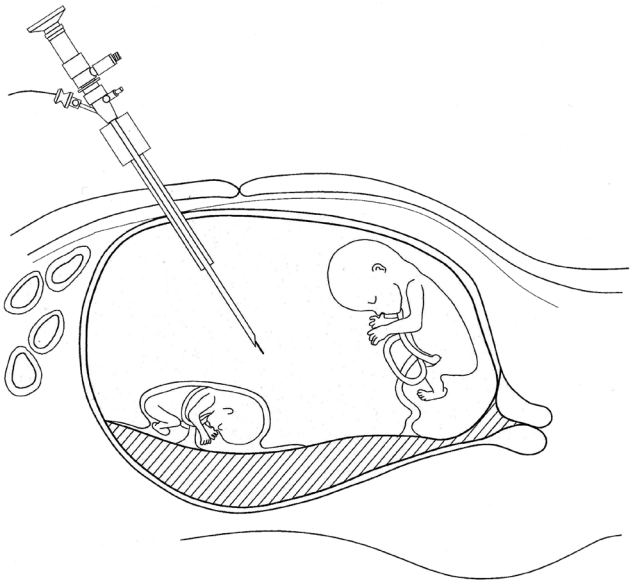

FIGURE 2 Schematic image of fetoscopic laser occlusion of vascular anastomoses in chronic twin-to-twin transfusion syndrome. The image shows a saggital view of the uterus with a posterior placenta. A fetoscope (2mm diameter) is placed under ultrasound guidance through the maternal abdominal wall into the recipient's sac with polyhydramnios. After studying the anatomy/angioarchitecture of the placenta vessels, a 0.7-mm neodymium:yttrium-aluminium-garnet (Nd:YAG) laser fiber is inserted in the fetoscope to ablate the anastomoses (from Deprest J, with permission).

treatments. Recently, Senat *et al* showed in a large multicenter randomized trial comparing fetoscopic laser surgery with serial amnioreduction that laser treatment leads to better survival rates and fewer neurological abnormalities in the neonate than serial amnioreduction[10]. The overall survival rate in the laser group was significantly higher compared to the amnioreduction group, 57% versus 41%, respectively (p = 0.01). Cystic periventricular leucomalacia grade III or IV was detected in 6% of the children in the laser group compared to 14% in the children in the amnioreduction group at 6 months of age (p = 0.02), but long-term neurodevelopmental outcome of the surviving children has not yet been reported. Two other ongoing multicenter randomized trials, one in the United Kingdom[138] and one in the United States (http://fetalsurgery.chop.edu), are also comparing serial amnioreduction with fetoscopic laser surgery. Whether fetoscopic laser coagulation of vascular anastomoses will emerge as the treatment of choice for chronic TTTS depends also on the results of these other trials. Some authors also suggest a stage-based treatment of chronic TTTS, in which milder TTTS cases are managed with amnioreduction and severe TTTS cases with laser surgery. Whether a tailored approach to management of chronic TTTS will improve outcome is currently under investigation[139].

Lastly, an international multicenter randomized controlled trial for the evaluation of septostomy versus serial amnioreduction has been performed[140]. No difference in overall survival was found between both treatments. The benefit as well as the rationale of septostomy has frequently been questioned[27;141]. Septostomy may result in complete disruption of the dividing membrane and the creation of iatrogenic monoamniotic twins[27;142]. Monoamniotic twins are known to be at risk for cord entanglement and are associated with severe perinatal morbidity and mortality. Moreover, results of a study with a mathematical model for chronic TTTS suggest that septostomy is unlikely to offer significant therapeutic efficacy[98].

A flow-chart showing the current management protocol for TTTS at our institution is presented in Figure 3.

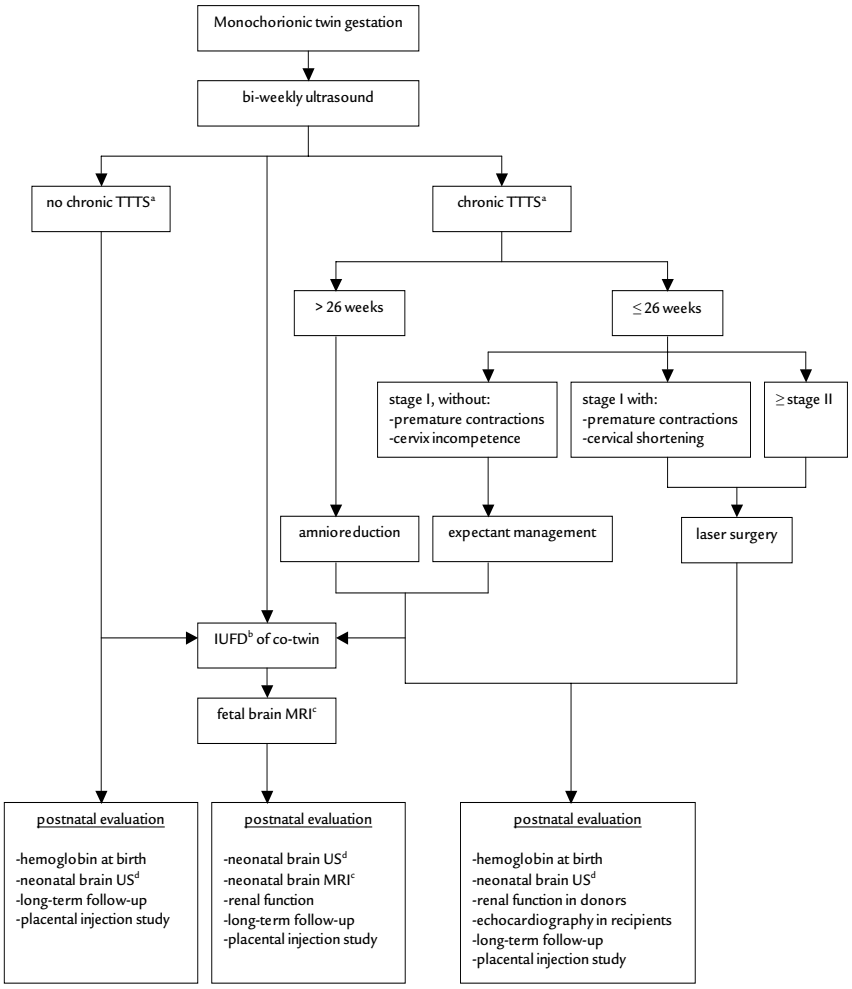

FIGURE 3 Flow-chart of antenatal and postnatal management in monochorionic twin gestations at our institution ([a]TTTS: Twin-to-twin transfusion syndrome, [b]IUFD: Intrauterine fetal demise, [c]MRI: Magnetic Resonance Imaging, [d]US: UltraSound)

Neonatal mortality and morbidity

Multifetal pregnancies have a 2 to 5 times higher risk of perinatal mortality compared to singleton pregnancies[143]. Higher mortality rates are mostly due to the higher proportion of infants with preterm delivery and low birth weights. Since preterm deliveries occur more often in multifetal gestations,

twins are also at risk for morbidity associated with prematurity such as chronic lung disease, periventricular leucomalacia, and intraventricular hemorrhage. Worse perinatal outcome is also specifically related to monochorionicity. Monochorionic twins have a significantly higher risk of adverse outcome than dichorionic twins (RR 2.5; 95% CI, 1.1-2.5)[3]. Additional morbidity found in surviving twins with TTTS includes neurological, cardiovascular and renal complications. Hypoxic-ischemic lesions to limbs, intestines and liver caused by infarctions have also been reported in TTTS survivors. Morbidity is known to be particularly high in surviving twins after intrauterine fetal death of their co-twin.

Neurological morbidity

Cerebral palsy is estimated to occur 7 times more often in twins than in singletons and is due to the higher incidence of prematurity and very low birth weight in twins[1]. The higher risk for cerebral damage in twins is also related to monochorionicity. Neurological morbidity is 7-fold higher in monochorionic twins compared to dichorionic twins[4] and is associated with selective intrauterine growth restriction[144], intrauterine fetal demise of a co-twin[145] and chronic TTTS[11;146]. Cerebral damage in chronic TTTS is presumed to be partly of antenatal origin and is related to hemodynamic disturbances[70;146]. The exact pathogenesis of cerebral damage is not fully understood yet. Hypoxic-ischemic damage caused by cerebral hypoperfusion is probably the major cause for cerebral injury in donor twins, whereas hyperviscosity and polycythemia causing vascular sludging may be an important cause for cerebral injury in the recipient[93]. Donors and recipients are equally at risk for adverse neurological outcome[12;129;146]. Early neonatal brain scans show that antenatally acquired cerebral white-matter lesions occur in 30 to 35% of survivors of chronic TTTS compared to only 3% in dichorionic twins[70;146]. Abnormalities on neonatal brain scans may also be secondary to postnatal injury associated with severe prematurity, which predisposes to periventricular leucomalacia and intraventricular hemorrhage. The incidence of major abnormal neonatal brain scans in chronic TTTS ranges from 17 to 41%[12;128;147;148]. The large difference in incidence is due to different definitions of abnormal scans

and relatively small sample sizes (inherent to the rarity of TTTS). Cerebral lesions include periventricular leucomalacia, cerebral white-matter cysts, severe intraventricular hemorrhage, cerebral infarct, ventricular dilatation and cerebral atrophy[12;128;147;148]. Minor lesions such as subependymal pseudocysts and lenticostriate vasculopathy have also been described in monochorionic twins with chronic TTTS[146;149]. Abnormal neonatal brain scans are reported less frequently in survivors of chronic TTTS treated with fetoscopic laser occlusion of vascular anastomoses than in survivors of chronic TTTS treated with serial amnioreduction[10].
Various studies have reported the long-term neurodevelopmental outcome in chronic TTTS. Rates of major neurodevelopmental deficiencies in children born after serial amnioreduction range from 5% to 25%[12;125;147;148;150]. Major neurodevelopmental sequelea in children born after fetoscopic laser coagulation of vascular anastomoses occur less frequently, and range from 2 to 11%[122;131;133;151;152]. However, results of the long-term outcome of the previously mentioned randomized trial form Senat *et al*[10] must be awaited before conclusions can be drawn on the possible beneficial aspects of laser surgery. Regardless of the antenatal treatment, the reported risks of neurological impairment in chronic TTTS remain high. Careful neurodevelopmental follow-up of all TTTS survivors is therefore of major importance to rule out cerebral palsy and global developmental delay. Whether neurological disabilities are mainly due to chronic TTTS or also partly caused by hemodynamic disturbances which may also occur in monochorionic twins without chronic TTTS, remains unclear. To address this issue, we are currently assessing the differences between long-term neurodevelopmental outcome between monochorionic twins with chronic TTTS treated with fetoscopic laser occlusion of vascular anastomoses and monochorionic twins without chronic TTTS[153].

Cardiovascular morbidity

Cardiovascular complications occur more frequently in monochorionic twins than in singletons, respectively 3.8% versus 0.6% and are mostly due to cardiac dysfunction occurring in monochorionic chronic TTTS gestations[19]. Congenital heart disease occurs 12 times more frequently in

monochorionic twins with chronic TTTS than in the general population and is found mainly in recipient twins[19]. Reported cardiovascular morbidity can be transient, progressive and sometimes persist beyond the neonatal period and includes fetal hypertension[83;154], hypertrophic cardiomyopathy[18;19;155], tricuspid regurgitation[156], left chamber myocardial infarction[157], pulmonary artery calcification[158] and right ventricular outflow tract obstruction[18;159;160].

Two theories have been postulated to explain the pathogenesis of cardiovascular morbidity in recipients with chronic TTTS. The first theory suggests that cardiovascular complications are a consequence of increased preload due to chronic hypervolemia causing cardiac hypertrophy. The second theory states that cardiovascular morbidity is due to an increased afterload induced by elevated levels of vasoconstrictive substances such as endothelin-1 found in recipients[84]. Higher rates of hypertension reported in recipients may support this second theory[12;83;154]. Whether cardiomyopathy in the recipient is primarily due to increased afterload or increased preload, is still open for debate.

Biventricular hypertrophy with prevalent left ventricular hypertrophic cardiomyopathy may be present in 40 to 100% of the recipient twins depending on the criteria[18;155;156;161]. Fetal hypertrophic cardiomyopathy may lead to hydrops fetalis in 10 to 15% of the recipient twins[161]. Nevertheless, hypertrophic cardiomyopathy appears to be reversible in most cases after delivery[155]. Cardiac hypertrophy may also lead to a functional obstruction of the outflow tract of the right ventricle, due to valvular or subvalvular pulmonary stenosis. Right ventricular outflow tract obstruction occurs in 5 to 11% of the recipients and is associated with high mortality rates[19;159;162]. Right ventricular outflow tract obstruction may be progressive and require urgent treatment with pulmonary balloon valvuloplasty or surgery after birth[18;159;163]

Improvement of cardiac function after delivery is also often reported in recipient twins, suggesting that removal of the causal factors helps the heart function to recover[155]. Whether removal of the causal factors by fetoscopic laser occlusion of the vascular anastomoses also results in a lower incidence of cardiac dysfunction in chronic TTTS is not yet known. We are currently performing a prospective study on echocardiographic abnormalities in monochorionic twins with chronic TTTS treated with laser

surgery compared to a control group of monochorionic twins without chronic TTTS[153].

Renal morbidity

Various renal complications have been reported in donor twins in TTTS and include renal cortical necrosis and fibrosis[164], transient renal insufficiency and hematuria[20], acute renal failure requiring long-term peritoneal dialysis[165], or permanent tubular dysfunction with polyuria due to renal tubular dysgenesis[21;166]. Autopsy studies in chronic TTTS report that renal tubular dysgenesis, characterized by loss of proximal convoluted tubules, is found in almost 50% of donor twins[21]. The pathogenesis of glomerular and tubular injury is probably secondary to hypoxic-ischemic injury due to chronic prenatal renal hypoperfusion in donor twins. Even though oliguric renal failure occurs frequently in donor twins, complete recovery of adequate renal function is usually reported[148]. Renal injury in donor twins may also lead, sporadically, to the development of chronic renal insufficiency requiring dialysis and kidney transplantation[12;165]. Renal function should be monitored carefully at birth in donor twins with TTTS by measuring urine output and serial serum creatinin levels to rule out renal insufficiency.

Antenatal hypoxic-ischemic lesions

Antenatal hypoxic-ischemic injury to various organs has been described mainly in recipient twins with TTTS, and includes lower limb necrosis[167-169], intestinal injury such as ileal atresia[170], and hepatic infarctions[171]. Most pathophysiologic mechanisms proposed to explain these injuries are based on hemodynamic disturbances. Necrotic tissue injury and gangrene can result from vascular sledging and peripheral ischemia due to the polycythemia-hyperviscosity syndrome since most of these injuries occur in recipient twins[167;168]. Idiopathic thrombosis, thrombotic injury induced by laser-surgery, anomalous vasculature and umbilical artery steal phenomenon have also been proposed as possible mechanisms[167;170;172].

Morbidity due to intrauterine fetal demise of co-twin

Risk of death or severe cerebral damage in the surviving twin after intrauterine fetal demise of a co-twin is 3 to 4-fold higher in monochorionic than dichorionic twins[14;32;173]. In the past, damage was thought to occur due to the release of thromboplastin and necrotic emboli from the demised fetus into the circulation of the surviving twin, causing disseminated intravascular coagulation, embolization and infarction[174-176]. However, current opinion is that damage results from acute exsanguination of the surviving twin into the low-pressure circulation of the demised co-twin, causing severe hypoxic-ischemic damage[30;32;70;173].

Severe neurological sequelae, such as multicystic encephalomalacy, occur in 20 to 40% of surviving twins after intrauterine fetal death of a co-twin[11;13-16]. Careful antenatal radiological evaluation by ultrasound or fetal magnetic resonance imaging should be performed after intrauterine fetal demise of a co-twin in a monochorionic twin gestation. Fetal magnetic resonance imaging detects brain damage earlier and with better definition of the brain abnormalities than ultrasound[177]. A multitude of abnormalities on neuro-imaging studies have been reported, including multicystic encephalomalacy, white-matter infarctions, hydranencephaly, holoprosencephaly, lisencephaly, polymicrogyria, and cortical atrophy associated with ventriculomegaly[178;179]. The type of cerebral abnormalities probably depends on the timing of intrauterine fetal demise of the co-twin. Intrauterine fetal demise of the co-twin in the early second trimester may lead to abnormalities related to disturbances in neuronal migration, such as polymicrogyria, whereas demise of the co-twin later during the third trimester may result in abnormalities typically associated with cerebral ischemic injury occurring in late gestation, such as white-matter infarctions or multicystic encephalomalacy[178;180].

Spontaneous fetal reductions in twin pregnancies diagnosed in the first trimester are not uncommon[181]. Approximately 30% of twin pregnancies will ultimately result in singletons[181]. This so-called “vanishing” twin phenomenon in monochorionic twins may also lead to severe cerebral damage[182]. Some authors hypothesize that a significant proportion of singletons with cerebral palsy of unknown etiology may in fact be surviving co-twins of undetected, initial monochorionic twin pregnancies[183].

A recent publication of a case report on multicystic encephalomalacy after first-trimester intrauterine fetal death in a monochorionic twin pregnancy, supports this hypothesis, and concludes that obstetricians and pediatricians should be aware that severe cerebral injury may occur earlier than previously thought[17]. Intrauterine fetal demise of a co-twin can also lead to renal cortical necrosis and subsequent renal failure, as well as splenic and hepatic infarctions in the surviving co-twin[174;184].

Conclusion

Though recent research has shed more light on the development of TTTS, the multitude of complex pathophysiologic mechanisms involved in the development of TTTS needs further exploration. The intrauterine management of TTTS remains a significant challenge in perinatal medicine. Although significant improvement in perinatal survival in TTTS has been achieved, this syndrome remains one of the most lethal conditions in perinatal medicine. Ongoing randomized controlled trials comparing different therapeutic regimens may eventually lead to universally accepted treatment protocols.
Considering the high incidence of cerebral white-matter damage, early neonatal brain scans and careful neurodevelopmental follow-up should be performed in all surviving twins to rule out severe neurological disabilities. Awareness of cardiovascular complications occurring in recipient twins and renal complications in donor twins may help improve neonatal care for these children. Surviving twins after intrauterine fetal demise of their co-twin are at high risk for developing severe cerebral and renal sequelae and require therefore adequate and complete work-up after birth.
Lastly, continuing close collaboration between obstetricians and neonatologists is crucial in order to improve the care of infants with TTTS.