Twin-twin transfusion syndrome: antenatal complications and postnatal outcome after fetoscopic laser therapy

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Twin-twin transfusion syndrome: antenatal complications and postnatal outcome after fetoscopic laser therapy

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TABLE OF CONTENTS

GENERAL INTRODUCTION

General Introduction

Twin pregnancies

Approximately 1-2% of all pregnancies are twin pregnancies.[1, 2] In two third of these twin pregnancies the fetuses are derived from two egg cells fertilized by two sperm cells. These twins are called dizygotic, or fraternal twins. In the other one third, both fetuses stem from one single egg cell, fertilized by a single sperm cell which divides itself early in pregnancy in two separate embryos. These twins are called monozygotic or identical twins. Dizygotic twin pregnancies are always dichorionic: the fetuses have their own placenta and their own amniotic sac (figure 1). One fourth of monozygotic twin pregnancies are also dichorionic, if the division of the embryo occurs within 3 days after conception. In the majority, three quarters of monozygotic twin pregnancies, division of the embryo occurs later and leads to monochorionic twins. Monochorionic twins share a placenta and a chorion but often have their own amniotic sac. In 1% of monozygotic twins division occurs more than a week after fertilization. These twins not only share a placenta but also share the amniotic sac, and are therefore called monochorionic monoamniotic twin pregnancies. The main characteristic of monochorionic twin pregnancies, and crucial difference with dichorionic twin pregnancies, is that the blood circulations of both twins are connected through vascular anastomoses on the shared placenta.

Monochorionic twins

Compared to dichorionic twin pregnancies the risk of complications and adverse outcome is higher for monochorionic twin pregnancies.[3] This increased risk is primarily attributed to the vascular anastomoses on the shared placenta. In 99% of monochorionic twin pregnancies the blood circulations are connected through vascular anastomoses on the shared placenta leading to an exchange of blood between the fetuses.[4] The rate of inter-twin transfusion depends on the amount, size and type of the anastomoses. Anastomoses can either be arterio-arterial, arterio-venous or veno-venous connections. The type of connection determines the direction of the blood flow. Arterio-venous connections have an unidirectional blood flow from an artery to a vein. Arterio-arterial and veno-venous connections are considered bidirectional.

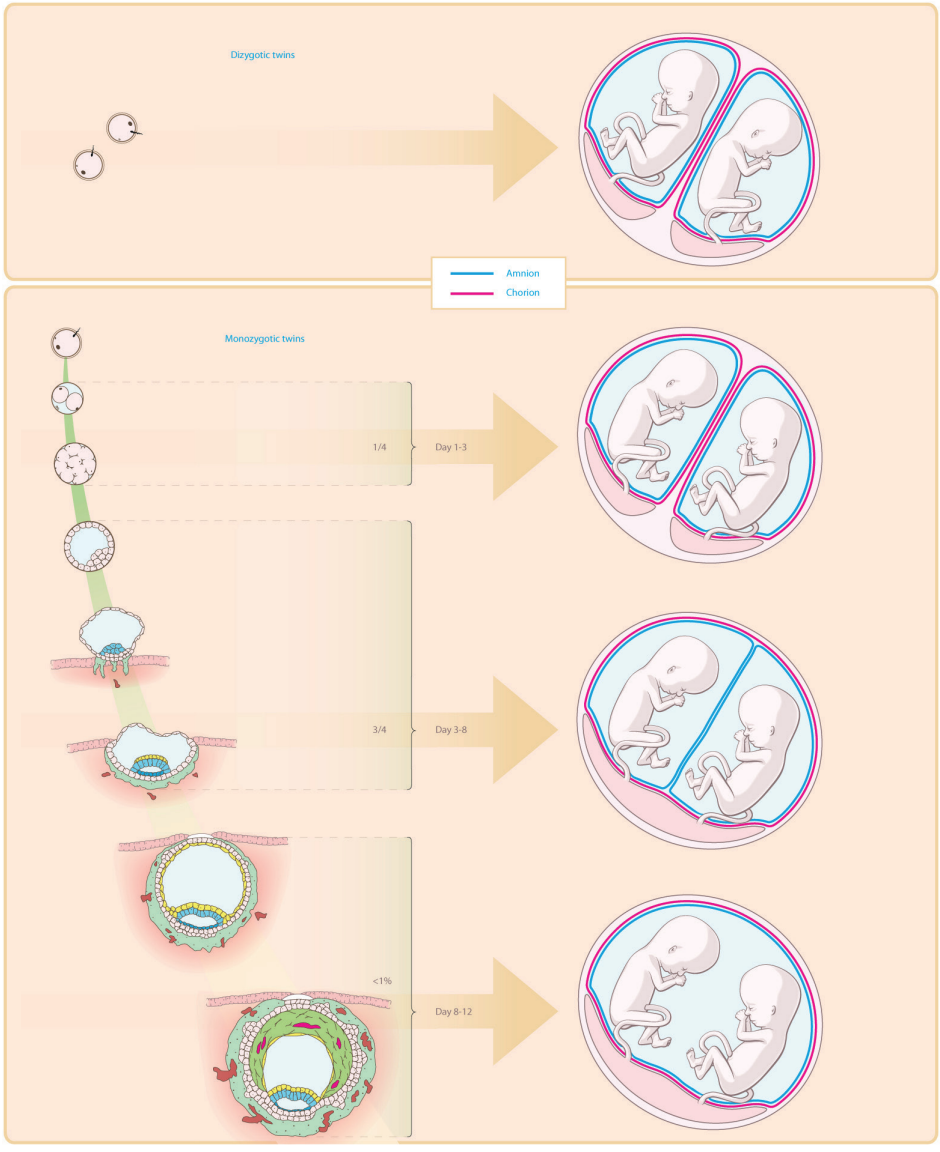

Figure 1. Monochorionic and dichorionic twins (*Illustration by Amanda Gautier)*

Twin-twin transfusion syndrome

In about 10% of the monochorionic twin pregnancies an imbalance in blood flow occurs leading to twin-twin transfusion syndrome (TTTS).[5] TTTS is caused by a larger *net* transfusion from one twin, the donor, to the other twin, the recipient, leading to hypovolemia in the donor and hypervolemia in the recipient.

Table 1. Stages of twin-twin transfusion syndrome based on ultrasound criteria[9]

Stage	Sonographic characteristics
1	Polyhydramnios with a deepest vertical pocket of ≥8 cm (or ≥10cm after 20 weeks of gestation) and oligohydramnios with a deepest vertical pocket of ≤2 cm
2	The bladder of the donor is not visible
3	Abnormalities on doppler (absent or reversed end-diastolic velocity in the umbilical artery, reversed flow in the ductus venosus or pulsatile flow in the umbilical vein)
4	Hydropic fetus
5	Demise of one or both fetuses

Hypovolemia in the donor leads to hypoperfusion, including renal hypoperfusion. The renin production in the kidneys of the donor is upregulated and the renin-angiotensin system is activated to maintain blood pressure resulting in oliguria and oligohydramnion.[6, 7] Eventually, the chronic under-perfusion of the kidneys in the donor can lead to renal tubular dysplasia and atrophy.[8]

Hypervolemia in the recipient leads to a higher cardiac load and polyuria. Polyuria increases the amount of amniotic fluid leading to a polyhydramnios. If left untreated, polyhydramnios can cause rupture of membranes and premature birth. The vasoactive hormones produced by the donor may reach the recipient through the placental anastomoses causing systemic hypertension and eventually hypertrophic cardiomyopathy and hydrops.[6, 7]

On sonographic examinations a so-called "stuck twin" image can be observed, where the donor twin lies in a cocoon of amniotic membranes without any amniotic fluid. This discrepancy in amniotic fluid is an important characteristic of TTTS and is *the* diagnostic criterium for TTTS. The severity of TTTS is classified by 5 different stages that can be observed on ultrasound (Table 1).[9]

Fetoscopic laser surgery

Without treatment TTTS is often lethal (73-100%).[10] Demise of one fetus leads to a drop in blood pressure thereby exposing the other fetus to the risk of acute exsanguination through placental anastomoses. The subsequent hypovolemic shock can damage the brain and other vital organs or may even cause demise. Polyhydramnios can induce premature labour. Since the 30's amniodrainage is

performed to reduce the amount of amniotic fluid, thereby preventing premature delivery.[11] Survival rates after amniodrainage increased to 60% with a double survival rate of 48%.[12]

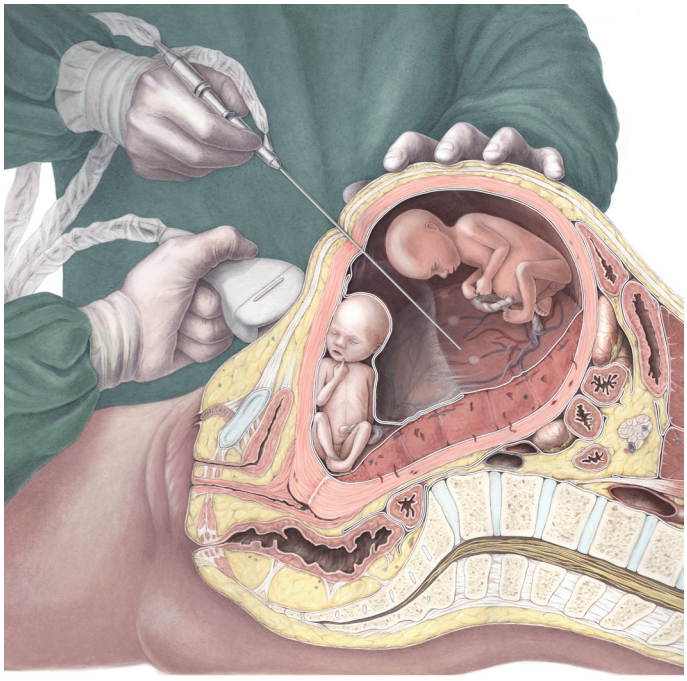

Figure 2. Fetoscopic laser therapy *(illustration by Amanda Gautier)*

However, in 25-41% of TTTS survivors brain anomalies were observed on intracranial screening.[13, 14] At long-term follow-up 5 to 25% of the survivors had developed cerebral palsy.[14, 15] Fetoscopic laser surgery was first introduced in the 90's and has become the preferred treatment for TTTS.[16] The aim of this therapy is to separate the fetal blood circulations by coagulating all placental anastomoses. The fetal surgeon inserts a fetoscope through the abdominal wall of the pregnant woman and through the uterine wall into the amniotic sac of the recipient twin. The vascular pattern on the placental surface is then identified with the fetoscope. Followingly, all anastomoses between the twins are detected and coagulated, thereby 'dichorionizing' the placenta. Separating the blood circulations is a causal treatment for TTTS. Since the introduction of this treatment, survival rates gradually improved from 55% to 74%.[17, 18] Despite this substantial improvement there is still a chance anastomoses are missed, leading to recurrence of TTTS or post-laser twin anemia-polycythemia sequence (TAPS). Post-laser TAPS is a condition caused by a chronic transfusion through only a few miniscule vascular anastomoses causing anemia in the donor and polycythemia

in the recipient. [19] Unlike TTTS, an amniotic fluid discordance is lacking. TAPS can be detected antenatally by measuring a difference in middle cerebral artery peak systolic velocity (MCA-PSV) between donor and recipient higher than 0.5 Multiples of the Median (MoM). Other sonographic characteristics of TAPS include signs of fetal anemia in the donor like cardiomegaly and echogenic bowels, the so called starry-sky liver in the (polycythemic) recipient and placental dichotomy (placenta part of the donor twin is echogenic and can be enlarged compared to the recipient's part).[20] Postnatal diagnosis of TAPS is based on a high hemoglobin difference (>8g/dL) between donor and recipient, a high reticulocyte count ratio (>1.7) and miniscule vascular anastomoses on the shared placenta.[20] The last two criteria can differentiate TAPS from acute peripartum transfusion, as acute transfusion occurs through large arterio-arterial anastomoses and reticulocyte counts are similar between the anemic and polycythemic twin.

The aforementioned method of coagulating every individual anastomoses is called the Selective technique. To minimize the risk of residual anastomoses a new technique for laser coagulation was introduced in 2012. [18] Instead of only coagulating the visible vascular anastomoses, this technique intends a complete coagulation of the vascular equator from one placenta margin to the other. First the fetal surgeon identifies and coagulates every individual anastomosis, followed by a line over the vascular equator to 'connect the dots'. The principle is to coagulate all anastomoses, including the minuscule ones which could potentially be missed, thereby minimizing the risks of TTTS recurrence and post-laser TAPS. This technique is called the Solomon technique, referring to the Bible story about king Solomon's judgement.

ANTENATAL COMPLICATIONS AFTER LASER SURGERY

Follow-up and complications

Fetoscopic laser surgery usually takes place between 15 and 26 weeks of gestation with most procedures performed around 19 to 20 weeks of pregnancy.[18] After the procedure, the condition of the fetuses is routinely monitored, at least every two weeks, to ascertain recovery and to check for possible complications. Fetoscopic laser surgery is unfortunately not without risks. As in every surgery there are risks of incomplete surgery, infection and bleeding, risk of intrauterine fetal demise. Unique to a intrauterine procedure is the risk of damage to the membranes. Premature rupture of these membranes can lead to oligohydramnios due to leakage of amniotic fluid, intrauterine infection and premature birth and is associated with neonatal morbidity and mortality. Bleeding complications after fetoscopy could hamper visualization and lead to an incomplete procedure and residual anastomoses.

Residual anastomoses

Residual anastomoses can cause recurrence of the TTTS or post-laser TAPS. In both cases a reversal can occur, where the former donor becomes the recipient and the recipient the new donor. The reported rates of residual anastomoses vary between centers from 3.5% to 75%.[18, 21-23] However, most fetal therapy centers do not perform systematic placental examinations with color dye and residual miniscule vascular anastomoses (typical in TAPS) may then be missed. In this thesis we examined placenta's of a large cohort of TTTS treated with laser therapy. In **Chapter 1** we determined the rate of residual anastomoses after fetoscopic laser surgery and evaluated risk factors and outcomes. The rate of residual anastomoses was reported for the Solomon and the Selective technique.

Post-procedural amniotic band syndrome

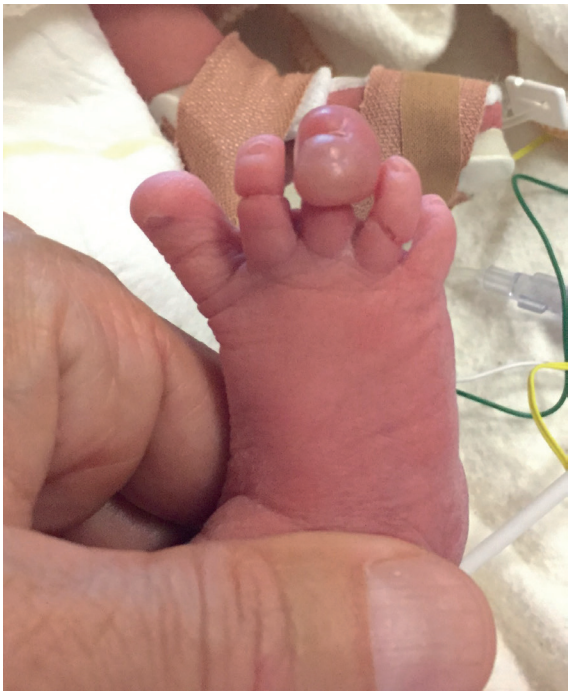

Figure 3. Toes of a patient with amniotic band syndrome

Another complication potentially related to damage to the fetal membranes is amniotic band syndrome. Amniotic band syndrome is a rare fetal condition where strands of amniotic membrane can cause constrictions, amputations, severe malformations or even fetal demise when a strand constricts the umbilical cord.[24] The etiology is unknown. Amniotic band syndrome can occur spontaneously

although associations with intrauterine procedures have been described in previous studies.[25-27] Therefore, amniotic band syndrome after intrauterine procedures is often called post-procedural (or pseudo) amniotic band syndrome, to distinguish it from spontaneous amniotic band syndrome. The prevalence of post-procedural amniotic band syndrome in TTTS treated with fetoscopic laser surgery is unknown. Only few case reports and case series are reported.[27-34] In **Chapter 2** we studied the rate of post-procedural amniotic band syndrome in a large single center cohort of TTTS treated with laser therapy and explored risk factors and outcomes.

Iatrogenic monoamniotic twin pregnancies

Damage to the dividing intertwin membrane between the amniotic sacs of the fetuses can cause it to rupture. Due to fetal movement a small rupture in the intertwin membrane often expands, leading to an iatrogenic monoamniotic twin (iMAT) pregnancy where both fetuses share the same amniotic sac. In spontaneous monoamniotic twin pregnancies the umbilical cords of both fetuses are per definition entangled due to fetal movements in the shared amniotic sac and the often proximate cord insertions.[35] Cord entanglement can result in fetal demise when the blood flow is interrupted by cord constriction. Iatrogenic monoamniotic twin pregnancies are also at risk for cord entanglement. However, the distance between cord insertions is often not proximate and the rate of cord entanglement is unknown, as is the risk of cord constriction and fetal demise. In **Chapter 3** we investigated the rate of iatrogenic monoamniotic twin pregnancies after fetoscopic laser surgery for TTTS and the rate of cord entanglement. In addition we explored risk factors and outcomes.

Placental abruption

Placental abruption is a complication in pregnancy where the placenta separates from the uterine wall before the fetus is born. Placental abruption can be partial or complete. As the fetus depends on the placenta for nutrients and oxygen, placental abruption can lead to severe complications such as brain damage and fetal demise. Several risk factors for placental abruption are described in previous studies, including maternal cocaine and tobacco use.[36, 37] Little is known about the risk of placental abruption in TTTS treated with fetoscopic laser surgery. Some small studies suggest an association between placental abruption and the Solomon laser technique.[38, 39] In **Chapter 4** we evaluated rates, risk factors and outcomes of placental abruption in a large multicenter cohort treated with laser surgery for TTTS.

POSTNATAL OUTCOME AFTER LASER SURGERY

Neurodevelopmental outcome

Despite aforementioned perinatal complications, survival rates of TTTS have improved considerably since the introduction of fetoscopic laser therapy. These improving survival rates demand a shift in scope to the long-term outcome and quality of life of TTTS survivors. Comorbidities and neurodevelopmental impairment have an immense impact on quality of life of children and their families. Therefore the counseling of future parents in pregnancies complicated by TTTS should not only include survival rates, but also information about long-term outcomes of TTTS survivors. Fetal therapy centers should not focus on survival rates only, instead, the primary outcome should be intact survival, without significant impairments. Follow-up programs are essential to reliably determine intact survival. Several fetal therapy centers have follow-up programs to monitor the neurodevelopment of TTTS survivors. However, studies are often small and an uniform approach is lacking. In **Chapter 5** we give an overview of the available literature on neurodevelopmental outcomes in TTTS survivors treated with laser therapy. We evaluated rates of cerebral palsy (CP) and neurodevelopmental impairment (NDI). **Chapter 6** is a review of the available literature on long-term neurodevelopmental outcome in all complicated monochorionic twin pregnancies, including TTTS, TAPS and selective fetal growth restriction (sFGR). Most fetal therapy centers assessed TTTS survivors at age 2. Data on neurodevelopment in older children is scarce. Nevertheless follow-up is crucial as some problems may surface only later in life, when children are socially and intellectually more challenged. Developmental problems present in toddlers may dissolve at an older age and new problems may arise.[40] Therefore evaluation of the neurodevelopmental outcomes in a cohort of TTTS survivors at age 2 and 5 years treated with laser therapy was part of this thesis. In **Chapter 7** we evaluated rates of CP and NDI in TTTS survivors that were born premature and/or small for gestational age. We compared neurodevelopmental outcome at 5 years to the results of their assessment at the age of 2.

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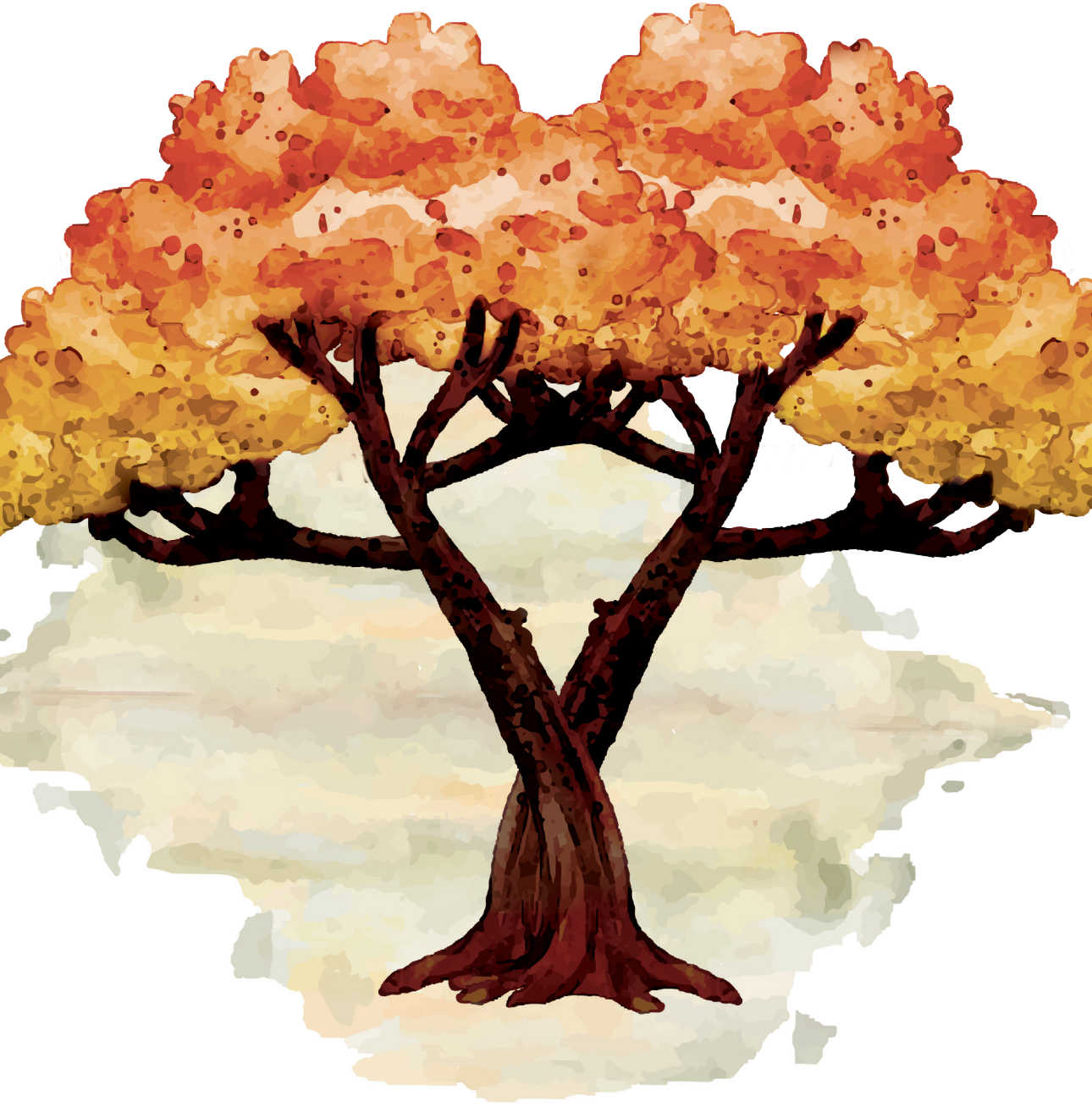
ANTENATAL COMPLICATIONS



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Chapter 1

Incidence and risk factors for residual anastomoses in twin-twin transfusion syndrome treated with laser surgery: a 15-years single-center experience

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ABSTRACT

Objectives: To evaluate the incidence of residual anastomoses (RA) after laser therapy for twin-twin transfusion syndrome (TTTS) and investigate risk factors for incomplete laser surgery.

Material and Methods: All available TTTS placentas treated with laser at our center between 2002-2016 were injected with color dye to assess the presence of RA. We evaluated the incidence of RA over the past 15 years by dividing the cohort into three time-periods, and studied the association with risk factors and neonatal outcome.

Results: Overall, RA were detected in 21.0% (78/371) of placentas. The incidence of RA decreased from 38.8% (26/67) in the initial period to 11.7% (16/137) in the most recent period ($p < 0.001$). On multivariate analysis, several risk factors were independently associated with the risk of RA, including Solomon laser technique (OR 0.17 95% CI 0.09-0.33) and estimation of surgical success (OR 19.28 95% CI 8.17–45.49). Premature delivery and neonatal morbidity occurred more often in TTTS cases with RA.

Conclusions: The incidence of RA after laser for TTTS decreased significantly in the past 15 years, mainly due to the use of the Solomon technique, and is now below 15%.

INTRODUCTION

Placental vascular anastomoses connecting the circulations of both fetuses are present in almost every monochorionic twin pregnancy and may lead to the development of severe complications such as twin-twin transfusion syndrome (TTTS) [1]. Fetoscopic laser coagulation of placental vascular anastomoses is the best treatment for TTTS [2]. The aim of fetoscopic laser coagulation is to achieve two separate circulations by coagulating all intertwin vascular anastomoses. Anastomoses may however be missed during fetoscopic surgery, causing severe postoperative complications such as recurrent TTTS and twin anemia polycythemia sequence (TAPS) [3-5]. The incidence of these residual anastomoses (RA) varies greatly between the studies from 3.5% up to 75% [5-9]. The large variation in incidence of RA is partly due to methodological limitations related to the study design and often too small sample size. Incomplete laser surgery and RA may be related to various factors, including different laser surgery techniques, experience of the operator (learning curve effect) and location of the placenta (anterior or posterior).

The objective of this study is to evaluate the incidence and consequences of RA after laser therapy for TTTS over the years in a large single center cohort and investigate the role of potential risk factors associated with incomplete laser surgery.

METHODS

Study design

All consecutive cases with TTTS treated with fetoscopic laser surgery at the Leiden University Medical Center (LUMC) were eligible for this study. The LUMC is the national referral center for fetal surgery in the Netherlands. We included all TTTS cases delivered between April 1, 2002, and December 31, 2016, in which the placenta was examined and injected after delivery. The TTTS placentas are routinely injected with color dye to assess the presence of RA using a previously reported injection technique [10]. In case of delivery in another center, the placenta was shipped to our hospital for color dye injection. For this study, we excluded placentas with severe placental maceration due to fetal demise of one or more infants. Part of the placental data used in this study has been used in previous reports [3, 5, 6, 11]. The study was approved by the Leiden University Medical Centre Medical Ethics Committee.

The following antenatal variables were collected: TTTS stage, gestational age at laser, laser technique (Selective or Solomon technique), estimation of surgical success according to the operator (recorded directly after laser therapy), location of the placenta (anterior or posterior), number of anastomoses coagulated and the year

laser surgery took place. TTTS was defined according to the Eurofoetus criteria [2]. The cut-off was defined as a vertical pocket of amniotic fluid of ≤2 cm for the donor and ≥10 cm for the recipient after 20 weeks' gestational age (or ≥8 cm before 20 weeks' gestational age). Stages of TTTS were determined according to the Quintero staging [12]. The presence of post-laser TAPS was defined as Doppler ultrasound examination showing an increased middle cerebral artery peak systolic velocity (MCA-PSV) > 1.5 multiples of the median (MoM) in one fetus, suggestive for anemia, accompanied by a decreased MCA-PSV < 1.0 MoM in the co-twin, suggestive for polycythemia [4]. Postnatal TAPS was defined as both an inter-twin hemoglobin difference of > 8 g/dL at birth and at least one of the following: reticulocytosis in the donor with an intertwin reticulocyte count ratio > 1.7 and/or the presence of only small (diameter <1 mm) anastomoses after placental injection [13]. Estimation of surgical success was defined as whether the surgeon thought all the anastomoses had been coagulated directly after the laser surgery, which was recorded in the patient's records. To study the association between gestational age at laser and RA, we calculated the interquartile range (IQR) of the gestational age at laser. We then divided TTTS cases into three categories: early laser group (first quartile), late laser group (third quartile), and the average laser age group (mid-spread, i.e. between upper and lower quartiles).

During the study period, both the Selective and Solomon laser technique were used to treat TTTS. The principle of the Selective technique is to coagulate all inter-twin anastomoses that could be visualized during fetoscopy, whereas the aim of the Solomon technique is to draw a line along the placental vascular equator in order to coagulate even the tiny hardly visible or nonvisible anastomoses. Examples of color-dye-stained placentas treated with the Solomon laser technique and with the Selective technique are shown in Figures 1 and 2.

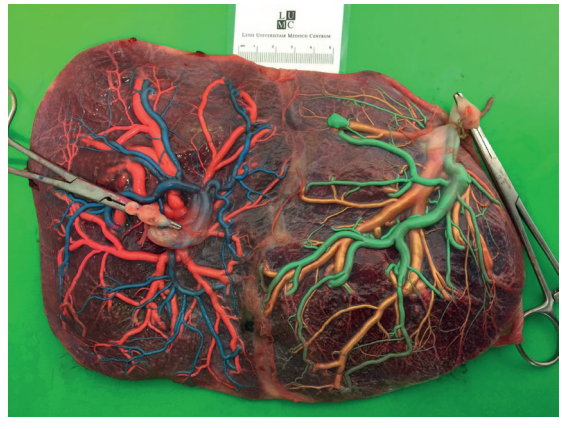

Figure 1. TTTS placenta treated using the Solomon laser technique.
Blue and green dye was used to stain the arteries, pink and yellow were used to stain the veins. No residual anastomoses were detected.

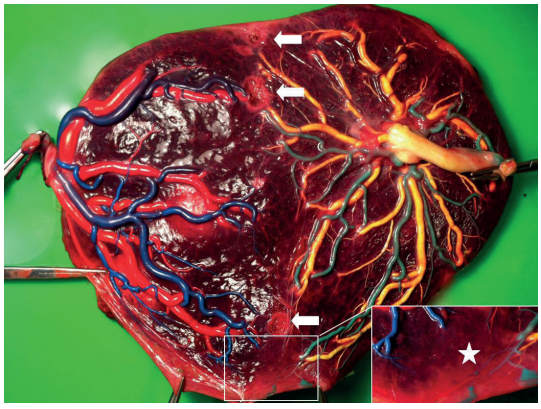

Figure 2. TTTS placenta treated using the Selective laser technique.

The white arrows indicate the laserspots. The white star indicates a veno-arterial anastomosis. (picture previously published in Fetal Diagnosis and Therapy [15])

The Selective laser technique was routinely used between January 2002 and March 2007. From March 2007 until October 2012 both the Selective and the Solomon techniques were performed during the open-label randomized controlled Solomon trial [5]. Since October 2012, after completion and evaluation of the Solomon trial results, the Solomon laser technique was routinely used, due to the favorable results. To study the association between study period and RA, we divided the cohort of TTTS cases into three groups; pre-Solomon period, the Solomon-study period and the post-Solomon period.

The following postnatal variables were recorded: gestational age at birth, birth weight, neonatal mortality (death of an infant within 28 days after birth) and neonatal morbidity. Neonatal morbidity was defined as the presence of one of the following complications: respiratory distress syndrome needing treatment with surfactant, patent ductus arteriosus requiring medical treatment or surgical closure, necrotizing enterocolitis grade ≥ 2, severe anemia requiring a blood transfusion on the first day after birth, severe polycythemia requiring a partial exchange transfusion on the first day after birth, severe cerebral damage which was defined as the presence of one of the following occurrences: cystic periventricular leukomalacia grade ≥ 2, intraventricular hemorrhage grade ≥ 3, ventricular dilatation greater than the 97th percentile, porencephalic or parenchymal cysts, arterial or venous infarction or other severe cerebral lesions associated with adverse neurological outcome.

The primary outcome was the incidence of RA assessed with color dye injection of the placenta. As secondary outcomes we studied the association between RA and potential risk factors and the association between RA and neonatal morbidity and mortality.

Statistical analysis

Group differences were compared using an independent samples *t* test. Antenatal risk factors for RA were compared using univariable logistic regression. A *p* value < 0.05 was considered to indicate statistical significance. The following potential predictors of the presence of RA were studied in a univariable logistic regression model: laser technique, laser period, gestational age at laser surgery, Quintero stage, location of the placenta, and the estimation of surgical success. Predictors of RA that were significant ($p < 0.05$) in the univariable analysis were included in a multivariable logistic regression model to measure the independent effects. The results of the logistic models were expressed as odds ratio (OR) and 95% confidence interval (CI). Data on neonatal outcome were compared using a generalized estimating equation (GEE) to account for the fact that findings between co-twins are not independent. Likewise, neonatal outcome variables that appeared significant in the univariable GEE were included in a multivariable GEE. Results were defined in percentages, mean and standard deviation or median and IQR, depending on the distribution, and OR with a 95% CI. All statistical data were analyzed using SPSS version 23.0 (IBM, Chicago, IL, USA).

RESULTS

During the 15 year study period, 645 monochorionic twin pregnancies were treated with fetoscopic laser surgery for TTTS at our center. A total of 436 (67.6%) pregnancies resulted in two liveborn infants. We excluded 99 (22.7%) liveborn cases due to fixation of the placenta in formalin (n = 5) , placental damage (n = 11), or loss of the placenta (n = 83). A total of 34 (16.3%) placentas of cases with one or more fetal demises could be injected. The derivation of our population is presented in Figure 3.

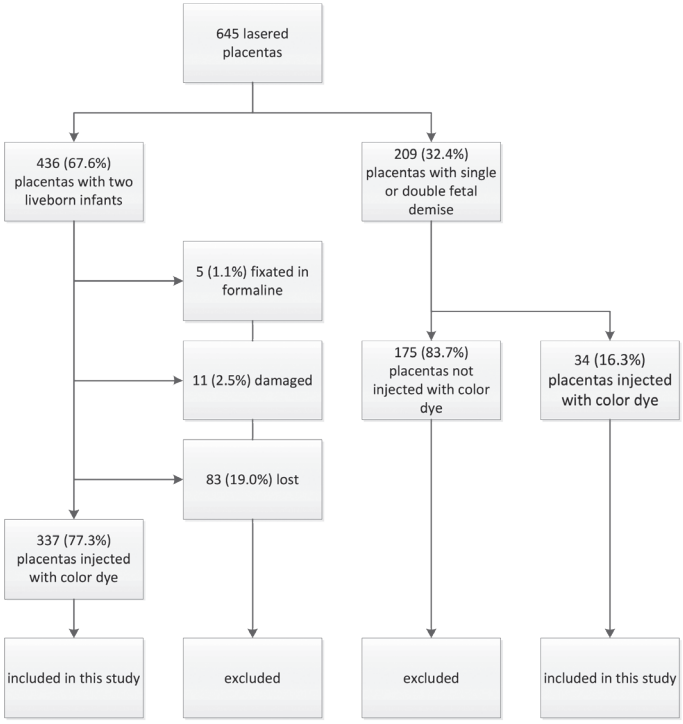

Figure 3. Derivation of study population

Mean gestational age at birth in the group of lost placentas was significantly higher compared to the group included in the study, 33.3 versus 31.9 (p = 0.01). Of the 371 placentas included in the study, 249 (72.5%) were delivered in our center and 122 (27.5%) elsewhere and subsequently shipped to our center. Most placentas that were lost were from twins delivered elsewhere (91.6%, 76/83) and probably not shipped over after birth. The baseline characteristics of our population are presented in Table 1. Post-laser TAPS was found in 53 of 645 cases (8.2%). Recurrent TTTS was found in 11 pregnancies (1.7 %). Of the placentas with RA, 47.4% developed post-laser TAPS or recurrent TTTS. Reintervention with laser surgery was performed in 12 pregnancies and 17 twins were managed with intrauterine blood transfusions. In 3 of the 12 cases with a laser reintervention, laser surgery was unsuccessful and RA were found on the postpartum examination of the placenta. These placentas were therefore analyzed in the RA group. RA were not found in only two placentas, whereas seven placentas could not be injected.

Table 1. Baseline characteristics in 371 TTTS pregnancies treated with laser

Quintero stage, n (%)	**I**	47 (12.7)
	II	124 (33.4)
	III	183 (49.3)
	IV	17 (4.6)
Gestational age at laser- weeks [a]		20.0 (18.0-22.0)
Anterior placenta, n (%)		156 (42.0)
Anastomoses detected during fetoscopy [a]		6.0 (4.0 - 8.0)
Sectio caesarea, n (%)		138 (37.2)
Born at our center, n (%)		269 (72.5)
Female gender, n (%)		185 (49.9)

[a] given as median (IQR)

Overall, RA were detected in 68 (21.0%) placentas. We found a clear decline in the incidence of RA during the years, from 38.8% (26/67) in the first period (pre-Solomon period: January 2002 to May 2007) to 11.7% (16/137) in the most recent period (post-Solomon period: July 2012 to December 2016) (OR 4.80, 95% CI 2.89 – 7.96, p <0.001) (Figure 4). The Selective laser technique was associated with an increased risk of RA compared to the Solomon laser technique, 31.6% (50/158) versus 13.1% (28/213) (OR 0.33, 95% CI 0.19 –0.55, p < 0.001).

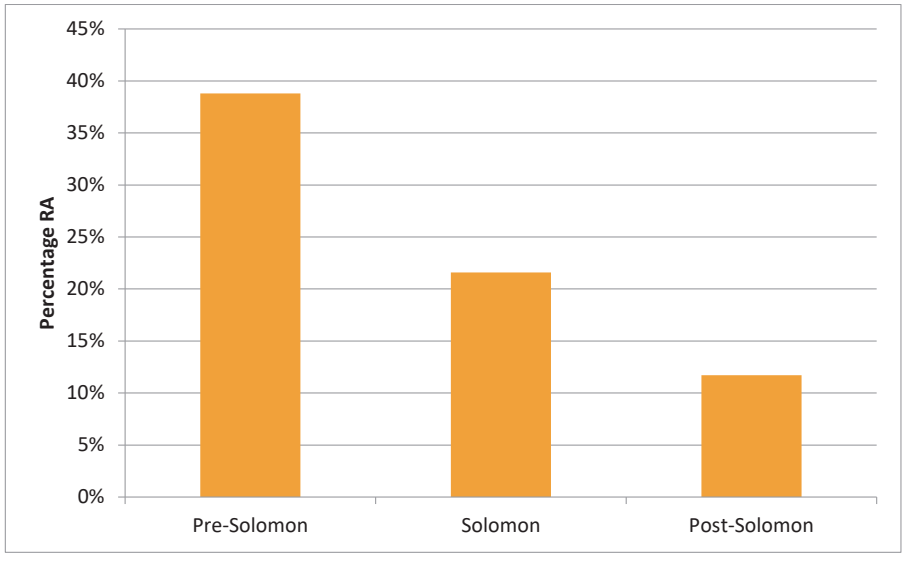

Figure 4. Incidence of residual anastomoses in periods of three years

We found a clear association between the estimation of surgical success and the presence of RA. RA were found in 63.4% (26/41) of cases when the surgeon thought the laser therapy was incomplete, compared to 15.8% (52/330) when laser surgery was thought to be complete (OR 11.33, 95% CI 5.96 – 21.56, p <0.001). When the Solomon technique was performed, RA were still found in 7.6% (14/184) of cases considered complete according to the surgeon.

Laser therapy was performed at a median age of 20 weeks (IQR 18-22 weeks). RA were detected slightly more frequently in the early laser group (< 18 weeks) (OR 1.48, 95% CI 0.78 – 2.81) and significantly more frequently in the late laser group (> 22 weeks) (OR 2.76, 95% CI 1.48 – 4.81) compared to the average age at laser group, 21.1% (19/90) and 32.6% (30/92) versus 15.3% (29/189), (p = 0.235 and p = 0.001) respectively.

TTTS cases with stage 1 had the lowest rate of RA (12.8%, 6/47), whereas the highest rate of RA was detected in cases with TTTS stage 4 (29.4%, 5/17) (OR 2.85, 95% CI 1.10 – 7.40, p = 0.032).

The incidence of RA was higher in anterior placentas (24.4%, 38/156) than in posterior placentas (18.6%, 40/215), but the difference was not significant (OR 1.41, 95% CI 0.85-2.33, p = 0.18).

Multivariable logistic regression was performed using all variables with a significant association with RA in the univariable logistic regression. An exception was made for the time period in which laser therapy took place, since this variable was highly correlated with the type of laser technique (Selective laser technique being performed routinely in the early periods and the Solomon technique in the latter time periods). Therefore only laser technique (Selective versus Solomon) was analyzed in the multivariable analysis. We found that four risk factors were independently associated with increased risk of RA including Selective laser technique, opinion of the surgeon directly after surgery, early and late gestational age at laser and Quintero stage 2 (Table 2).

Table 2. Antenatal risk for residual anastomoses

Characteristics		RA (n = 78)	No RA (n = 293)	*p*-value	Univariate OR (95% CI)	*p*-value	Multivariate OR (95% CI)
Study period, n (%)	**Pre-Solomon**	26 (38.8)	41 (61.2)	**<0.001**	4.80 (2.89 – 7.96)		
	Solomon	36 (21.6)	131 (78.4)	**0.001**	2.08 (1.32 – 3.27)		
	Post-Solomon	16 (11.7)	121 (88.3)	-	reference		
GA at laser, n (%)	**<18 wks**	19 (21.1)	71 (78.9)	0.235	1.48 (.78 – 2.81)	**0.04**	2.15 (1.03 – 4.46)
	18-22 wks	29 (15.3)	160 (84.7)	-	reference	-	
	>22 wks	30 (32.6)	62 (67.4)	**0.001**	2.76 (1.48 – 4.81)	**0.001**	3.20 (1.58 – 6.48)
Quintero stage, n (%)	**I**	6 (12.8)	41 (87.2)	-	reference	-	
	II	31 (25.0)	93 (75.0)	**0.016**	2.28 (1.17 – 4.45)	**0.019**	3.70 (1.24 – 11.08)
	III	36 (19.7)	147 (80.3)	0.125	1.67 (.866 – 3.23)	0.256	1.85 (0.64 – 5.33)
	IV	5 (29.4)	12 (70.6)	**0.032**	2.85 (1.10 – 7.40)	0.818	1.22 (0.23 – 6.34)
Location placenta, n (%)	**posterior**	40 (18.6)	175 (81.4)	-	reference		
	anterior	38 (24.4)	118 (75.6)	0.18	1.41 (0.85-2.33)		
Laser technique, n (%)	**Solomon**	28 (13.1)	185 (86.9)		reference	-	
	Selective	50 (31.6)	108 (68.4)	**<0.001**	0.33(0.19-0.55)	**0.000**	0.17 (0.09-0.33)
Estimation of surgical success, n (%)	**complete**	52 (15.8)	278 (84.2)	-	reference	-	
	incomplete	26 (63.4)	15 (36.6)	**<0.001**	11.33 (5.96 – 21.56)	**0.000**	19.28 (8.17 – 45.49)

RA= residual anastomoses, OR= odds ratio

Table 3. Neonatal outcome in the group with two live born infants with and without residual anastomoses

Variables	RA (n = 136)	No RA (n = 538)	*p*-value	Univariate OR (95% CI)	*p*-value	Multivariate OR (95% CI)
GA at birth in weeks [a]	31.9 (28.5 – 34.1)	33.3 (30.4 – 35.7)	**0.005**	3.75 (1.51 – 9.36)		
Birth weight in grams [a]	1518 (1101 – 1974)	1790 (1308 – 2225)	**0.002**	10.11 (2.33 – 43.95)		
Respiratory distress syndrome, n (%)	39 (28.7)	89 (16.5)	**0.038**	1.83 (1.04 – 3.22)	0.386	0.71 (0.33 – 1.53)
Patent ductus arteriosus, n (%)	12 (8.8)	17 (3.2)	**0.044**	2.58 (1.03 – 6.47)	**0.043**	2.66 (1.03 – 6.88)
Necrotizing enterocolitis, n (%)	1 (0.7)	14 (2.6)	0.133	0.21 (0.03 – 1.62)		
Severe cerebral injury, n (%) [b]	12 (8.8)	29 (5.4)	0.337	1.44 (0.69 – 3.00)		
Anemia at birth, n (%)	29 (21.3)	10 (1.9)	**<0.001**	13.75 (6.40 – 29.55)	**0.000**	15.56 (6.98 – 34.70)
Polycythemia at birth, n (%)	20 (14.7)	5 (0.9)	**<0.001**	17.65 (6.65 - 46.84)	**0.000**	24.61 (8.90 – 68.08)
Neonatal mortality, n (%)	14 (10.3)	16 (3.0)	**0.019**	2.65 (1.18 – 5.97)	0.510	1.51 (0.44 – 5.14)

RA= residual anastomoses,
[a] Given as median (interquartile range)
[b] Severe cerebral injury was defined as PVL ≥2, IVH ≥3, ventricular dilatation, arterial or venous infarct or other severe cerebral injury

The presence of RA was associated with an increased risk of premature delivery, low birth weight, respiratory distress syndrome, patent ductus arteriosus, anemia at birth, polycythemia at birth and neonatal mortality (Table 3). Gestational age at birth and birth weight were highly associated with all other variables. To correct for intervariable associations and correlation with gestational age at birth and birth weight, we performed a multivariable GEE on all variables which showed a significant correlation with RA in the univariable GEE. Presence of RA was independently associated with an increased risk of patent ductus arteriosus and anemia and polycythemia at birth.

DISCUSSION

Our study shows a strong decrease in the incidence of RA after fetoscopic laser coagulation in our center over the past 15 years, suggesting an improvement in the completeness of laser surgery. The incidence of RA dropped from 38.8% in the first period (January 2002 to March 2007) to 11.7% in the most recent period (October 2012 to December 2016), once the Solomon laser technique was routinely used in all cases. Our findings confirm the significant impact of the Solomon technique on the reduction of RA and completeness of laser surgery [3, 5]. Our study also confirms that the estimation of surgical success, directly after laser, is highly predictive of the presence of RA. When surgeons thought that surgery was incomplete, RA were then detected in 63.4% of cases. However, in approximately 15% of the procedures considered complete by the surgeon, RA could still be found. Close monitoring is therefore needed for all post-laser therapy pregnancies, even if the surgeon thinks that the operation was successful. We advise to perform at least biweekly Doppler ultrasound examinations after laser surgery, to screen for signs of anemia and polycythemia (TAPS) or recurrent TTTS. A novel finding in this study is the increased risk of RA in TTTS treated with laser at an early or at a late gestational age, i.e. before 18 weeks of gestation and after 22 weeks of gestation at the time of surgery. Hypothetically, anastomoses may be missed more frequently during laser surgery early in pregnancy as these anastomoses are then smaller and may be harder to visualize during fetoscopy. In contrast, anastomoses may also be missed more frequently late in pregnancy because of the larger size of the fetuses which may block the view on the vascular equator. Another explanation is that the size of the placenta may then be too large to oversee the whole vascular equator, especially the placenta margin, and the length and angle of the scope might not be sufficient enough. Increased awareness of these factors may be required to avoid missing anastomoses when performing laser surgery at an early or late gestational age. Another novel and quite remarkable finding in this study is the risk Quintero stage 2 and 4 confer for RA compared to Quintero stage 1. The cause of this association is

not clear. However, this study might be underpowered to compare Quintero stages since the groups with Quintero stage 1 and 4 were relatively small, and the study was not designed to evaluate possible causes for the associations.

Our study also confirms the association between RA and adverse neonatal outcome, in particular lower gestational age at birth and birth weight, neonatal mortality and various neonatal morbidities including respiratory distress syndrome, patent ductus arteriosus and hematological complications (anemia or polycythemia at birth). As previously shown, the presence of RA is associated with the development of post-laser TAPS and recurrent TTTS due to the persistence of intertwin fetal transfusion [3].

The strength of this study is the large time span and number of injected placentas that were used and the systematic and accurate method of injection with colored dye. However, care should be taken when interpreting our results due to the retrospective nature of our study and the loss to follow-up. Since the gestational age at birth in the group with placentas which were lost was higher, a selection bias towards the inclusion of more severe cases (with lower gestational age at birth) might have occurred. This could have led to an *over*estimation of the incidence of RA. Another inevitable limitation of this study is the impossibility to inject placentas with fetal demise. Hypothetically, fetal demise may have occurred more frequently in cases of incomplete laser surgery (and thus RA), and this may in turn have led to an *under*estimation of the incidence of RA.

Lastly, this study did not evaluate the effect of the learning curve and growing expertise of the surgeon. To investigate this important factor, a cumulative sum analysis should be performed for each operator. This effect has already been shown in a previous study in our center [14].

In conclusion, the incidence of RA (and therefore post-laser TAPS and recurrent TTTS) after fetoscopic laser coagulation for TTS has rapidly decreased over the years, due to the introduction of the Solomon laser technique and growing laser expertise (learning curve effect). Nevertheless, RA are still not infrequent, particularly in cases treated at an early or late gestational age. Further reduction of RA is important, given the association with adverse neonatal outcome.

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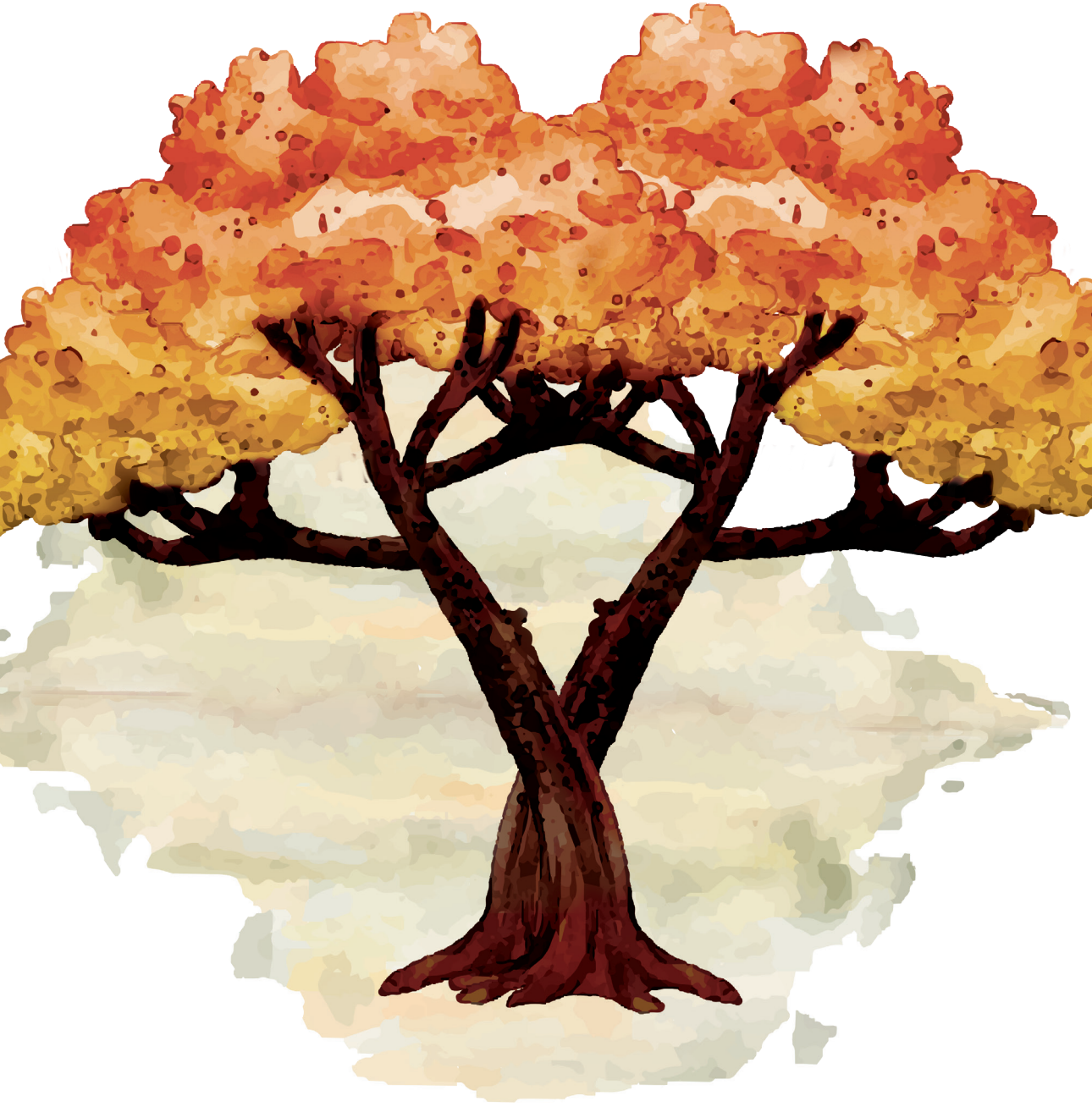

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Chapter 2

Placental abruption after fetoscopic laser surgery in twin-twin transfusion syndrome; the role of the Solomon technique

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ABSTRACT

Introduction: Twin-twin transfusion syndrome (TTTS) is a complication in monochorionic twin pregnancies which is preferably treated with fetoscopic laser surgery. A few small studies suggested a possible association between the Solomon laser technique and placental abruption.

Methods: The objective of this study is to compare the rate of and to explore potential risk factors for placental abruption in TTTS treated with fetoscopic laser surgery according to the Selective and Solomon laser technique. We conducted a large retrospective cohort study of consecutive TTTS-cases treated with fetoscopic laser surgery in Shanghai, China and Leiden, the Netherlands treated with either the Selective laser technique (Selective group) or Solomon laser technique (Solomon group).

Results: The rate of placental abruption in the Selective group versus the Solomon group was 1.7% (5/289) and 3.4% (15/441), respectively ($p = 0.184$). No risk factors for placental abruption were identified. Placental abruption was associated with lower gestational age at birth ($p = 0.003$) and severe cerebral injury ($p = 0.003$).

Conclusion: The prevalence of placental abruption in TTTS after fetoscopic laser surgery is low, although it appears higher than in the overall population. Placental abruption is associated with a lower gestational age at birth, which is associated with severe cerebral injury. The rate of placental abruption was not significantly increased with the use of the Solomon technique. Continued research of placental abruption in TTTS is necessary to determine why the rate is higher than in the overall population.

INTRODUCTION

Twin-twin transfusion syndrome (TTTS) affects approximately 10% of all monochorionic twin pregnancies.[1] The preferred treatment is fetoscopic laser surgery to separate the blood circulations of the twins by coagulating all inter-twin anastomoses on the placenta. Two different techniques are available to separate the fetal circulations: in the Selective technique all inter-twin anastomoses at the placental surface are identified and coagulated; whereas in the Solomon technique, after coagulation of the individual anastomoses, an additional line is coagulated on the placental surface, from one edge of the placenta to the other along the vascular equator, connecting all individual laser spots. The Solomon trial showed a significant reduction in the prevalence of post-laser twin anemia polycythemia sequence and recurrent TTTS when the Solomon technique was used.[2] Other complications including premature rupture of membranes, infection and iatrogenic monoamnionicity were comparable between the techniques.[2] A lesser known complication is placental abruption. Placental abruption is the preterm detachment of the placenta from the uterine wall characterized by severe abdominal pain, vaginal blood loss, uterine contractions and fetal distress or, even, fetal demise. The prevalence of placental abruption ranges from 3.3 to 11.9 per 1000 pregnancies and 12.4 per 1000 twin pregnancies.[3, 4] Various risk factors are reported, including trauma, hypertension, preeclampsia, maternal age, parity, drug use, smoking, thrombophilia, previous placental abruption and, multiple gestations.[5] Literature on placental abruption in TTTS is limited; the rate of placental abruption in TTTS treated with laser therapy ranges from 1.4 to 5.6%.[6-10] Two small studies suggest an increased risk of placental abruption after laser therapy with the Solomon technique of 7.9 and 14.0% compared to 1.4 and 3.1%. [9, 10]

The objective of this study is to compare the rate of placental abruption in TTTS treated with laser surgery either with the Selective or the Solomon laser technique, and to identify potential risk factors in a large consecutive cohort treated at two Fetal Therapy centers in China and The Netherlands.

METHODS

We included all consecutive TTTS-cases treated with fetoscopic laser surgery in the Leiden University Medical Center (LUMC), The Netherlands and in the Shanghai First Maternity and Infant Hospital (SFMIH), China, between January 2002 and January 2020. The SFMIH started with fetoscopy in 2011, and therefore, all cases from this center were treated between January 2011 and January 2020. Cases were excluded when the information on the delivery or used laser technique was not available or when laser therapy was not feasible. Due to geographic differences between the Netherlands and China, we included in China only pregnancies treated and delivered in the SFMIH. In the Netherlands we included all pregnancies treated and delivered in the LUMC or in a referring partner center, if sufficient details of delivery were available. The Research Ethics Board of both participating centers approved the study protocol of this retrospective study.

Fetoscopic laser surgery was performed using a 1.0, 1.3, 2.0 or 3.3 mm fetoscope (Karl Storz, Tuttlingen, Germany) with a cannula of 8 or 10 French and a 400 or 600 µm laser fiber connected to a diode or Nd:YAG laser device (Dornier MedTech, Wessling, Germany). The laser procedure was followed by draining the excessive amniotic fluid to the deepest pocket of 6cm. [2] In the LUMC the Selective technique was performed from 2002 to 2012 and the Solomon technique from 2007 to 2020. In the overlapping period from 2007 to 2012, both techniques were performed as this center first conducted a pilot study and then initiated the Solomon trial, comparing the two laser techniques. In the SFMIH the Selective technique was performed between 2011 and 2015, and the Solomon technique between 2015 and 2019. From ultrasound records and discharge letters we collected the following variables: TTTS stage [11], placental location, gestational age at laser (in weeks), laser technique, energy use (in Joules), maximum power setting (in Watt), duration of the fetoscopy (in minutes), gestational age at birth (in weeks), signs of placental abruption, birth weight (in grams), fetal demise, neonatal survival (survival beyond 28 days after birth) and severe cerebral injury defined as periventricular leukomalacia ≥ grade 2, intraventricular hemorrhage ≥ grade 3, ventricular dilatation ≥ 97th percentile, arterial or venous infarction, porencephalic or parenchymal cysts or other severe cerebral lesions. [12, 13] Two researchers assessed all cases to classify placental abruption. The diagnosis of placental abruption was based on the diagnosis of the obstetrician in the medical record. When the diagnosis of placental abruption was not registered in the medical record by the obstetrician, placental abruption was defined based on two clinical observations, an antenatal and a placental/intraoperative observation. Antenatal observations included: excessive vaginal bleeding, severe abdominal pain, uterine hypertonicity, fetal distress, maternal clotting disorder based on consumption coagulopathy or signs of maternal shock. Placental or intraoperative observations were defined as one of the following:

retroplacental hemorrhage on ultrasound, indentation of the placental surface or an unusual amount of clots at placental examination, bloody amniotic fluid, couvelaire uterus or a detached placenta in the setting of caesarean section. Two researchers assessed all cases to classify if the aforementioned criteria were met (P.J.C.K and F.S.).

The primary outcome was the rate of placental abruption after the Selective laser technique (Selective group) compared to the Solomon technique (Solomon group). Secondary outcomes were the perinatal outcomes of placental abruption cases, the influence of intraoperative conditions as gestational age, energy used and TTTS stage, on the risk of placental abruption and the rate of placental abruption over time.

Statistical analysis

Proportions of laser technique and characteristics were analyzed using a χ^2 test or a Fisher's exact test. An association between laser technique and continuous variables was analyzed with a unpaired t-test or a Mann-Whitney U test, according to the distribution of data. Potential risk factors for placental abruption were explored using a univariate logistic regression. The relation between placental abruption and neonatal outcome variables was analyzed using a generalized estimating equation as we considered data of co-twins not independent. The rate of placental abruption over time was compared over the years with a Mantel-Haenszel test for trend. A *p*-value below 0.05 was interpreted as statistically significant. Variables that proved significant in the univariate test were analyzed in the multivariate logistic regression or generalized estimating equation. Statistical analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

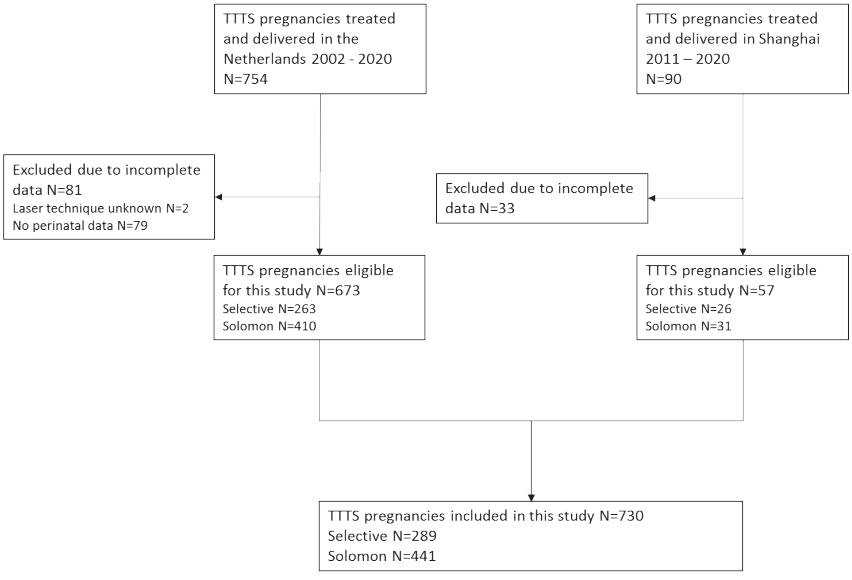

Figure 1. Flow diagram of the study population

RESULTS

Between March 2002 and January 2020, 754 pregnancies treated in The Netherlands were eligible for this study (shown in Figure 1). Perinatal data were missing for 81 pregnancies, mostly from early years and when delivery took place in referring centers. In total, 673 pregnancies were included in this study of which 9 dichorionic triplets and 4 monochorionic triplets. In Shanghai, 217 pregnancies were treated in SFMIH between 2011-2019, of which 57 were monitored and delivered in the hospital after the laser surgery and had complete medical records (shown in Figure 1). The overall prevalence of placental abruption was 2.7% (20/730). The rate of placental abruption in the Selective group was 1.7% (5/289) versus 3.4% (15/441) in the Solomon group (odds ratio [OR] 0.50; 95% confidence interval [CI]) 0.18-1.39; p = 0.184) (shown in Table 1).

Table 1. Characteristics of Selective and Solomon technique

	Selective technique (n = 289)	**Solomon technique (n = 441)**	**OR (95% CI)**	***p*-value**
Placental abruption	5 (2)	15 (3)	0.50 (0.18-1.39)	0.184
Laser energy (Joules)	4199 (2301-7891)[a]	4943 (3039-7881)[b]		0.123
Duration of fetoscopy (minutes)	30 (22-40)[c]	28 (20-36)[d]		**0.015**
Maximum laser power	45 (35-50)[e]	40 (30-50)[f]		**<0.001**
PPROM<32 weeks	85 (30)[g]	123 (28)	0.92 (0.67-1.28)	0.675
Perforation of intertwin membrane	57 (20)	67 (15)	0.74 (0.50-1.09)	0.131
Double survival	176 (61)	310 (71)[h]	1.59 (1.16-2.18)	**0.004**
Post-laser TAPS/ Recurrent TTTS	37 (21)[c]	24 (7)[i]	0.28 (0.16-0.49)	**<0.001**

Data is presented as n (%) or median (interquartile range), OR = Odds ratio, CI = confidence interval, PPROM= preterm premature rupture of membranes, [a]= data missing for 109 cases; [b]= data missing for 86 cases; [c]= data missing for 112 cases; [d]= data missing for 40 cases; [e]= data missing for 69 cases; [f]= data missing for 57 cases; [g]= data missing for 1 case; [h] = data missing for 6 cases; [i] = data is missing for 95 cases.

Comparing the Selective to the Solomon technique, maximum power use appeared significantly higher and the duration of fetoscopy significantly longer when the Selective technique was used, 45 W (IQR 35-50) compared to 40 W (IQR 30-50) (p < 0.001) and 30 min (IQR 22-40) and 28 min (IQR 20-36; p = 0.015) respectively. However, maximum power use and duration of fetoscopy were not associated with placental abruption. The median maximum used power was 45.0 W (IQR 30.0-50.0) in placental abruption cases and 40.0 W (IQR 35.0-50.0) in the group with no placental abruption (OR 0.98 95% CI; 0.94-1.02, p = 0.331) (shown in Table 2). Duration of fetoscopy was

comparable between the groups with and without placental abruption, respectively 30.0 min (IQR 24.0-36.0) in the group with placental abruption and 30.0 min (IQR 20.0-39.0) in the group without placental abruption (OR 1.01 95% CI; 0.98-1.04, p = 0.401). Information on used laser energy was available for only 535 cases, due to inconsequent reports of energy use in surgery records (shown in Table 2). The median energy use was 3567 J (IQR 1822-5809) in abruption cases and 4781 J (IQR 2780-7948) in the cases without placental abruption (p = 0.075). Placental location, gestational age at laser and TTTS stage were not different between the cases with and without placental abruption. PPROM before 32 weeks gestation was not associated with placental abruption and occurred in 25% (5/20) of placental abruption cases versus 29% (203/710) overall (p = 0.723).

Table 2. Characteristics of placental abruption cases

	Placental abruption (n = 20)	**No placental abruption (n = 710)**	**OR (95% CI)**	***p*-value**
GA at laser (weeks)	19.0 (16.7-20.6)	20.0 (17.7-22.9)	0.89 (0.77-1.03)	0.124
Placenta located anterior	10 (50)	272 (38)	0.62 (0.26-1.51)	0.296
Quintero stage 1	2 (10)	93 (13)	reference	
2	7 (35)	239 (34)	1.36 (0.28-6.68)	0.703
3	11 (55)	344 (48)	1.49 (0.32-6.83)	0.610
4	0 (0)	34 (5)		0.998
Solomon technique	15 (75)	426 (60)	2.00 (0.72-5.56)	0.184
Selective technique	5 (25)	284 (40)	reference	
Energy use (Joules)	3567 (1822-5809)[a]	4781 (2780-7948)[b]	0.85 (0.71-1.02)	0.075
Maximum power use (Watt)	45.0 (30.0-50.0)	40.0 (35.0-50.0)	0.98 (0.94-1.02)	0.331
Scopytime (minutes)	30.0 (24.0-36.0)[c]	30.0 (20.0-39.0)[d]	1.01 (0.98-1.04)	0.403
PPROM < 32 weeks	5 (25)	203 (29)[e]	0.83 (0.30-2.32)	0.723

Data is presented as n (%) or median (interquartile range), OR = Odds ratio, CI = confidence interval, GA = gestational age, PPROM = preterm premature rupture of membranes; [a] = data missing for 4 cases; [b] = data is missing for 191 cases; [c] = data is missing for 3 cases; [d] = data is missing for 149 cases; [e] = data is missing for 1 case

The Solomon technique was associated with a decreased rate of recurrent TTTS or post laser twin anemia polycythemia sequence (OR 0.28; 95% CI 0.16-0.49; $p < 0.001$) and an higher double survival rate 71% (310/441) compared to 61% (176/289) ($p = 0.004$) (shown in Table 1). Pregnancies complicated by placental abruption delivered at an earlier gestation, 28.5 (IQR 27.0-31.8) weeks compared to 32.0 (IQR 29.0-35.0) weeks (OR 0.12; 95% CI 0.03-0.49, $p = 0.003$) (shown in Table 3). Severe cerebral injury was detected in 6 of 32 (19%) surviving children after placental abruption, compared to 50 of 1048 (5%) surviving children in the group without placental abruption (OR 4.56; 95% CI 1.67-12.45, $p = 0.003$). In multivariate analysis, correcting for gestational age at birth, severe cerebral injury was not associated with placental abruption ($p = 0.190$).

When the prevalence of placental abruption was compared between time cohorts of five years (2002-2006, 2007-2011, 2012-2016, 2017-2019), an increasing prevalence was observed from 1.5 (2/131) to 6.1% (7/114) ($p = 0.06$). Double survival rates increased from 56 to 73% ($p = 0.012$).

Table 3. Perinatal outcome in cases with placental abruption

	Placental abruption (n = 40 infants)	**No placental abruption (n = 1424 infants)**	**OR (95% CI)**	***p*-value**
GA at birth (weeks)	28.5 (27.0-31.8)	32.0 (29.0-35.0)[a]	0.12 (0.03-0.49)	**0.003**
Fetal demise	5 (13)	276 (19)	0.56 (0.19-1.67)	0.297
Neonatal mortality	3 (9)[b]	46 (4)[c]	2.33 (0.72-7.50)	0.155
Severe cerebral injury[d]	6 (19)[e]	50 (5)[f]	4.56 (1.67-12.45)	**0.003**
Survival beyond 28 days without cerebral injury	24 (65)[g]	985 (73)[h]	1.49 (0.70-3.21)	0.305

Data is presented as n (%) or median (interquartile range), OR = Odds ratio, CI = confidence interval, GA = gestational age; [a] = data missing for 20 cases; [b] = data missing for 2 cases; [c] = data missing for 8 cases; [d] = defined as PVL ≥ grade 2, IVH ≥ grade 3, ventricular dilatation, arterial or venous infarction, other severe cerebral injury; [e] = data missing for 3 cases; [f] = data missing for 100 cases; [g] = data is missing for 3 cases; [h] = data is missing for 81 cases

DISCUSSION

We report placental abruption in the largest cohort of TTTS pregnancies treated with fetoscopic laser surgery, to date. The prevalence of this intrauterine complication is 2.7%. We found no significant increased risk of placental abruption in the Solomon group compared to the Selective group.

A recent small study by Lanna et al. reported placental abruption in 3.1% (9/287) of pregnancies treated with the Selective technique compared to 14.0% (12/86) in the Solomon technique ($p < 0.001$). [10] Concordant with these results, Baschat et al. reported placental abruption in 1.4% (1/71) of TTTS treated with the Selective technique, compared to 7.9% (6/76) in pregnancies treated with the Solomon technique. [9] Both studies have a small sample size and Baschat et al. did not specify their criteria for placental abruption. An association between placental abruption and the Solomon technique was not observed in our study, although placental abruption was more frequently diagnosed in recent years, when the Solomon technique was used. In the period where both techniques were used, no difference in placental abruption was detected. In the previously mentioned studies, the two laser techniques were performed subsequently; the Solomon technique was used in the more recent years. The higher prevalence of placental abruption in the Solomon group could therefore merely be an increasing prevalence of placental abruption over time. In addition we found an increase in double survivors over the years. As more twins are carried for a longer duration of pregnancy, more effort is required of the placenta even as the resistance of the decidual layer weakens. Better short-term survival rates directly after laser surgery could therefore lead to an increased prevalence of later complications. Following a similar course as the increasing PPROM rates described by the study of Stirnemann et al, other explanations of this increasing prevalence over time could be either a relation to an overall increasing prevalence of placental abruption in the general population, as described by Tikkanen et al in many countries. [14, 15] Or, the increased prevalence is a result of increased awareness, advancement of ultrasound and pathology techniques and improved electronic patient records. Especially the increasing availability of clinical details in patient records, could lead to information bias in retrospective studies.

The prevalence of placental abruption in the overall population ranges from 0.33 to 1.2% according to a very large study in the United States, Canada, Denmark, Sweden, Spain, Norway and Finland.[4] Smaller studies in the Netherlands and China report a rate of placental abruption of respectively 0.22 and 0.57%. [16, 17] Salihu et al reported an increased risk of placental abruption in twin (1.2%) and triplet (1.6%) pregnancies compared to singletons (0.6%) in the United States. [3] In two previous studies in TTTS treated with Selective laser surgery, placental abruption was reported in 1.7-2.2%. [7, 8]

Senat et al reported placental abruption in 1.4% of TTTS pregnancies treated with laser and in 2.9% of TTTS pregnancies treated with amnioreduction. [6] The study by Lanna et al reported placental abruption in 5.6% (21/373) of TTTS pregnancies treated with laser therapy versus 1.2% (3/243) in uncomplicated monochorionic twins, excluding selective intrauterine growth restriction. [10] The rate of placental abruption in this study falls in the range of the previously reported rates of 1.4-5.6% in TTTS treated with laser surgery. This percentage seems slightly higher than the rate in uncomplicated multiple gestations of 1.2-1.6%. If this higher rate is a direct result of the disease or the treatment remains unclear as laser therapy is the preferred treatment and the study of Senat et al is the only study reporting the rate of placental abruption in TTTS treated otherwise.

If a causal relation exists between TTTS or fetoscopic laser surgery and placental abruption remains, thus, unclear. It is obvious that laser surgery does cause damage to the placental surface. Studies of placental histology after laser surgery are scarce, leading to little knowledge about the tissue damage caused by the laser and the deepness of coagulation in the chorionic layers. Akkermans et al reported an association between the severity of placental damage and PPROM and early delivery. [18] In this study, severe placental damage was associated with a higher total amount of energy use and a lower power setting. A relation between placental damage and placental abruption was not reported. In our study, no association was observed between placental abruption and used laser energy or power settings. The severity of placental damage was not included in this study. Nevertheless, a relation between placental damage and placental abruption possibly exists. To minimalize placental damage, a more superficial coagulation of anastomosis could benefit the placental condition. As hypothesized by Akkermans et al, high power settings could lead to more effective coagulation and consequently, a lower total energy use. Nevertheless, more placenta histology studies are necessary to assess placental damage after laser surgery in relation to complications. This knowledge could help to establish strategies to avoid such complications.

Another remarkable finding is the increased duration of fetoscopy in the Selective technique. This difference could possibly be attributed to a learning curve effect as described by Peeters et al. [19] Duration of fetoscopy was not associated with placental abruption.

In this study, placental abruption was associated with preterm birth resulting in an increased risk of severe cerebral injury. No risk factors for placental abruption were found. Continued research is necessary to understand more about placental abruption in TTTS. Especially, an uniform definition of placental abruption, detailed examination of the placental damage and standardized prospective recording of data of complications and outcome could improve the knowledge of placental abruption in TTTS.

Strengths and limitations

A limitation of this study is the retrospective nature. As placental abruption is a clinical diagnosis, it is most reliably diagnosed by the obstetrician assisting the delivery. Possibly, in some cases placental abruption may have been misdiagnosed in this study leading to an under- or overestimation. The design of the study made it impossible to completely blind the researchers that collected the data and classified the cases as placental abruption for the used laser technique. In addition, over the years patient records have become more extensive due to advancement in electronic patient systems and better communication with referring centers. This might have led to underdiagnosing in the earlier years in the Selective group. Another limitation is the lack of internationally agreed criteria to diagnose placental abruption, which hampers comparison with other studies. Our definition rests on the opinion of the treating obstetricians as we believe placental abruption is primarily a clinical diagnosis. A previous study reported wide discrepancies between pathological diagnosis of placental abruption and clinical observations. [20] Another limitation is the lack of data on amnion fluid reduction (duration and amount). During laser surgery amniotic fluid of the recipient's polyhydramniotic sac is routinely drained causing a decrease in uterus size. As a consequence the available surface area of decidua underneath the placenta shrinks, which can potentially lead to placental abruption. A small study in polyhydramnios in singleton pregnancies reported no difference in placental abruption between the group treated with amnioreduction and the untreated group. [21] However, a large study in TTTS treated with laser surgery is necessary to identify whether a possible association between amnioreduction and placental abruption in this group exists. Nevertheless, we present the largest cohort study of placental abruption in TTTS treated with fetoscopic laser surgery to date.

Conclusions

The rate of placental abruption in TTTS pregnancies treated with fetoscopic laser surgery was 2.7% and was not associated with the type of laser technique (Selective versus Solomon technique). We could not identify any risk factors for placental abruption. Continued research in TTTS is necessary to understand potential complications. Therefore we recommend standardized, prospective recording of complications and outcome after fetoscopy.

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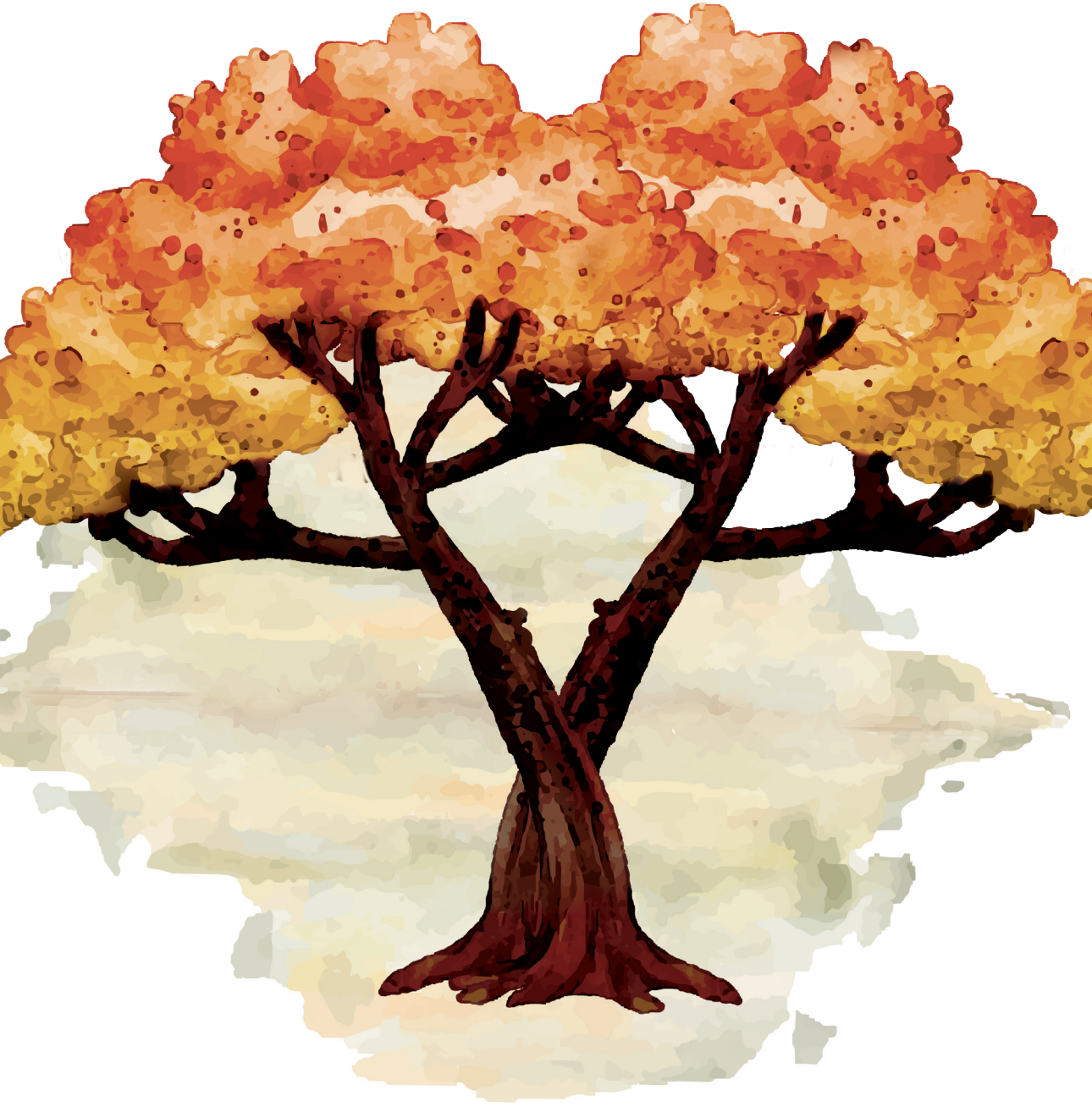

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Chapter 3

Prevalence, risk factors and outcome of postprocedural amniotic band syndrome after fetoscopic laser surgery in twin-twin transfusion syndrome: a large single center case series

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ABSTRACT

Background: Postprocedural amniotic band syndrome is a condition that is associated with intrauterine interventions, and it is characterized by a constriction of the limbs or umbilical cord by fibrous strands, leading to edema, amputation, and/or fetal demise.

Objective: To evaluate the prevalence of, risk factors for and the outcome of postprocedural amniotic band syndrome after fetoscopic laser surgery in twin-twin transfusion syndrome cases.

Methods: All consecutive cases of twin-twin transfusion syndrome treated with fetoscopic laser coagulation of the vascular anastomoses at our center between January 2002 and March 2019 were included in the study. The occurrence of postprocedural amniotic band syndrome in these cases was recorded, and the potential risk factors were analyzed.

Results: Postprocedural amniotic band syndrome was detected, at birth, in 2.2% (15/672) of twin-twin transfusion syndrome cases treated with fetoscopic laser surgery, in both the recipients (10/15, 67%) and the donors (5/15, 33%). Postprocedural amniotic band syndrome primarily affected the lower extremities (11/15, 73%) and, less frequently, the upper extremities (2/15, 13%), both the upper and lower extremities (1/15, 7%), or the umbilical cord (1/15, 7%). Postprocedural amniotic band syndrome led to the amputation of toes in 5 of 15 cases (33%) and resulted in fetal demise because of constriction of the umbilical cord in one case (7%). The independent risk factors identified for postprocedural amniotic band syndrome were lower gestational age at laser surgery (odds ratio per week 1.43; 95% confidence interval 1.12-1.79, $p = 0.003$) and the presence of postprocedural chorioamniotic membrane separation on antenatal ultrasound examination (odds ratio 41.66, 95% confidence interval 5.44-319.25, $p < 0.001$).

Conclusion: The prevalence of postprocedural amniotic band syndrome is low, but, when present, it may lead to severe consequences, with amputation of extremities or fetal demise occurring in more than one-third of the cases. Lower gestational age at the time of laser therapy and chorioamniotic membrane separation are independent risk factors for the postprocedural amniotic band syndrome.

INTRODUCTION

Amniotic band syndrome is a fetal condition in which strands of the amniotic membrane encircle digits, limbs or the umbilical cord of a fetus, leading to edema, hypoplasia, amputation, or even fetal death. The reported prevalence of amniotic band syndrome ranges from 1:1200 to 1:15000 of livebirths. [1] Postprocedural amniotic band syndrome (PABS) is a rare iatrogenic complication that is associated with invasive intrauterine procedures such as amniocentesis, amnioreduction, tracheal occlusion for congenital diaphragmatic hernia, thoracoamniotic shunt placement and fetoscopic laser therapy in twin-twin transfusion syndrome (TTTS). [2-7] Because this is a rare complication, the amount of data available on PABS in TTTS cases treated with laser therapy is limited, and the identification of possible risk factors is based on a small number of series or casuistic reports. Several potential risk factors for PABS in TTTS have been described and include preterm premature rupture of membranes (PPROM) and inadvertent septostomy. [7,8]

The aims of this study were to describe the occurrence of PABS after fetoscopic laser surgery from a consecutive cohort of TTTS cases at our center, with specific focus on the prevalence, risk factors and outcome, and to summarize the findings reported in the literature on PABS.

METHODS

All consecutive cases of TTTS treated with fetoscopic laser surgery at the Leiden University Medical Center (LUMC) between January 2002 and March 2019 were included in this cohort study. Patients' medical charts and ultrasound findings were reviewed for the presence of PABS. Some of the data on PABS in this cohort have already been reported in a previous publication in 2014. [9] The LUMC is the national referral center for fetal therapy in the Netherlands. The study was approved by the Medical Ethics Committee of the LUMC. We confirmed the presence of PABS either sonographically by the detection of endangered blood flow or soft-tissue changes such as constriction, edema or amputation, or postnatally by the presence of constriction rings, edema or amputation. In the case of autoamputation, PABS was confirmed when an encircling band was present on the affected body appendage.

We excluded cases with incomplete medical records regarding delivery and neonatal outcome. The following variables were collected from ultrasound records, operation reports and discharge letters: TTTS stage, gestational age at laser treatment, laser technique used (Selective or Solomon), procedure-related rupture of the intertwin membrane leading to iatrogenic monoamnionicity, PPROM before 32 weeks of gestation, ultrasound reports of chorioamniotic membrane separation, limb edema, disrupted blood flow to the limbs or in the umbilical cord and signs

of limb amputation, presence and location of the amniotic bands (detected either antenatally by ultrasound or after delivery), donor or recipient status of the fetus, intra-uterine fetal demise (IUFD), and gestational age at birth. [9] We defined iatrogenic monoamnionicity either as a perforation of the intertwin membrane detected during the laser procedure or at ultrasound examinations during follow-up, or as cord entanglement observed during an antenatal ultrasound or at delivery. We defined chorioamniotic membrane separation as a separation of the amnion and chorion observed in at least 1 postprocedural ultrasound examination.

TTTS was defined according to the Eurofoetus criteria for amniotic fluid discordance: polyhydramnios in the recipient sac, identified by a deepest vertical pocket (DVP) of at least 8 cm before 20 weeks of gestation and at least 10 cm after 20 weeks of gestation, and oligohydramnios in the donor sac with a DVP of maximum 2 cm at any gestational age. [10] The stages of TTTS were determined according to the internationally accepted criteria. [11] Fetoscopic laser surgery was performed using a 1.0 mm, 1.3 mm or 2.0 mm fetoscope (Karl Storz, Tuttlingen, Germany) and an 8 or 10 French cannula with a 400-µm laser fiber (Dornier MedTech, Wessling, Germany or Tobrix Professional Medical Equipment, Waalre, The Netherlands) connected to a diode or Nd:YAG laser device (Dornier MedTech, Wessling, Germany).

A search of the literature up to December 2019 was carried out in PubMed, using the Medical Subject Heading terms 'amniotic band syndrome' and 'fetofetal transfusion'. Articles were included when they were published in English, reported cases of amniotic bands that were present after laser surgery for TTTS, and included sufficient clinical details such as gestational age at laser surgery, gestational age at birth and location of the amniotic bands. Articles with insufficient clinical details or TTTS cases treated with other interventions were excluded. The overall median gestational age at the time of laser treatment and at the time of birth, the proclivity of PABS to affect one fetus over the other (donor vs recipient), the fetal limbs most often affected, and the possible risk factors were determined by combining the data from the cases at our center and from the cases reported in literature.

Continuous variables were reported as the mean ± standard deviation or as the median (interquartile range [IQR]). A χ^2 test or Fisher exact test was used to compare proportions. The potential risk factors for amniotic band syndrome were analyzed using logistic regression analysis, and the variables from a univariate analysis with a p value less than 0.05 were included in the multivariate analysis. The following risk factors were included in the risk factor analysis: gestational age at laser at laser treatment, PPROM before 32 weeks of gestation, iatrogenic monoamnionicity and postprocedural chorioamniotic membrane separation. The correlation was calculated using a Pearson or Spearman rank correlation depending on the distribution of the

continuous data. Statistical analysis was performed using SPSS Statistics version 25 (IBM SPSS Statistics for Windows, Version 25.0, IBM Corp, Armonk, NY).

RESULTS

Between January 2002 and March 2019, 733 pregnancies treated with fetoscopic laser therapy for TTTS were eligible for inclusion in the study, with 381 (55%) of these delivered at our center and 311 (45%) delivered at the referring center. In total, 61 (8%) cases, all of which were outborn, were excluded from the study because of incomplete data, and 672 cases (92%) were included in the study. A total of 15 cases (2.2%) of PABS were identified, of which 33% (5/15) occurred in the donors and 67% (10/15) in the recipients (p = 0.21). All PABS cases were detected only at birth and were not identified during antenatal ultrasound evaluations. In some cases, with extensive chorioamniotic membrane separation, the presence of amniotic bands was suspected, but this was, however, not confirmed antenatally. The characteristics of the affected cases are summarized in table 1. Amniotic bands were located around the upper extremities in 13% (2/15) of the cases, around the lower extremities in 73% (11/15) of the cases, around both the upper and lower extremities in 1 case (7%), and around the umbilical cord in 1 case (7%). In this last case (case 10), constriction of the cord by the amniotic band led to fetal demise (Figure 1). Amputation of limbs occurred in 5 of 15 cases (33%), and all involved the toes.

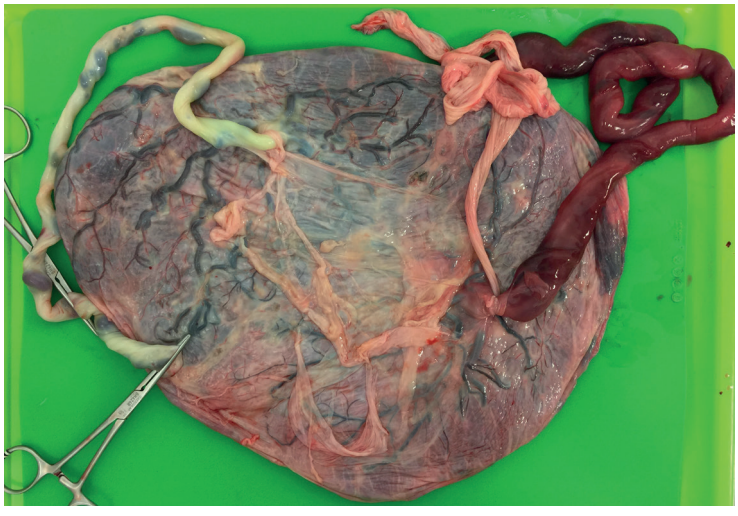

Figure 1. Amniotic band constricting umbilical cord of donor, leading to fetal demise

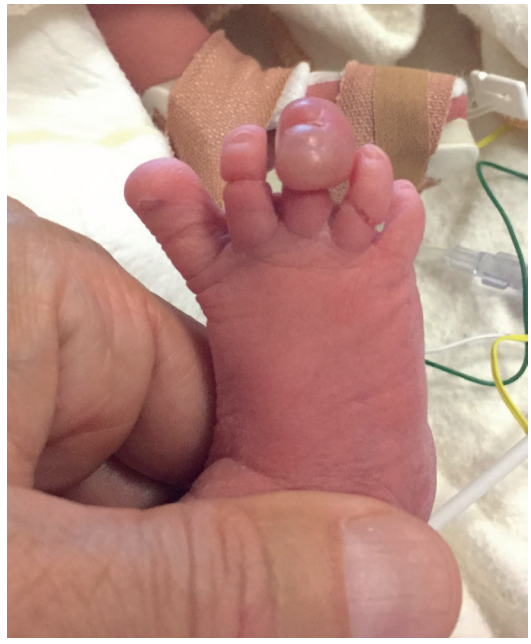

Figure 2. Right foot of a recipient with amniotic bands constricting digits II, III, and IV

The risk factors for PABS are summarized in Table 2. The median gestational age at laser surgery in the group with PABS was lower compared with the group without PABS, which was determined to be 17.0 (IQR, 16.2-17.9) weeks and 20.0 (IQR, 17.7-22.0) weeks, respectively (odds ratio [OR] per week, 1.43; 95% confidence interval [CI], 1.12 – 1.79; $p = 0.003$). In 14 of 15 (93%) cases of PABS, chorioamniotic membrane separation was observed during antenatal ultrasound examinations compared with only 165 of 656 (25%) in the group without PABS (OR, 41.66; 95% CI, 5.44-319.25; $p < 0.001$). In 7 of 14 (50%) of our PABS cases with chorioamniotic membrane separation, the chorioamniotic membrane separation was detected in both sacs. In 6 of 14 cases (43%) the chorioamniotic membrane separation was detected in the sac of the affected twin, and in 1 of 14 cases (7%), it was detected in the sac of the unaffected twin. We found no difference in PPROM or iatrogenic monoamnionicity between the groups with or without PABS. Chorioamniotic membrane separation was correlated to early gestational age (in weeks) at laser surgery (correlation coefficient *r*, -0.16; $p < 0.001$). However, in the multivariate analysis, both chorioamniotic membrane separation and lower gestational age at laser surgery were independently associated with PABS (OR 32.90; 95% CI, 4.25-254.54; $p = 0.001$ and OR per week, 1.30; 95% CI, 1.03-1.61; $p = 0.025$, respectively).

Table 1. Detailed information of PABS cases from our center

Case	Affected fetus	Affected body part	GA at laser (weeks)	GA at birth (weeks)	Laser technique	IUFD	PPROM	Iatrogenic MA	Chorioamniotic membrane separation
1	recipient	left foot, digit I-V	16.4	22.6	Selective	both*	unknown	yes	yes
2	donor	left lower leg, left foot digit II, III, right foot digit II-V	15.0	29.7	Selective	no	yes	no	yes
3	recipient	right upper arm	18.0	27.3	Solomon	no	no	no	yes
4	donor	"toes"	17.7	33.6	Solomon	recipient	no	no	yes
5	recipient	right hand digit II	16.3	30.6	Solomon	no	yes	yes	yes
6	recipient	left foot digit I-IV, right foot digit I, II, IV	17.0	33.1	Solomon	no	no	no	yes
7	recipient	both feet digit II-IV	17.9	29.3	Selective	no	no	no	yes
8	donor	left foot digit I-III, right foot digit I-IV	17.0	35.9	Selective	no	no	no	yes
9	recipient	right foot digit II-IV	17.0	36.4	Solomon	no	no	no	yes
10	donor	umbilical cord	22.6	34.2	Solomon	donor	no	no	yes
11	recipient	left ankle	23.0	36.0	Solomon	no	no	no	yes
12	recipient	right foot digit II-IV	16.9	36.3	Solomon	no	no	no	yes
13	donor	right foot digit II-III	15.0	38.6	Selective	no	no	no	no
14	recipient	right ankle	16.0	30.6	Solomon	no	no	yes	yes
15	recipient	right foot digit III-IV, right hand digit I, left arm	16.2	36.4	Solomon	no	unknown	no	yes
	recipient 67%	**upper limbs 13% both 7%** **lower limbs 73% other 7%**	**17.0 (16.2-17.9)**	**33.6 (29.7-36.3)**		**20%**	**15%**	**20%**	**93%**

Data are presented as median (interquartile range) or percentages. PABS=post-procedural amniotic band syndrome, GA=gestational age, IUFD=intrauterine fetal demise, PPROM=preterm premature rupture of the membranes, MA= monoamnionicity, *no bands on the umbilical cords

Table 2. Risk factors for PABS

Characteristics	Amniotic band (n = 15)	No amniotic band (n = 657)	Univariate OR (95%CI)	*p*-value	Multivariate OR (95% CI)	*p*-value
GA at laser (weeks)	17.0 (16.2-17.9)	20.0 (17.7-22.0)	1.43 (1.12-1.79)	**0.003**	1.30 (1.03-1.61)	0.025
PPROM (<32weeks)	2/13[a] (15)	195/654[b] (30)	0.43 (0.09-1.95)	0.273		
Iatrogenic monoamnionicity	3/15 (20)	115/654[b] (18)	0.85 (0.24-3.07)	0.808		
Chorioamniotic membrane separation	14/15 (93)	165/656[c] (25)	41.66 (5.44-319.25)	**<0.001**	32.90 (4.25-254.54)	0.001

Data are presented as median (interquartile range) or n/N (%). PABS=post-procedural amniotic band syndrome , OR= odds ratio, CI= confidence interval, GA= gestational age, PPROM=preterm premature rupture of the membranes, [a]= data missing for 2 cases, [b] = data missing for 3 cases, [c] = data missing for 1 case

Our literature search on the occurrence of PABS after laser surgery as treatment for TTTS yielded a total of 24 articles. Eleven articles did not meet our inclusion criteria. In addition, 5 articles were excluded; 3 of these articles reported on PABS cases without clinical details, and 2 reported on PABS in TTTS cases that were treated with other interventions. [4,8,12-14] Eight articles were eligible, yielding a total of 20 cases of PABS with clinical details in 18 pregnancies; in 2 of the pregnancies both the donor and recipient were affected by PABS. [7,15-21] Adding the cases reported in our series yielded a total of 35 PABS cases in 33 pregnancies. When we combined the cases in the literature (summarized in Table 3) with those in our series, most PABS cases seemed to occur in the recipients (27/35, 77%). PABS involved mostly the lower extremities (19/35, 54%) and, to a lesser extent, the upper extremities (8/35, 23%), both the upper and lower extremities (4/35, 11%), or the umbilical cord (5/35, 14%) (Figure 2). PABS led to amputation in 11 of 34 cases (32%), which only involved the fingers (2/11) or toes (9/11). Fetal demise occurred in all cases (5/5) in which amniotic strands were encircling the umbilical cord. Iatrogenic monoamnionicity was present in 5 of 23 (22%) of the cases with amniotic bands, whereas 9 of 29 (31%) cases had PPROM.

Table 3. Overview of PABS cases reported in the literature

Author, year	Case	Affected fetus	Affected body part	GA at laser (weeks)	GA at birth (weeks)	Timing of detection	IUFD	PPROM	Iatrogenic MA	Chorioamniotic membrane separation
Winer et al, 2008 [7]	1	recipient	both legs	21	26	2 cases of 8	donor	no	NA	NA
	2	recipient	left arm	23	34	detected	donor	no	NA	NA
	3	recipient	right leg	16	33.5	antenatally	donor	yes	NA	NA
	4	recipient	right leg	21	30		donor	yes	NA	NA
	5	recipient	right foot	19	25.5		donor	yes	NA	NA
	6	recipient	left arm	19	33		donor	no	NA	NA
	7	recipient	left arm	20	30		no	yes	NA	NA
	8	recipient	right hand	16	31		donor	yes	NA	NA
Kuranaratne et al, 2011 [15]	9	recipient	left foot dig I and II, right foot dig I to III	17	29	postnatal	no	NA	NA	NA
Rodrigues et al, 2012 [16]	10	donor	left arm, digits left and right feet	16.4	39.7	postnatal	recipient	no	possible	NA
Shamshirsaz et al, 2012 [17]	11	recipient	left foot dig I to III	16.6	33.1	postnatal	no	no	no	NA
Ting et al, 2016 [18]	12[a]	recipient	right arm, left leg umbilical cord	18.9	29.3	antenatal	donor	no	yes	NA
	13[a]	donor				postnatal				
	14	recipient	left hand, dig I to III	18.3	26.1	postnatal	both	no	no	no
Lafitte et al, 2017 [19]	15	recipient	face, umbilical cord	21.1	27.6	postnatal	recipient	yes	no	yes
	16	recipient	face, right hand dig I to IV, umbilical cord	16.1	30.7	postnatal	recipient	no	no	yes
Nassr et al, 2019 [20]	17[a]	recipient	right arm, ankle umbilical cord	18.0	27.0	antenatal	donor	yes	yes[b]	yes
	18[a]	donor				antenatal				
Li et al, 2019 [21]	19	recipient	right foot, dig I	NA	NA	postnatal	donor	NA	no	NA
	20	recipient	right leg	NA	NA	postnatal	no	NA	no	NA
Summary	**20**	**recipient 85%**		**18.3 (16.5-20.5)**	**30.0 (27.0-33.1)**	**antenatal detection 25%**	**78% (14/18)**	**44% (7/16)**	**25% (2/8)**	**75% (3/4)**
Our cohort, 2019	**15**	**recipient 67%**		**17.0 (16.2-17.9)**	**33.4 (29.7-36.3)**	**antenatal 0%**	**20% (3/15)**	**15% (2/13)**	**20% (3/15)**	**93% (14/15)**
Total[c]	**35**	**recipient 77%**		**17.4 (16.3-19.0)**	**30.7 (28.0-34.2)**	**antenatal 14%**	**53% (17/32)**	**31% (9/29)**	**22% (5/23)**	**89% (17/19)**

Data are presented as median (interquartile range) or % (n/N). PABS=post-procedural amniotic band syndrome, GA=gestational age, IUFD = intra-uterine fetal demise, PPROM = preterm premature rupture of membranes, MA = monoamnionicity, NA = not available, [a] = case 12 & 13 and case 17 & 18 are of the same twin pairs, [b] = after second procedure to release PABS, [c] = summary of literature and present cohort

DISCUSSION

Principal findings

We report here on the largest case series of PABS occurence after fetoscopic laser surgery for the treatment of TTTS. Our findings highlight that although PABS is a rare complication with a prevalence of approximately 2%, it is associated with a high risk of amputation of fingers and toes or even fetal demise in cases of PABS wherein the umbilical cord is constricted. Although limited by the relative small sample size, risk factor analysis shows a possible association of PABS with chorioamniotic membrane separation and early gestational age at laser treatment.

Clinical implications

The prevalence of PABS in our study corroborates the results of previous studies that reported a prevalence ranging from 1.5% to 3.3%. [7-9,12] To date, 8 other smaller case series with clinical details of PABS after fetoscopic laser therapy for TTTS have been reported in the literature. [7,15-21] Adding the previously reported cases to the cases in our series yielded a total of 35 PABS cases. There were some differences between our cohort and the smaller case series reported in the literature. These differences could possibly be explained by publication bias, as the published case reports described the more severe cases of PABS, whereas milder cases often remain unpublished. In addition, the description of PPROM, perforation of the intertwin membrane, and chorioamniotic membrane separation in the literature was often incomplete, leading to underreporting bias. The true prevalence of the various risk factors is most probably higher than reported in this article.

Cruz-Martinez et al. reported an association between the rupture of the intertwin membrane and PABS ($p < 0.001$), with 50% (4/8) of PABS cases in their study being iatrogenic monoamniotic. [8] Winer et al reported an association between PPROM and PABS ($p = 0.05$), as 63% (5/8) of the PABS cases occurred in conjunction with PPROM before 33 weeks. [7] These associations were not supported by the results of our study. Instead, our findings suggested that 2 other risk factors are associated with an increased risk of PABS, namely chorioamniotic membrane separation and lower gestational age at laser surgery. As indicated in this study, chorioamniotic membrane separation was observed during prenatal ultrasound examination in 93% (14/15) of PABS cases compared with 25% (165/656) in pregnancies without PABS. The overall prevalence of chorioamniotic membrane separation reported in this study is comparable to the 18.8% prevalence found in a recent study by De Zoysa et al.[22] In addition, fetoscopic laser surgery was performed 3 weeks earlier in the group with PABS compared with the average gestational age of 20 weeks in the group without PABS. These findings suggest a possible relation between early gestational

age at laser treatment and an increased risk of chorioamniotic membrane separation leading to PABS. In general, the amniotic and chorionic membranes fuse after the first trimester, at approximately 14 weeks of gestation.[23] Hypothetically, fetoscopic intervention at an earlier gestational age may increase the risk of fetal membrane disruption, as the process of fusion is not completed, causing chorioamniotic membrane separation. The ruptured floating sheets of amnion may form strings and entrap the upper and lower extremities. In accordance with our results, Ortiz et al. and Takano et al. reported an increased risk of chorioamniotic membrane separation when fetoscopy occurred before 18 and 20 weeks of gestation, respectively (OR 2.94; 95% CI, 1.64-5.28 and OR 3.38; 95% CI, 1.44-7.93).[24,25] A possible association between chorioamniotic membrane separation and PABS after intrauterine interventions (eg, amniocentesis or fetoscopy for diaphragmatic hernia) has been hypothesized previously by Graf et al and Lewi et al.[5,26] To the best of our knowledge, this is the first study to show an association between chorioamniotic membrane separation and PABS in TTTS after laser surgery. It is important to note that causation needs to be distinguished from mere association, and our study was not designed to evaluate a possible causal association.

This study also highlights the difficulty of antenatal detection of amniotic bands because all PABS cases in our case series were only detected postnatally. Most amniotic bands in this study constricted either fingers or toes, with the arms or legs being affected only in a small number of cases. The presence of bands around fingers or toes are probably more difficult to detect sonographically than bands around an arm or a leg. This could explain why PABS in this study was not diagnosed antenatally. This is in accordance with the literature, as accurate antenatal detection was reported in only 4 cases and fetoscopic surgical intervention to release the PABS was performed in 2 cases. Timely prenatal detection of entrapped digits, limbs or umbilical cords would allow for therapeutic fetoscopic intervention to release the amniotic bands. Gueneuc et al. reported that fetoscopic amniotic band release resulted in a functional limb in 70.4% (19/27) of the cases of twins and singletons with spontaneous or PABS, based on data from their own center and from previous studies. [27] However, reintervention has to be considered carefully for every individual case because fetoscopy may also increase the risk for other complications (such as PPROM or infection), thereby affecting the survival of and complications in both twins. Of note, Winer et al reported that PABS occurred exclusively in the recipients. However in our study, PABS was detected in both donors and recipients. Increased awareness about the detection of PABS antenatally through ultrasound should therefore not focus on recipients alone.

Strengths and Limitations

The data from this study should be interpreted with caution, as bias may have been introduced because of the retrospective nature of the study and the potential risk of under- or overreporting. In addition, the limited sample size restricted the statistical analysis various risk factors. We performed an explorative multivariate risk factor analysis, although the number of cases was too small to derive reliable conclusions about causation. Nevertheless, this is the largest case series of PABS to date, and the combination of our data with the results of previous smaller series gives caregivers more reliable information on the prevalence of, risk factors for, and the outcomes of PABS after fetoscopic laser surgery for TTTS.

Conclusions

PABS is a rare but severe complication of fetoscopic laser surgery in TTTS cases that can lead to mutilations, amputations, or even fetal demise. We found that a low gestational age at laser surgery and chorioamniotic membrane separation were independently associated with an increased risk of PABS. Increased awareness and limb surveillance using ultrasound, particularly in cases with early laser surgery or chorioamniotic membrane separation, may improve antenatal detection, and possibly the likelihood of successful antenatal treatment.

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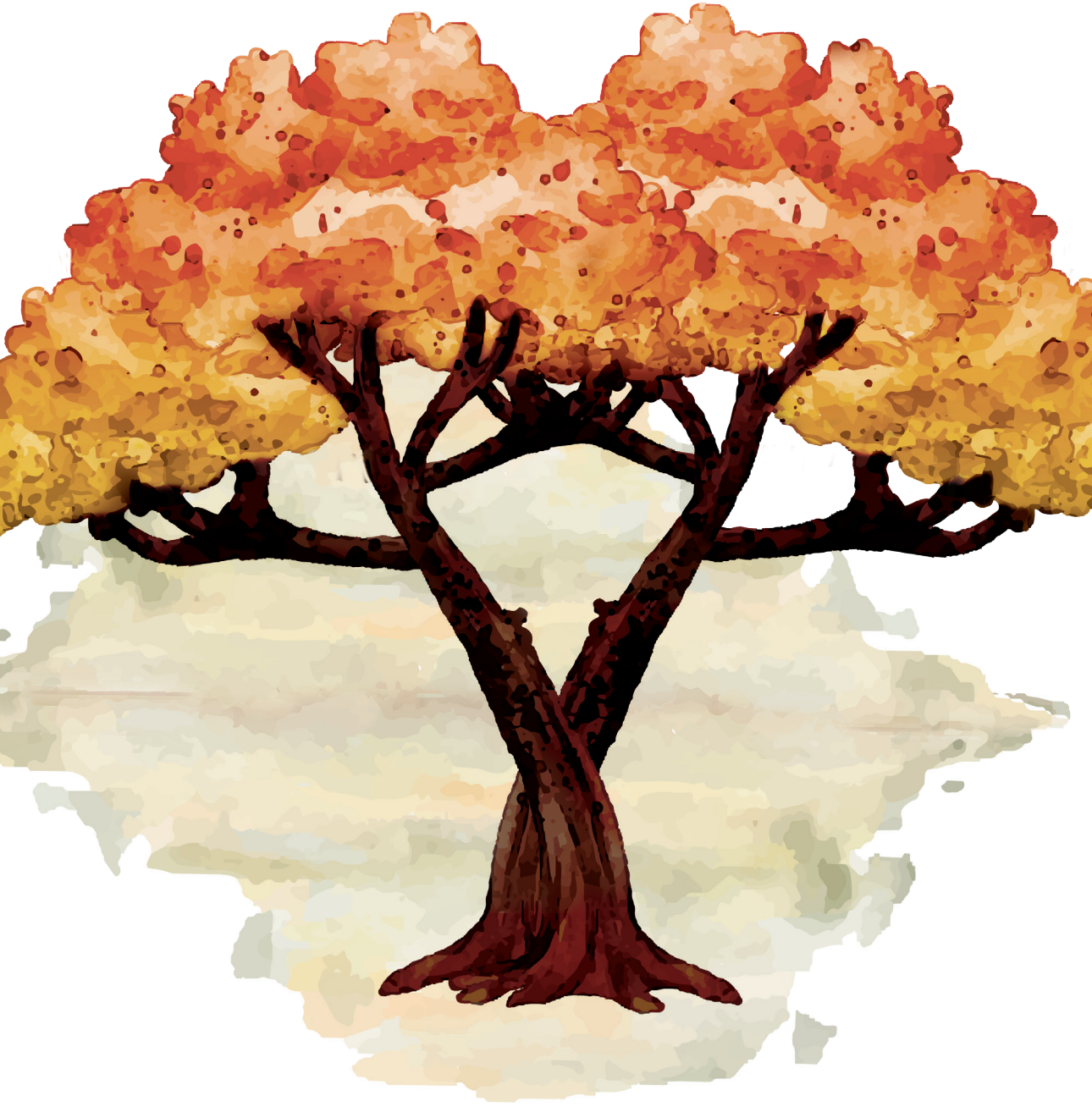

4

Chapter 4

Intertwin membrane perforation and umbilical cord entanglement after laser surgery for twin-twin transfusion syndrome: prevalence, risk factors, and outcome

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ABSTRACT

Introduction: Perforation of the intertwin membrane can occur as a complication of fetoscopic laser surgery for twin-twin transfusion syndrome (TTTS). Data on the occurrence and the risk of subsequent cord entanglement are limited. The objective of this study was to assess the prevalence, risk factors and outcome of intertwin membrane perforation, and cord entanglement after laser surgery for TTTS.

Methods: In this multicenter retrospective study, we included all TTTS pregnancies treated with laser surgery in two fetal therapy centers, Shanghai (China) and Leiden (the Netherlands) between 2002 and 2020. We evaluated the occurrence of intertwin membrane perforation and cord entanglement after laser, based on routine fortnightly ultrasound examination and investigated the risk factors and the association with adverse short- and long-term outcomes.

Results: Perforation of the intertwin membrane occurred in 118 (16%) of the 761 TTTS pregnancies treated with laser surgery and was followed by cord entanglement in 21% (25/118). Perforation of the intertwin membrane was associated with higher laser power settings, 45.8 Watt versus 42.2 Watt (p = 0.029) and a second fetal surgery procedure 17% versus 6% (p < 0.001). The group with intertwin membrane perforation had a higher rate of caesarean section (77% versus 31%, p < 0.001) and a lower gestational age at birth (30.7 versus 33.3 weeks of gestation, p < 0.001) compared to the group with an intact intertwin membrane. Severe cerebral injury occurred more often in the group with intertwin membrane perforation, 9% (17/185) versus 5% (42/930) respectively (p = 0.019). Neurodevelopmental outcome at 2 years of age was similar between the groups with and without perforation of the intertwin membrane and between the subgroups with and without cord entanglement.

Conclusion: Perforation of the intertwin membrane after laser occurred in 16% of TTTS cases treated with laser and led to cord entanglement in at least 1 in 5 cases. Intertwin membrane perforation was associated with a lower gestational age at birth and a higher rate of severe cerebral injury in surviving neonates.

INTRODUCTION

Twin-twin transfusion syndrome (TTTS) complicates 10-15% of all monochorionic-diamniotic twin gestations and is caused by an unbalanced intertwin blood flow through placental anastomoses.[1, 2] Fetoscopic laser photocoagulation of the vascular anastomoses is the only causal treatment for TTTS and results in major improvements of outcome with perinatal survival rates ranging from 70 to 90%. [3, 4] Although very effective, fetoscopic laser surgery can be associated with a number of complications.[5-8] One important complication is rupture of the intertwin amniotic membranes, creating an iatrogenic monoamniotic twin (iMAT) pregnancy. Data on the occurrence of iMAT after fetoscopic laser surgery are scarce and reported rates vary greatly from 1.3% to 20%.[6, 9-11]

One of the main risks of monoamnionicity is umbilical cord entanglement. In *spontaneous* monoamniotic twin pregnancies, umbilical cord entanglement occurs in almost all pregnancies and is the leading cause of fetal mortality.[12-15] Inpatient or outpatient fetal monitoring is often advised, starting as early as 26 weeks' gestation. An elective caesarean section is then often performed around 32-34 weeks' gestation to avoid further risks due to cord entanglement. Whether these management strategies in *spontaneous* monoamniotic twin pregnancies are also necessary for *iatrogenic* monoamniotic pregnancies is not known, as the prevalence, risk factors and outcome in iMAT with or without cord entanglement remain to be elucidated. More data are necessary for the development of scientifically based clinical management strategies for these pregnancies.

Our primary aim was to evaluate the prevalence of perforation of the intertwin membrane and subsequent cord entanglement after fetoscopic laser therapy for TTTS. Our secondary aims were to evaluate risk factors for iMAT and cord entanglement and the association with adverse short- and long-term outcomes.

METHODS

All TTTS-pregnancies treated with fetoscopic laser surgery at the Leiden University Medical Center (LUMC, the Netherlands) and the Shanghai First Maternity and Infant Hospital (SFMIH, China) between January 2002 and January 2020 were eligible for this study. The LUMC is the Dutch national referral center for fetal therapy and the SFMIH is one of the major fetal therapy centers in China. The LUMC (the Netherlands) started with fetoscopic laser surgery in August 2000, whereas the SFMIH (China) started with fetoscopy later on in 2011. We therefore included TTTS cases from the SFMIH treated between January 2011 and January 2020. We excluded spontaneous monoamniotic twins, TTTS cases with perforation of the intertwin membrane *prior* to laser surgery and cases where follow-up information after laser therapy was

incomplete. The Research Ethics Board of both participating centers approved the study protocol of this retrospective study (G20.015 and 2018yxy27).

TTTS was defined by the diagnostic criteria provided in the Eurofoetus protocols and classified according to the internationally agreed staging system.[16, 17] Fetoscopic laser surgery was performed by well-trained fetal surgeons. The operation procedure has been described in detail previously.[6, 18] In the Netherlands, the selective technique was exclusively performed from 2002 to 2007. From 2008 to 2012, the Solomon trial was conducted in which both techniques were used. From 2012 onward the Solomon technique is standard care. In the SFMIH, the selective technique was performed from 2011 to 2015, whereafter the Solomon technique became standard treatment. A subset of patients (n = 142) included in this study also participated in the Solomon trial [3] and a subset of LUMC patients (n = 338) has been previously reported by Peeters et al.[6]

Sonographic examinations were performed within 24 h after surgery and subsequently at least fortnightly until the end of the pregnancy with the aim to monitor fetal condition and to detect complications such as perforation in the intertwin membrane and the occurrence of cord entanglement. Technical difficulties and complications, including unintentional perforation of the intertwin membranes, were reported directly after surgery. A standardized ultrasound protocol that includes specific assessment of the intertwin membranes was used. Perforation of the intertwin membranes was defined according to previously reported definitions.[19] We diagnosed iMAT when either filling of the amniotic sac of the donor was observed intraoperative or directly after surgery or when free-floating intertwin membranes or cord entanglement was detected during follow-up.

Chorionicity and amnionicity were determined in the first trimester of pregnancy by ultrasound examination. After delivery, macroscopic examination of the placenta and membranes was performed and presence of umbilical cord entanglement was recorded. All available placentas were routinely injected with colored dye according to our previously published protocol and analyzed using ImageJ software (version 1.51).[20-22] Umbilical cord insertion was considered velamentous when it was located directly in the membranes. Insertions located less than 1 cm from the placental edge were labelled as marginal and insertions more than 1 cm from the placental edge as central. [23]

Data on obstetric and neonatal outcomes were derived from medical records. In cases in which delivery took place in another Dutch hospital, data were retrieved from referring obstetricians and pediatricians. Due to geographical differences, patients treated in SFMIH were only included when delivered in the same hospital.

The following variables were collected: TTTS stage, placental location (anterior or posterior), gestational age at laser, laser technique, duration of fetoscopy, used energy, maximum power setting, a second fetal surgery procedure, location of the cord insertions, gestational age at birth, mode of delivery, birth weight, sex, fetal demise and neonatal mortality, and severe neonatal morbidity.

A second fetal surgery was defined as a second fetoscopic laser surgery procedure or an amniotic fluid drainage, intrauterine transfusion, umbilical cord occlusion, or a intracardiac potassium chloride injection. Severe neonatal morbidity was defined as one of the following: respiratory distress syndrome needing treatment with surfactant, patent ductus arteriosus requiring medical treatment or surgical closure, necrotizing enterocolitis grade ≥ 2, severe anemia requiring a blood transfusion on the first day after birth, severe polycythemia requiring a partial exchange transfusion on the first day after birth or severe cerebral injury. Severe cerebral injury was defined as the presence of cystic periventricular leukomalacia grade ≥ 2, intraventricular hemorrhage grade ≥ 3, ventricular dilatation greater than the 97the percentile, porencephalic or parenchymal cysts, arterial or venous infarction or other severe cerebral lesions associated with adverse neurological outcome on neonatal ultrasound.

All TTTS-survivors treated with fetoscopic laser coagulation and born in The Netherlands were routinely assessed at 2 years of age by a team of pediatricians, psychologists, and physical therapists to assess the presence of severe neurodevelopmental impairment (NDI), except for children born between 2006 and 2007 (due to organizational reasons). Severe NDI was defined as at least one of the following: Bayley-III-NL cognitive and/or motor scores < 70, CP GFMCS ≥ grade 3, blindness or severe visual impairment and/or severe hearing impairment requiring amplification. Mild NDI was defined as CP grade 1 or 2, cognitive and/or motor test scores <85, mild visual and/or hearing impairment.

Statistical analyses

Continues variables were reported as mean (SD) or median (range) or median (interquartile range [IQR]), and group differences were analysed using the Mann–Whitney U-test or independent Student's *t*test, as appropriate. X^2 test or Fisher's exact test was used to analyze proportions. Trend analysis was performed to determine the rate of iMAT over the years. Risk factor analyses were performed using logistic regression models with iMAT or cord entanglement as primary outcome. The following potential risk factors for iMAT were included in the analysis: TTTS stage, placental location, laser technique, duration of fetoscopy, gestational age at laser, used laser energy, maximum laser power, and the occurrence of a second fetal surgery procedure. The following potential risk factors for cord entanglement were

included in the analysis: sex, TTTS stage, placental location, laser technique, duration of fetoscopy, gestational age at laser, and the location of cord insertions. Neonatal and long-term outcome data were analyzed using a generalized estimating equation to correct for the relation between twins. All analyses were performed using SPSS version 25.0 (IBM, Armonk, NY, USA). A *p* value of <0.05 was considered significant.

RESULTS

In the Netherlands, 752 women with TTTS pregnancies treated with laser were eligible for this study. In Shanghai, 217 TTTS pregnancies were treated in SFMIH between 2011 and 2019, of which 90 were monitored and delivered in their hospital after the laser surgery. We excluded 81 TTTS cases (9.6%, 81/842) due to incomplete data (LUMC, n = 48 (6.4%); SFMIH, n = 33 (36.7%))(figure 1). During the study period, perforation of the intertwin membrane occurred in 16% (118/761) of cases. In 38% (45/118) perforation of the intertwin membrane was detected during surgery or at ultrasound examination 1 day after the procedure.

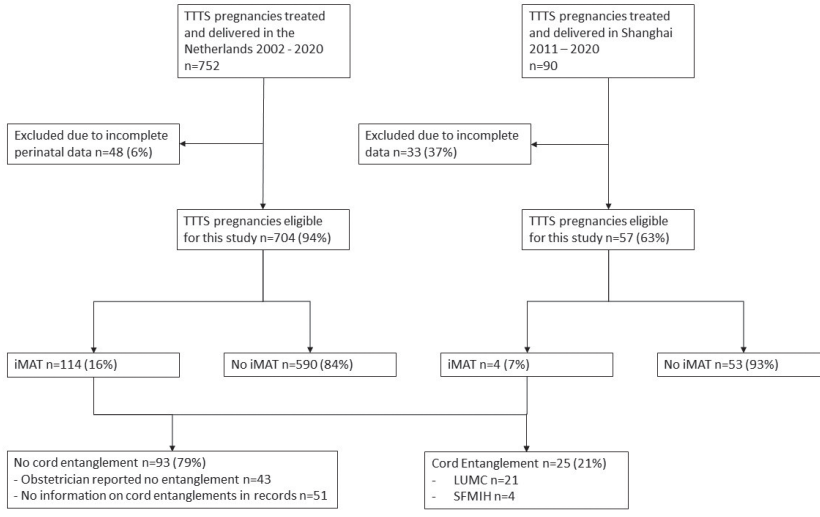

Figure 1. Flowchart depicting the derivation of our population.

iatrogenic Monoamniotic Twin

Clinical characteristics and risk factor analysis in TTTS pregnancies with and without iMAT are depicted in Table 1. In the group of pregnancies with iMAT, median gestational age at laser surgery was 20.4 (IQR 18.0-23.3) weeks compared to 19.8 (IQR 17.7 – 22.1) weeks in the group without iMAT (p = 0.050). Maximum laser power was higher in iMAT pregnancies; 45.8 ± 14.5 Watt compared to 42.2 ± 13.6 Watt in the no iMAT group (p = 0.024). iMAT occurred more frequently in TTTS cases requiring a second consecutive fetal surgery procedure, 17% (20/118) versus 6% (36/643) in the group without iMAT (p < 0.001). Second fetal surgeries included laser surgery (n = 11), amniondrainage (n = 10), intrauterine transfusions (n = 15), umbilical cord coagulations (n = 14), intracardiac kaliumchloride injections (n = 2), amnionpatch (n = 1), and laser surgery followed by intrauterine transfusions (n = 2).

Gestational age at birth in TTTS pregnancies with and without iMAT was 30.7 weeks (IQR 28.4-32.9) and 33.3 weeks (IQR 29.7-35.9) (p < 0.001), respectively (Table 3). Perinatal survival rates were similar between pregnancies with and without iMAT. iMAT pregnancies without fetal demise were hospitalized in 53% of cases at a mean of 28 + 5 weeks of gestation (±21 days) for fetal monitoring and an elective caesarean section was scheduled between 32 and 34 weeks' gestation. In 20% (24/118) spontaneous delivery occurred before 28 weeks of gestation. Severe neonatal morbidity was similar in the groups with and without iMAT, but severe cerebral injury occurred more often in the iMAT group, 9% (17/185) versus 5% (42/930) respectively (p = 0.019). When corrected for gestational age at birth the association between iMAT and severe cerebral injury was not significant (p = 0.342). Neurodevelopmental outcome at 2 years of age was available for 125 iMAT survivors and 617 TTTS survivors without a ruptured intertwin membrane (Table 3). Lost-to-follow-up rate in children born in the Netherlands of at least 2 years of age was 22% (36/161) in iMAT survivors and 27% (234/851) in the group without iMAT. Severe NDI in the iMAT and no iMAT group was detected in 8% (10/125) and 6% (35/617), respectively (p = 0.507). In Figure 2, the rate of iMAT is reported over the years.

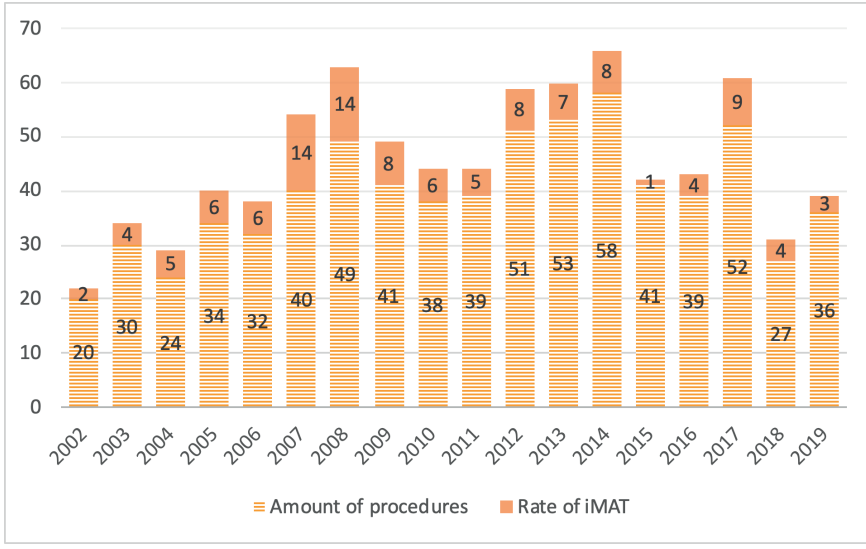

Figure 2. Rate of iMAT over the years

Umbilical cord entanglement

Umbilical cord entanglement was detected in 21% (25/118) of cases in the iMAT group (Table 2). An example of an iMAT placenta with cord entanglement is shown in Figure 3. Cord entanglement was detected on ultrasound examinations in 84% (21/25) of cases. In 4 cases, cord entanglement was not mentioned in the ultrasound records but detected at placenta evaluation. Cord entanglement was the most likely cause of death in two pregnancies, where the cord of the earlier demised twin circled the cord of the larger twin leading to a second fetal demise at 25 and 28 weeks of gestation. We found a significant association between cord entanglement and TTTS stage 1 and with the use of Solomon technique.

Perinatal mortality, severe neonatal morbidity, and severe NDI at 2 years of age were similar in iMAT pregnancies with and without cord entanglement (Table 3).

Table 1. Clinical characteristics of 761 pregnancies with twin–twin transfusion syndrome (TTTS) treated with laser therapy, with and without a intertwin membrane perforation (iMAT).

	iMAT group (n = 118)	no iMAT group (n = 643)	OR 95% CI	*p*-value
Placenta location				
Anterior	54 (46)	248 (39)	1.34 (0.90-1.99)	0.146
Posterior	61 (52)	380 (59)	0.74 (0.50-1.09)	0.130
Lateral	3 (3)	15 (2)		
TTTS stage				
I	12 (10)	89 (14)	0.64 (0.33-1.24)	0.185
II	37 (31)	221 (34)	0.91 (0.60-1.38)	0.648
III	65 (55)	302 (47)	1.39 (0.93-2.05)	0.106
IV	4 (3)	31 (5)	0.69 (0.24-2.00)	0.497
Laser technique				
Selective	56 (47)	254 (40)[a]	0.73 (0.49-1.08)	0.113
Solomon	62 (53)	387 (60)		
GA at laser (weeks)	20.4 (18.0-23.3)	19.7 (17.7-22.1)	1.06 (1.00-1.12)	**0.050**
Duration of fetoscopy (minutes)	30 (20-40)[b]	29 (21-39)[c]	1.00 (0.99-1.02)	0.707
Laser energy (kJ)	5.7 (2.6-9.1)[d]	4.6 (2.7-7.7)[e]	1.01 (0.98-1.03)	0.516
Maximum laser power (Watt)	45.8 ±14.5[f]	42.2 ± 13.6[g]	1.02 (1.00-1.03)	**0.024**
Second fetal surgery procedure	20 (17)	36 (6)	3.44 (1.91-6.19)	**<0.001**

Data given as n (%) or mean ± standard deviation or median (interquartile range). TTTS = twin-to-twin transfusion syndrome; iMAT = iatrogenic monoamniotic twin; OR = odds ratio; CI = confidence interval; GA = gestational age. [a]= data missing for 2 cases; [b]= data missing for 32 cases; [c] =data missing for 129 cases; [d] = data missing for 31 cases; [e] = data missing for 177 cases; [f] = data missing for 29 cases; [g] = data missing for 110 cases.

Table 2. Risk factor analysis for cord entanglement (CE) in 118 iMAT pregnancies.

		iMAT group with CE n = 25	iMAT group without CE n = 93	OR 95% CI	*p*-value
Female		10 (40)	54 (58)	0.53 (0.21-1.31)	0.170
TTTS stage	1	5 (20)	6 (7)	3.63 (1.01-13.07)	**0.049**
	2	7 (28)	31 (33)	0.78 (0.29-2.05)	0.613
	3	13 (52)	52 (56)	0.85 (0.35-2.07)	0.727
	4	0	4 (4)		
Placental location anterior		10 (40)	44 (47)	0.874 (0.30-1.82)	0.516
Laser technique	Selective	6 (24)	50 (54)		
	Solomon	19 (76)	43 (46)	3.68 (1.35-10.05)	**0.011**
Duration of the fetoscopy (min)		28 (20-35)	30 (20 - 45)	0.98 (0.94-1.01)	0.185
GA at laser (weeks)		20.2 (18.1-23.0)	20.4 (17.6-23.4)	0.97 (0.85-1.10)	0.596
Interval septostomy to birth (days)		47.2 ± 26.5[c]	51.3 ± 33.4[d]	1.00 (0.99-1.02)	0.660
Cord insertion type					
Central – central		10 (50)[c]	21 (29)[d]	2.43 (0.88-6.69)	0.086
Central – marginal/velamentous		7 (35)	40 (56)	0.43 (0.15-1.21)	0.109
Marginal/velamentous – marginal/ velamentous		3 (15)	11 (15)	0.98 (0.25-2.45)	0.976

Data presented as n (%) or median (interquartile range); OR = odds ratio; CI = confidence interval; iMAT = iatrogenic monoamniotic twin; CE = cord entanglement; CI= confidence interval; TTTS = twin-twin transfusion syndrome; GA = gestational age; [c] = 5 placentas were lost; [d] = 11 placentas were lost.

Table 3. Short and long-term outcome in TTTS cases with and without iMAT and with and without cord entanglement

	iMAT group n = 118 pregnancies n = 236 children	**no iMAT group n = 643 pregnancies n = 1289 children**	***p*-value**	**iMAT with CE n = 25 pregnancies n = 50 children**	**iMAT without CE n = 93 pregnancies n = 186 children**	***p*-value**
GA at birth (weeks)	30.7 (28.4-32.9)	33.3 (29.7-35.9)	**<0.001**	30.1 (28.3-32.8)	30.7 (28.6-33.0)	0.875
Birth weight (grams)[a]	1558 (1144 – 1959)	1960 (1490 – 2425)[b]	**<0.001**	1395 (1005-1851)	1550 (1136-1932)	0.239
Delivery by caesarean section	88 (75)	203 (32)[c]	**<0.001**	21 (84)	67 (72)	0.230
Perinatal survival (>28 days)	194 (82)	980 (76)		41 (82)	153 (82)	
No survival	10 (8)	81 (13)	0.212	2 (8)	8 (9)	0.924
Single survivor	22 (19)	145 (23)	0.512	5 (20)	17 (18)	0.845
Double survival	86 (73)	417 (65)	0.092	18 (72)	68 (73)	0.911
Severe neonatal morbidity	57 (33)	174 (26)	0.143	16 (52)[d]	41 (29)[e]	0.084
Severe cerebral injury	17 (9)[f]	42 (5)[g]	**0.019**	5 (15)	12 (8)	0.243
Severe NDI	10 (8)[h]	35 (6)[j]	0.507	2 (7)[e]	8 (8)[k]	0.906
Mild-moderate NDI	15 (12)	107 (17)	0.217	6 (22)[e]	9 (9)[k]	0.129

Data given as n (%) or median (range). iMAT = iatrogenic monoamniotic twin; GA = gestational age. [a]= IUFD was excluded; [b]= data is missing for 11 cases; [c]= data missing for 6 cases; [d] = data missing for 8 cases; [e]= data is missing for 14 cases; [f]=data missing for 9 cases; [g]= data missing for 45 cases; [h]= data missing for 69 cases; [j]= data missing for 358 cases; [k] = data is missing for 56 cases.

DISCUSSION

This large cohort study on iatrogenic rupture of the intertwin membranes after laser shows a prevalence of 16% with a subsequent cord entanglement of only 21%. Rupture of the intertwin membrane was associated with a higher maximum power setting at laser surgery and repeated fetoscopic procedures.

Previous studies often reported a lower rate of iMAT after laser surgery, ranging from 1.3% to 9.0%.[9-11] However, most of these studies were either small or assessment of iMAT was not performed routinely, which could have led to underreporting. In contrast, the current study was performed in a very large consecutive cohort and the assessment of the intertwin membrane was part of the standardized protocol in which a sonography was performed within 24 h after surgery and subsequently at least fortnightly until the end of the pregnancy. The iMAT rate in this study was comparable to the 20% rate previously reported by our research group in a subset of these patients (n = 338).[6] The relatively higher iMAT rate demonstrated in this study emphasizes the importance of careful routine assessment of the intertwin membranes during sonographic follow-up to detect cord entanglement.

In this study, a second fetal surgery procedure was associated with the rupture of the intertwin membrane. This could be expected as a second procedure damages the amniotic membranes twice and thereby increases the risk of rupture. We also found an association with higher laser power settings. A possible explanation could be that higher laser power is associated with a more difficult procedure. The difficulty of the procedure may be a confounder that influences both the perforation of the intertwin membrane and maximum power settings. Contributing to this theory is the higher amount of anterior located placentas in the iMAT group, 46% (54/118) compared to 39% (248/643). The approach of an anterior located placenta is considered to be more difficult. The fetoscope can be tangential to the placental surface, causing the surgeon to use a higher power setting. In addition, during the introduction of the fetoscope, it may be more difficult to avoid damage to the intertwin membrane as the places to enter the recipients sac are limited. To our knowledge, there are no previous studies reporting a relation between higher laser power settings and complications after laser therapy. One study reported an association between lower power settings and placental damage.[24] The same study described an association between placental tissue damage and higher energy use. The authors speculated that the usage of an higher power setting for a short time is more efficient, leads to lower energy use, and is therefore negatively associated with collateral damage. In accordance with this theory, Mort et al reported an association between high laser energy use above 13.8kJ (75th percentile) and delivery prior to 32 weeks.[25] Of note, the median energy use in our cohort was much lower (4.8kJ, IQR 2.7-7.9). No association

between laser energy and iMAT was detected in this study or in a previous study by Brock et al. [26] Future studies should include laser power settings and used laser energy to determine if there is a true association between laser power, total amount of energy used, and damage to the intertwin membrane.

We found that gestational age at birth was significantly lower and caesarean delivery rates were higher in iMAT. This is consistent with the results of the meta-analysis of Nassr et al. [27] In both our centers, patients with iMAT are often hospitalized from 28 weeks of gestation for fetal monitoring and an elective caesarean section is planned at 32-34 weeks of gestation. Therefore, a likely explanation for this finding is that the intensive fetal monitoring in the iMAT cases results in preterm delivery. This is probably motivated by the risk of fetal demise due to cord entanglement in monoamniotic pregnancies. Importantly, severe cerebral injury occurred significantly more often in the iMAT group and was associated with the premature delivery. Finding the right balance between continuation of the pregnancy with the risk of cord accidents and preterm delivery with the accompanying complications of prematurity remains a challenge for perinatologists. Despite the increased risk of severe cerebral injury in the iMAT group, the risk of long-term NDI was not significantly higher. The lack of association could partly be due to the high lost-to-follow-up rate and lack of power.

In this study, cord entanglement occurred in 21% of iMAT pregnancies. This is comparable to the rate of 17% described in a previous study. [28] Cord entanglement was associated with the Solomon laser technique. As the Solomon technique is performed in more recent years, the higher rates of cord entanglement might also be explained by improvement of the sonographic follow-up examinations and accurate reporting of cord entanglement in patient records. Detailed descriptions of delivery and placental examination were more often lacking in the older patient records. The true rate of cord entanglement is therefore possibly higher than the rate reported in this study. In addition, we found an association between TTTS stage 1 and cord entanglement. This result should be interpreted with caution as the low numbers hamper a valid risk assessment. Cord entanglement was diagnosed in the antenatal period during the routine ultrasound in 84% of cases. In the other 16%, cord entanglement was not reported in ultrasound records, either because the reporting was inaccurate or chorion amnion separation and lack of amniotic fluid after PPROM impaired visualization in these cases.

We expected an increased risk of entanglement when both umbilical cords were inserted centrally. Presumably, a shorter distance between cord insertions could result in higher risk of cord entanglement. However, no significant association was detected.

Cord entanglement occurred in only 1 in 5 of the iMAT pregnancies, 3% of all TTTS pregnancies. The lack of cord entanglement in 4 out of 5 iMAT pregnancies mandates a different approach for this group than the management of *spontaneous* monoamniotic twin pregnancies. The strict treatment strategies of early hospitalization, extensive monitoring and an elective preterm delivery may be more harmful than beneficial. Monoamniotic twins in this study were born earlier in gestation and the rate of severe cerebral injury associated with prematurity was higher. Although in this study the rates of mild-moderate and severe long-term NDI were comparable between TTTS survivors with and without iMAT, extreme or very preterm delivery is associated with high mortality and morbidity rates and poorer long-term neurodevelopmental outcomes.[29, 30] The lack of adverse outcome in twins with cord entanglement may be attributed to the strict management strategies of early and extensive monitoring and the elective preterm caesarean section, or cord entanglement poses a smaller threat than obstetricians fear. Some studies in spontaneous monoamniotic gestations demonstrate that monoamnionicity and cord entanglement in themselves are not associated with increased perinatal morbidity and mortality.[31-35] The results of this study warrant a debate on the best management strategies in iMAT pregnancies. We propose a more personalized approach to each monoamniotic twin pregnancy depending on the gestational age at intertwin membrane rupture and the presence of cord entanglement on sonographic follow-up.

Strengths and limitations

An important limitation of this study was its retrospective nature. Detailed descriptions of the umbilical cords after delivery were often lacking, possibly leading to an underreporting of cord entanglement. In 36% (42/118) of patient records, the obstetrician reported that no cord entanglement was observed after delivery. In 42% (51/118), an observation of the umbilical cords was not specifically reported. Therefore, we expect the true rate of cord entanglement may lie between 21% (25/118) and 37% (25/67). In addition, not all placentas were available for examination after delivery, and follow-up data on morbidity and long-term outcome were only available for part of the group. Another limitation is that around 10% of TTTS cases were excluded due to incomplete data, of which 1/3 of cases from SFMIH. Whether this could have led to an under- or overestimation of our findings is not clear. Finally, although this is the largest study investigating iMAT after laser surgery treatment for TTTS, the absolute number of cases with cord entanglement was still relatively low, hampering a valid risk factor analysis. Consequently, the absence of a significant association in these analyses could (partly) be ascribed to a lack of power. Larger prospective studies with standardized screening protocols and systematic reports of iMAT and cord entanglement are needed to determine rates and consequences

of intertwin membrane perforation and cord entanglement. More information of rates and consequences can provide a validated base for management strategies of these complicated pregnancies. A strength of this study is the use of a standardized sonography protocol during follow-up that included specific assessment of the intertwin membranes and placental examination after the delivery. In addition, a large cohort of TTTS survivors with and without a ruptured intertwin membrane was evaluated at the age of 2 years. Follow-up of this high-risk group is of utmost importance to improve treatment strategies, to refine counselling, and to offer timely support in children with neurodevelopmental difficulties. [36]

Conclusion

This study demonstrates that the intertwin membrane may rupture in 16% of TTTS pregnancies after laser surgery and may be followed by umbilical cord entanglement in 21% of cases. The occurrence of iMAT was associated with lower gestational age at birth and higher rates of severe cerebral injury but not with increased risk of perinatal mortality or adverse long-term outcome. This is a large retrospective study comprising 18 years of consequently heterogenous and incomplete data. Nevertheless, the results of this study warrant critical evaluation of the current clinical management guidelines involving iMAT pregnancies with or without cord entanglement. Larger multicentre studies are necessary to improve the knowledge and management of iMAT pregnancies.

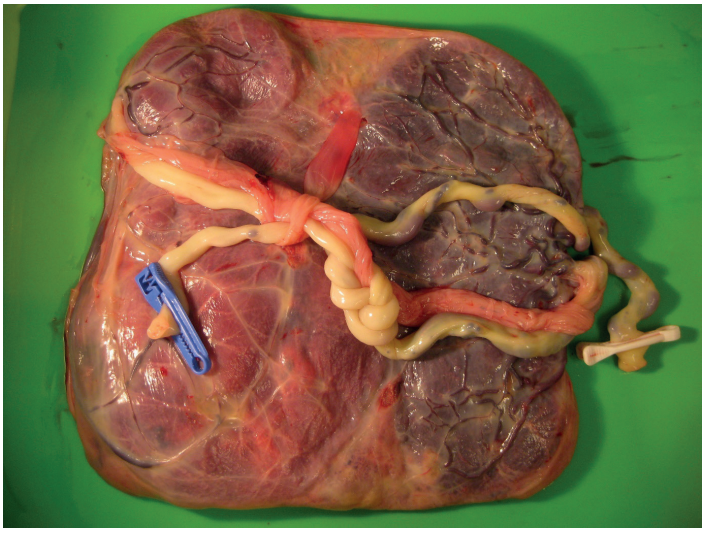

Figure 3. Iatrogenic monoamniotic twin (iMAT) placenta with umbilical cord entanglement.

A caesarean section was performed at 30 1/7 weeks of gestation. Of note, the intertwin membrane was also entangled between the two cords.

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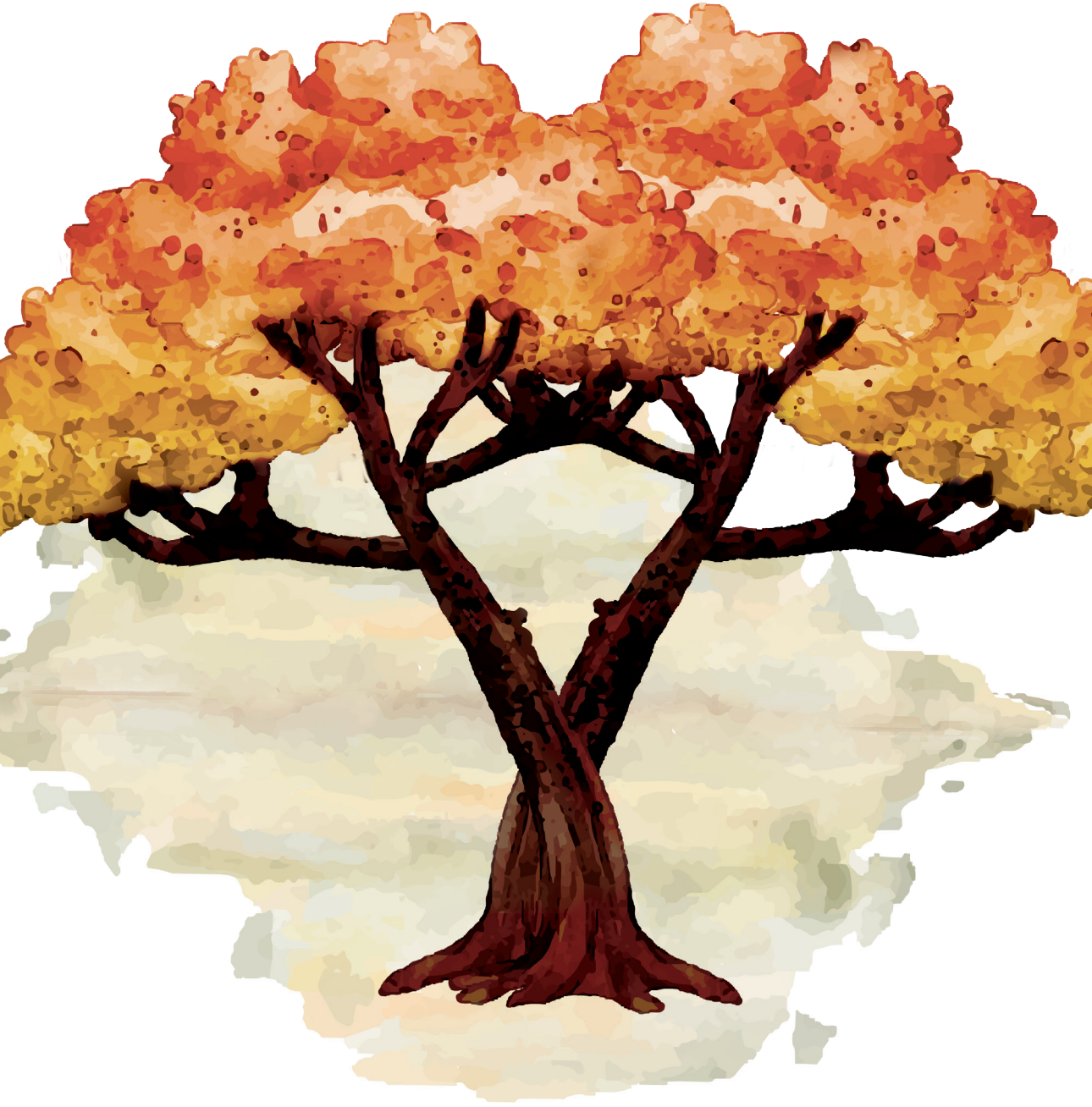
Postnatal outcome



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Chapter 5

Long-term follow-up of complicated monochorionic twin pregnancies: focus on neurodevelopment

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ABSTRACT

Monochorionic twin pregnancies have an increased risk of morbidity and mortality. Due to the advancements in screening and treatment strategies, mortality rates have decreased. Improving survival rates demands a shift in scope toward longterm outcomes. In this review we focus on neurodevelopmental outcome in survivors from complicated monochorionic twin pregnancies, including twin-twin transfusion syndrome (TTTS), twin anemia-polycythemia sequence (TAPS), acute peripartum TTTS, acute perimortem TTTS, selective fetal growth restriction (sFGR) and monoamnionicity. Our aim is to provide an overview of the current knowledge on the long-term outcome in survivors, including psychomotor development and quality of life, and provide recommendations for future research and follow-up programs.

INTRODUCTION

Monochorionic (MC) diamniotic twins are identical twins that share one placenta. All MC twin placentas have vascular anastomoses connecting the circulation of the two fetuses, which leads to intertwin blood transfusion. In most cases, blood transfusion between the two fetuses is in balance, resulting in an uncomplicated MC twin pregnancy. However, in the case of unbalanced feto-fetal transfusion, severe complications may occur such as twin-to-twin transfusion syndrome (TTTS) or twin anemia polycythemia sequence (TAPS). Another complication in MC twin pregnancies occurs in the case of unequal sharing of the placenta, which can lead to selective fetal growth restriction (sFGR).[1] In rare cases, identical twins share not only one placenta but also a single amniotic sac (monoamniotic), which can result in umbilical cord entanglement.

Early detection and improved treatment strategies for these conditions have led to a decrease in mortality. The increase in perinatal survival demands a shift in focus from survival to quality of life and long-term outcome. The aim of this review is to give a summary of the current knowledge on the long-term outcome in complicated MC pregnancies, to report risk factors and provide recommendations for future research and follow-up protocols.

Long-term neurodevelopmental outcome in twin-twin transfusion syndrome (TTTS) fetoscopic laser surgery

TTTS occurs in approximately 10% of all MC twin pregnancies.[1] Untreated, TTTS has a very poor survival rate. Until the late 1990s serial amnioreduction was the standard of care, reducing the pressure on the placenta and the cervix, thereby restoring to some extent blood flow and preventing immature delivery. [2] Amnioreduction decreased mortality to 50%, yet long-term follow-up studies report cerebral palsy (CP) ranging from 5 to 23%, with a mean of 14%. [3] The long-term neurodevelopmental impairment (NDI), including cognitive, motor, and/or sensorineural disabilities, ranges from 14 to 26%, with a mean of 20%. These numbers must, however, be viewed with caution as methodology and especially definitions of NDI differ widely between studies. Fetoscopic laser surgery has been shown to be the best first-line treatment, a causative treatment aimed at dichorionizing the placenta and arrest the inter-twin transfusion.[4] Since the introduction of laser surgery in the early 1990s, survival rates following laser surgery have increased from 55% to 74%. [5, 6] Fetoscopic centers around the world initiated long-term follow-up programs and studies to evaluate the neurodevelopmental outcome of TTTS survivors at different time points using various outcome measures and definitions of NDI. Table 1 summarizes 26 follow-up studies published between 1999 and 2021.

Table 1: Long-term outcome in twin-twin transfusion syndrome treated with fetoscopic laser surgery

Author, year	Outcome measure	Age	CP % (n/N)	NDI % (n/N)	Lost to FUP	Comments
1. De Lia, 1999[8]	Neurologic exam	14 ±10 months	4 (3/93)	NA	0%	NDI not reported, no developmental test, FUP at young age, no controls
2. Sutcliffe, 2001[9]	Neurologic exam, Griffiths Scale	mean 24 (17-32) months	9 (6/66)	9 (6/66)	19%	47% only information from GP, 54% incomplete developmental test, no controls
3. Banek, 2003[10]	Neurologic exam, Griffiths Scale, Snijders-Oomen Intelligence test	median 22 months	11 (10/89)	11 (10/89)	0%	severe developmental delay not included as criterion for NDI, 11% minor neurologic deficiencies, no controls
4. Graef, 2006[11]	Neurologic exam, Griffiths Scale, Snijders-Oomen Intelligence tests	median 3 years 2 months	6 (10/167)	8 (13/167)	2%	98% inclusion, incomplete developmental tests, no controls
5. Lenclen, 2009[12]	Neurologic exam, ASQ	mean 23 months	10 (9/88)	11 (10/88)	13%	gestation matched DC controls
6. Lopriore, 2009[13]	Neurologic exam, Bayley scales	mean 24 months	6 (17/278)	18 (50/278)	6%	Large multi-center study, no controls
7. Salomon, 2010[14]	Neurologic exam, Amiel-Tison, ASQ, Wechsler scales	mean 6-72 months	13 (9/69)	13 (9/69)	25% (at 6 years)	FUP to 6 years, no controls
8. Gray, 2011[15]	Neurologic exam, Griffiths and Bayley scales	mean 25 (21-46) months	4 (5/113)	12 (14/113)	3%	mixed developmental tests e.g. Griffiths and two versions of Bayley scales, no controls
9. Chang, 2012[16]	Neurologic exam, Bayley scales, MRI	1 year (corrected age)	5 (3/59)	7 (4/59)	3%	FUP at young age, no controls
10. Graeve, 2012[17]	Neurologic exam, K-ABC, national screening, questionnaires	median 77 (59-124) months	NA	9 (17/190)	25%	CP not reported, 53% no neurologic exam, 57% no developmental test
11. Kowitt, 2012[18]	Clinical exam, evaluation of hearing and vision and questionnaire	median 52 (24-120)	3 (1/38)	8 (3/38)	28%	No developmental test, small sample size

Author, year	Outcome measure	Age	CP % (n/N)	NDI % (n/N)	Lost to FUP	Comments
12. Swiatkowska-Freund, 2012[19]	Clinical exam	Mean 6 months	7 (7/100)	NA	7%	only CP reported, no developmental test, FUP at young age, no controls
13. McIntosh, 2014[20]	GHQ, Bayley scales and Wechsler scales	mean 48 (30-69) months	2 (1/50)	4 (2/50)	16%	no neurologic exam, small sample size, no controls
14. Tosello, 2014[21]	ASQ, clinical exam	median 37 (4-60) months	6 (2/35)	NA	20%	small sample size, NDI not reported, 31% (11/35) at least one ASQ score <-2SD
15. Vanderbilt, 2014[22]	Amiel Tison exam, BDI	mean 24 months	3 (3/100)	4 (4/100)	51%	Lost to FUP 51% with majority Quintero stage IV, no controls
16. Müllers, 2015[23]	Patient correspondence and pediatric evaluation	median age 4 years (6 months-7 years)	4 (4/106)	14 (15/106)	10%	no developmental test, NDI based on 'neurodevelopmental concerns' from patient correspondence and pediatric evaluation, no controls
17. Campos, 2016[24]	Clinical exam, Bayley screening test	5.5 (± 1.4) and 9.8 (± 1.9) months	18 (6/33)	NA	0%	NDI not reported, 'inadequate' Bayley screen: 18% cognitive domain, 9% receptive- and 21% expressive communication, 24% fine- and 24% gross motor, small sample size, 22 term singleton controls
18. Sananès, 2016[25]	ASQ	2 to 5 years	NA	13 (17/126)	44%	CP not reported, no neurologic exam, 44% lost to FUP with majority Quintero I, 13% (17/126) at least one ASQ score <-2SD, no controls
19. van Klink, 2016[26]	Neurologic exam, Bayley scales, GMFCS	mean 24 months	3 (6/216)	4 (9/216)	6%	FUP in 2 of the 5 participating trial centers, large multicenter study, 94% inclusion rate, no controls

Author, year	Outcome measure	Age	CP % (n/N)	NDI % (n/N)	Lost to FUP	Comments
20. Korsakissok, 2018[27]	ASQ, parental questionnaire, information attending physician	mean 59.3 (24-96) months	5 (3/58)	12 (7/58)	45%	No neurologic exam, 30% moderate neurological abnormalities, no controls
21. Sommer, 2018[28]	GMFCS, evaluation of hearing and vision	18 months corrected GA	15 (2/13)	NA	61%	NDI not reported, no developmental test, small sample size, preterm (<29 weeks GA) TTTS survivors vs. preterm DC twins
22. Schou, 2019[29]	ASQ, telephone interview parents	25 months ± 11	6 (5/86)	11 (9/86)	18%	Mixed methods for follow-up, TTTS survivors increased risk NDI compared to uncomplicated MC twins
23. Spruijt, 2019[30]	Bayley scales, neurologic exam, GFMCS	2 years	2 (4/258)	3 (7/241)	15%	Large sample size with standardized neurologic and developmental tests, no controls
24. Matsushima, 2020[31]	Tsumori's Mental Development Test and Kyoto Scale of Psychological Development 2001, MRI	3 years, 6 months	3 (6/188)	9 (16/188)	5%	Mixed methods for FUP, no controls
25. Rüegg, 2020[32]	Parental questionnaires, Bayley scales, neurologic exam	50 (7-111) months	5 (2/42)	7 (3/42)	38%	Bayley scales only in TTTS survivors born premature or SGA, no difference with DC controls
26. Knijnenburg, 2021[33]	Bayley Scales, Wechsler scales, neurologic exam, M-ABC, GMFCS	5 years	3 (2/73)	12 (9/73)	32% (at 5 years)	Only TTTS survivors born premature or SGA age were included in 5 year FUP, no controls
Total			**5.2% (126/2405)**	**9.2% (225/2443)**		
Range			**2-18%**	**4-18%**		

CP, cerebral palsy; NDI, neurodevelopmental impairment; NA, not assessed; TTTS, twin-twin transfusion syndrome; NND, neonatal death; FUP, follow-up; ASQ, Ages Stages Questionnaire; GP, general practitioner; GA, gestational age; DC, dichorionic; SD, standard deviation; K-ABC, Kaufman Assessment Battery for children; GHQ, General Health Questionnaire; BDI, Battelle Developmental Inventory.
Of note: Two studies [70], [71] are not included in this table because the included children are more fully described in these studies [13], [26].

In total, 39% (10/26) studies used a composite outcome measure termed NDI including CP, severe motor and/or cognitive developmental delay (scores below 2 SD), and bilateral blindness or deafness requiring amplification with hearing aids. In addition to a neurologic examination, cognitive development was assessed with Ages and Stages Questionnaire (ASQ) or Bayley scales in 54% (14/26) studies. In other studies multiple methods of follow-up and definitions of NDI were used. CP was diagnosed using the Gross Motor Functioning Classification Scale in 20% (5/24) studies.[7] Two studies did not report CP.

The reported CP rate ranges from 2% to 18% with a mean of 5% (126/2405). [8-33] NDI ranges from 4% to 18%, with a mean rate of 9% (225/2443). Eight studies reported mild NDI, including scores < 1SD on a developmental test or neurological deficiencies with prospect to normalization or with no significant impact on quality of life, in 0 to 34%.[14, 17, 18, 20, 26, 27, 30, 33] Although the timing of follow-up assessment of TTTS survivors ranges from 6 months to 6 years of age, the majority of studies (11/26, 42%) report neurodevelopmental outcome at two years of age. Longitudinal studies with follow-up at school age, are missing. A recent study from our center evaluated 73 TTTS -survivors born premature and/or small for gestational (< 1500 grams and <P10) at both 2 and 5 years. [33] We observed an increase in NDI rate compared to their 2 year assessment. The rate of mild to moderate NDI increased from 25 to 34% and the rate of severe NDI increased from 9 to 12%. These results emphasize the importance of follow-up beyond 2 years. Twins treated with fetoscopic laser surgery for TTTS seem at risk of long-term neurodevelopmental 'lagging behind', which means that the children do not deteriorate but struggle to achieve the age-appropriate milestones, thereby 'growing into their deficits'.

Several risk factors for long-term NDI have been reported, including advanced GA at fetoscopic laser, cerebral injury, low gestational age at birth and low birth weight, in particular fetal growth restriction. [34] Whether neuroimaging technologies (cerebral ultrasound and/or magnetic resonance imaging, MRI) are useful or not in predicting the long-term neurodevelopment remains a subject of debate. Two studies used (neonatal) cranial imaging in combination with the long-term neurodevelopmental assessment. Chang et al. (2012) reported two TTTS survivors with a severe cerebral injury on MRI, but normal neurologic examinations at a corrected age of 1 year, and one survivor with a normal MRI but severe neurologic impairment.[16] Spruijt et al (2019) reported normal neonatal cranial ultrasound examinations in the majority of children diagnosed with NDI at 2 years of age (10/17).[30] However, the severe cerebral injury was associated with decreased Bayley motor scores (p = 0.012). Large prospective outcome studies are required to determine the predictive value of neuroimaging in MC twins.

Long-term neurodevelopmental outcome in post-laser- and spontaneous twin anemia polycythemia sequence (TAPS)

TAPS develops either spontaneously in 3-5% of MC pregnancies or after laser therapy for TTTS in 2-16%. [35] To date, no consensus has been reached on the optimal treatment in TAPS. Whether fetal surgery (fetoscopic laser coagulation of vascular anastomoses, selective reduction, intrauterine transfusions), obstetrical interventions (elective preterm birth), or expectant management may or may not improve the outcome remains to be determined. Data on the long-term outcome is scarce and limited to a few small studies. A research group from Japan studied the long-term outcome of three twin pairs who developed TAPS after laser surgery and detected bilateral deafness and cognitive delay in a 9-year-old donor and spastic paralysis and cognitive delay in a 2-year-old recipient.[36] The largest post-laser TAPS follow-up study thus far was performed by our research group and included 47 post-laser TAPS cases managed at our center. The rate of severe NDI and mild impairment was 9% and 17%, respectively, which is within the range of NDI reported in case series of TTTS treated with laser. We found no difference in the outcome between donors and recipients after post-laser TAPS. [35] Low gestational age and low birth weight were significant risk factors for lower cognitive scores. In addition, the post-laser TAPS subgroup of eight survivors treated with intrauterine transfusions had significant lower cognitive scores than those who underwent expectant management, laser reintervention, and selective reduction procedures.

For spontaneous TAPS, available literature on the neurodevelopmental outcome is limited to two studies. In a small study, Han et al. evaluated the long-term outcome in 17 spontaneous TAPS survivors from 11 MC pregnancies and found no cases with CP at 2 years of age in survivors. [37] The developmental outcome was not assessed in this study. A larger long-term follow-up study by our research group detected a worse long-term neurodevelopmental outcome in spontaneous TAPS donors compared to recipients. [38] At a median age of 4 years, NDI was present in 18% of spontaneous TAPS donors compared to 3% in TAPS recipients (overall 9%). Mild-to-moderate NDI was present in 20% (15/74) of the donors and in 15% (6/40) of the recipients. Overall, donors showed higher rates of mild (-1 SD) cognitive impairment (35% vs. 18%), and lower rates of disease-free survival (45% vs. 80%) than recipients. Remarkably, a high rate of bilateral deafness was observed in spontaneous TAPS donors, 15% versus 0% in recipients. In all donors, deafness was based on auditory neuropathy spectrum disorder. The exact cause of the high rate of deafness in donor twins was unclear. This finding was not observed in TTTS donors or children who suffered from chronic fetal anemia based on erythrocyte alloimmunization. [39]

Long-term neurodevelopmental outcome in acute peripartum TTTS

Acute peripartum TTTS is a rare condition occurring in approximately 2% of MC twin pregnancies where acute intertwin transfusion occurs during birth, leading to large differences in hemoglobin levels between the donor and the recipient. [40, 41] In contrast to TAPS, there is no reticulocyte discordance as the reticulocyte count in donors did not have time to increase, reflecting the acute occurrence of the disorder. Donors can suffer from the sequelae of acute blood loss and hypovolemic shock, including cerebral injury. [42-44] However, data on short-term outcome in acute peripartum TTTS is limited and mainly based on casuistic reports.

The long-term outcome of survivors is currently unknown. Since this condition is rare, a collaboration in an international registry could be a solution to gather more data on the long-term outcome of survivors of acute peripartum TTTS.

Long-term neurodevelopmental outcome in acute perimortem TTTS

Acute perimortem TTTS occurs when one of the fetuses dies, leading to acute exsanguination and eventually death of the co-twin in up to 41% of cases.[45] When the co-twin survives, the acute exsanguination and hypovolemic shock may lead to severe cerebral injury in 26% of cases.[46] In a recent meta-analysis, combining the results of six different studies, brain abnormalities in fetal MRI were reported in 20% of 116 pregnancies. Postnatally, brain imaging was defined as 'abnormal' in 43% of 140 pregnancies reported by 12 studies.[45] Therefore cranial imaging, including fetal MRI, is important in this subgroup. Two cases of renal failure due to severe renal dysplasia were described in the surviving co-twin. [47, 48]

The long-term neurodevelopmental outcome is severely impaired in 29% of the survivors.[45] The rate of NDI is significantly higher compared to DC twins (10%) and represents the highest NDI rate compared to other MC complications (Figure 1). [45]

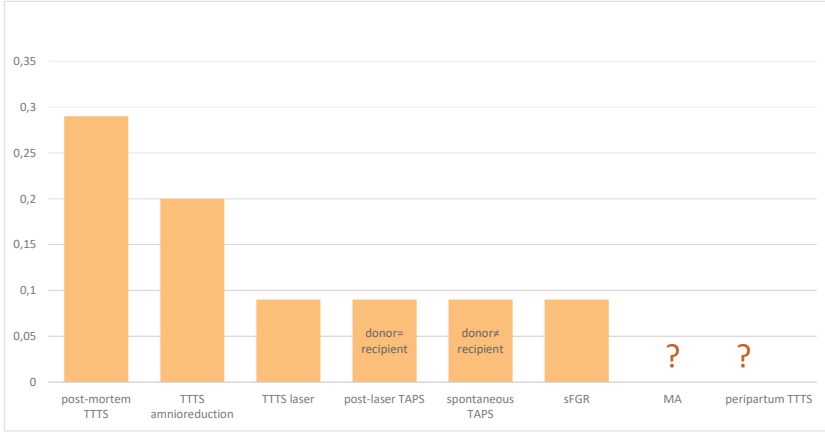

Figure 1. Risk of neurodevelopmental impairment in complicated MC twin pregnancies

Long-term neurodevelopmental outcome in selective fetal growth restriction (sFGR)

sFGR occurs in approximately 10-15% of all MC twin pregnancies and is caused by an unequal sharing of the placenta, often accompanied by a marginal or velamentous cord insertion of the smaller twin.[49, 50] sFGR is usually defined as an estimated fetal weight below the 10th percentile in the smaller twin and/or a birth weight discordance of more than 20%. The optimal management in MC twins with sFGR is not clear and there is still no international consensus on the best treatment strategy. Whether fetal surgery (fetoscopic laser coagulation of vascular anastomoses, selective reduction) or obstetrical interventions (elective preterm birth) may improve the (long-term) outcome remains to be determined. How to balance the benefit from prolonging the pregnancy in preventing prematurity-related injury against the risk of single fetal demise and concomitant damage to the co-twin is a clinical challenge and warrants further study. A systematic review shows that the incidence of severe cerebral injury in MC twins with sFGR varies greatly from 0% to 33%, with an estimated average of 8%.[51-53] The highest incidence of cerebral injury is reported in the pregnancies complicated by single fetal demise of a co-twin, in pregnancies with abnormal umbilical artery Doppler findings and in cohorts with a lower gestational age at birth. Table 2 summarizes the eight long-term follow-up studies in twins with sFGR. [54-61] Although the between-study variation in the definition of sFGR and methodology hampers comparability, the overall reported rate of CP ranges between 5 and 19% with a mean of 6% (17/289). NDI ranges from 1 to 42% with a mean of 9% (50/553). The growth restricted twins tend to show lower cognitive scores and more mild motor/neurological impairments. [55, 56, 58-60] Insight into the long-term outcomes will lead to improved prognostics, which are essential in parent counseling and crucial in the process of forming a management protocol specifically for twins with sFGR to optimally monitor and support their development.

Table 2: Long-term outcome in selective fetal growth restriction

Author, date	Definition of sFGR	Outcome measure and age at FUP	CP % (n/N)	NDI % (n/N)	Large vs small twin
1. Adegbite, 2004[54]	Birthweight discordance ≥ 20% and abdominal circumference ≤ 5th	Griffiths Scale at 24 months DC-twin controls	19 (5/26)	42 (11/26)	No difference test score small vs large twin, NDI increased compared to DC controls
2. Hack, 2009[55]	Birthweight discordance ≥ 20%	Griffiths Scale at 22 months	0 (0/14)	7 (1/14)	Test scores (trend) lower in small twin
3. Edmonds, 2010[56]	Continuous variable for birthweight discordance	Wechsler scales at 7-17 years	excluded	NA (n = 71)	Lower Wechsler verbal IQ in small twin
4. Halling, 2016[57]	Birthweight discordance ≥ 20%	Bayley scales at 24-42 months	NA	NA (n = 24)	No analysis small vs large MC twin Lower Bayley scores in sFGR MC twins vs sFGR DC twins
5. Rustico, 2017[59]	Estimated fetal weight <10th or estimated fetal weight difference ≥ 20%	No neurodevelopmental test, evaluation at 8 years	5 (9/191)	6 (11/191)	More mild NDI in small twin
6. Vedel, 2017[58]	Birthweight discordance >75th	ASQ up to 48-60 months	NA	NA (n = 119)	ASQ scores lower in small twin (p = 0.05)
7. Swamy, 2018[60]	Birthweight discordance ≥ 20% (12% (6/51) complicated by TTTS)	British Ability Scales, Strength Difficulties Questionnaire at 6 years	2 (3/58)	excluded from cognitive analysis	Lower scores in small twin
8. Groene, 2019 [61]	Estimated fetal weight <10th and TTTS	Bayley scales at 2 years, control group TTTS twins without sFGR	NA	9 (27/299)	No difference small vs large twin, no difference TTS + sFGR compared to TTTS without sFGR.
Total			**5.8% (17/289)**	**9.0% (50/553)**	
Range			**5-19%**	**1-42%**	

sFGR, selective fetal growth restriction; CP, Cerebral palsy; NDI, neurodevelopmental impairment; DC, dichorionic; NA, not assessed; IQ, intelligence quotient; ASQ, ages and stages questionnaire; TTTS, twin-twin transfusion syndrome.

Long-term neurodevelopmental outcome in monoamniotic (MA) pregnancies

Only in approximately 1% of monozygotic twin pregnancies do both twins share the same amniotic sac. [62] MA twin pregnancies can be challenged with all the aforementioned complications. Unique to spontaneous MA twin pregnancies is the 100% risk of cord entanglement, which is associated with an increased risk of fetal mortality. To prevent fetal demise and peripartum complications, MA pregnancies are usually delivered around 33 weeks of gestation by cesarean section. [63] The preterm delivery is a known risk factor for cerebral injury and long-term neurodevelopmental impairment. Rates of cerebral injury range from 0 to 15% depending on the gestational age.[64] However, data on the long-term neurodevelopmental outcome is not available. A (inter)national database for MA twin pregnancies could facilitate the study of the natural history and possible risk factors for adverse (long-term) outcome including the often elective preterm delivery and following complications accompanying prematurity.

Recommendations for uniform reporting, definitions and outcome measures of long-term neurodevelopment

The importance of long-term follow-up studies lies inthe necessity of evaluating fetal therapy and care of complicated MC twin pregnancies as well as in evidence-based counseling of future parents. In addition, when a center decides to treat fetuses in utero, with the knowledge that a significant proportion will develop long-term morbidity, this center also has the responsibility to ensure that survivors will eventually receive the care they need. A long-term follow-up should be an integrated component in the care of complicated MC twin pregnancies. Unfortunately, long-term neurodevelopmental studies are costly and difficult to perform and, consequently, hard to realize. Challenges include, among others, tracking families, organizing follow-up assessments with trained pediatricians and child psychologists, and complete data acquisition and analysis. Structured long-term follow-up programs of MC twins require a dedicated follow-up team including fetal medicine specialists, neonatologists, physiotherapists, child psychologists and research nurses.

A recurrent issue in the follow-up of complicated MC twins is the lack of a uniform approach. Definitions, methodology, and time points at the follow-up differ between studies and centers. Core outcome sets for the evaluation of care of MC twin pregnancy are essential and could help standardize outcome collection and reporting in follow-up studies. Multicenter efforts are of utmost importance to study the natural history in complicated MC pregnancies and the effect of interventions to determine optimal management (timing and type of intervention).

In most fetal therapy centers with follow-up programs, children are evaluated (with a validated test) for the first time at the age of 2 years. Outcome data later in childhood or puberty is often lacking. It is crucial to continuously assess child development including standardized measures of well-documented quality, with increasing reliability of results with increasing age of surviving MC twins. A proposition of a long-term follow-up schedule would include visits at the age of 5½, 8, 12 and 16 years. We propose the following recommendations for the long-term follow-up of cognitive, neurologic, motor, social-emotional and behavioral functioning (Table 3).

If feasible, cognition should be tested using standardized psychometric tests, such as Bayley and Wechsler scales, with age appropriate norms. Results should be interpreted by qualified professionals e.g. child psychologists. If parents and children have to travel long distances and/or are unable to travel, questionnaires such as Ages and Stages (ASQ) or the Parent Report of Children's Abilities (PARCA) are alternative, reliable screening tools. [65] To be able to compare results between studies, regardless of the definition of developmental impairment, it is crucial to report the number of children included for assessment with a specific test and the number of children scoring below a certain threshold of the test. For example, the number of children scoring below a Wechsler intelligence quotient of 70 (< -2SD) and with scores between 70 and 85 (> -2SD and < -1SD).

Neurologic functioning and the presence of CP should be diagnosed by a pediatrician using a standardized system such as Touwen and the gross motor function classification system (GMFCS) for CP. [7] Again, for comparison between studies, it is important to report the number of children within the different levels of functioning.

Various criteria are used to define NDI, a composite outcome including neurological, cognitive, motor, visual and auditory outcomes. We recommend severe NDI be defined as at least one of the following: CP GFMCS level 3-5, severe motor and/or cognitive developmental delay (-2 SD scores), bilateral blindness, or deafness requiring amplification with hearing aids. Mild-to-moderate NDI be defined as at least one of the following: CP level 1 to 2 on GFMCS, mild-moderate motor and/or cognitive developmental delay (-1SD scores), mild hearing loss, and/or mild visual impairment. Definitions of mild hearing loss and mild visual impairment should match the criteria as stated by the international classification of diseases (ICD) 11th revision. [66]

The use of systematic, homogeneous methods to evaluate development will benefit the comparability of studies. Comparing and combining the available literature will improve counseling of future parents of complicated MC twins and will enhance an early support to children at risk of developmental impairments. The ideal study design to evaluate new interventions in the management of complicated MC twin pregnancies is an adequately powered randomized controlled trial with 'survival without NDI' as the primary outcome. An international registry to record and evaluate the outcome in large groups of MC twins is necessary to improve our knowledge, specifically of subgroups.

CONCLUSION

Survival rates of complicated MC pregnancies are increasing due to improvement in prenatal care, but survivors are confronted with an increased risk of long-term impairments. Rates of CP in twins with TTTS, TAPS and/or sFGR are estimated to be around 5% and rates of severe NDI around 9-10% . Importantly, spontaneous TAPS donors are at increased risk of cognitive delay and deafness, highlighting the importance of support and an early (appropriate) hearing test. In sFGR, the smaller twin tends to score lower on cognitive tests, requiring more attention. The highest risk of permanent long-term impairment is reported in the group after acute postmortem TTTS, in which one in three survivors may develop NDI. Little is known about the long-term outcome in acute peripartum TTTS and monoamniotic twins. Evaluation of the risk of NDI in these two subgroups is urgently needed.

To put the results into perspective, in the general population, the rate of CP ranges from 2 to 3.5 per 1000 live births.[67] In children born between 32 and 36 weeks of gestation the prevalence of CP is estimated to be 7 in 1000. [68] Moderate-to- severe NDI is described in 2-3% in a healthy control group of 13689 Danish children in a study of group B streptococcal disease. [69] Comparing these rates with the long-term outcomes in complicated MC twins emphasizes the importance of subsequent dedicated follow-up in this high-risk group of children. To clarify and assess the impact of severe MC pregnancy complications on the long-term neurodevelopmental outcome of survivors, the inclusion of a control group of twins from uncomplicated MC pregnancies is essential.

A uniform follow-up program should be an important goal of every fetal therapy center in the world. An international registry to record and evaluate the outcome in large groups of MC twins is of paramount importance to increase current knowledge and improve management in specific subgroups.

Table 3: Proposition for systematic follow-up

Fetus	Newborn	2 years	5-6 years	8 years	12 years	16 years
Brain development: cerebral imaging (cranial ultrasound, MRI)						
	Senses: hearing test (ABR in TAPS donors) and screening for (sensorineural) deafness, vision test and ROP screening					
		Physical: General health, growth (catch-up), neurological exam (Touwen, Hempel), gross motor development (AIMS, Bayley scales, M-ABC), cerebral palsy (GMFCS).				
			Cognition: Bayley scales, Wechsler scales (IQ), ASQ or PARCA-R			
			Neuropsychological: learning difficulties (reading, mathematics), expressive and receptive language, executive functioning, memory, visual spatial abilities, fine motor development, sensory processing (Sensory Profile).			
			Psychosocial and behavioral: adaptive behavior (ABAS), attachment, internalizing (e.g. anxiety) and externalizing behavior (e.g. aggressive behavior), social skills, Quality of Life, sleep.			
				Educational: pre-academic skills, special needs education, comparison to age-appropriate level		
					Developmental disorders: e.g. attention deficit/hyperactivity, autism spectrum, disruptive mood dysregulation.	

MRI, magnetic resonance imaging; ABR, auditory brainstem response; TAPS, twin anemia polycythemia sequence; ROP, retinopathy of prematurity; GMFCS, gross motor functioning classification system; ASQ, ages and stages questionnaire; PARCA-R, parent report children's abilities revised; IQ, intelligence quotient, ABAS, adaptive behavior assessment system.

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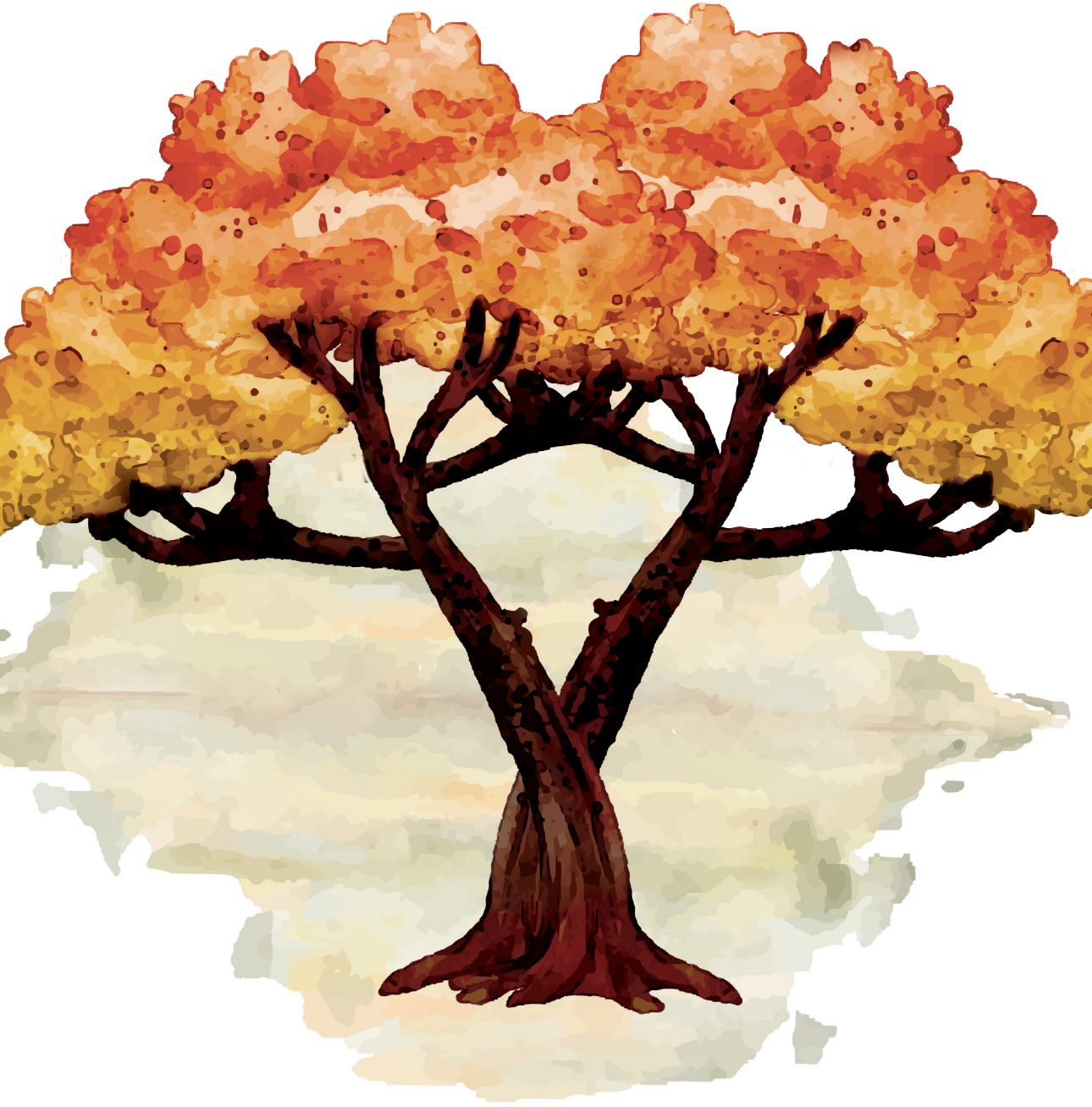

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Chapter 6

Neurodevelopmental outcome after fetoscopic laser surgery for twin-twin transfusion syndrome: a systematic review of follow-up studies from the last decade

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ABSTRACT

Objective: To review the literature on long-term neurodevelopmental outcome after fetoscopic laser surgery for twin-twin transfusion syndrome (TTTS).

Methods: A literature search in PubMed, Embase, Emcare, Web of Science, Cochrane library and Academic Search Premier was performed. Inclusion criteria were studies between 2009 and 2019 in TTTS-survivors treated with fetoscopic laser surgery and followed-up after the neonatal period with cognitive developmental tests and neurologic exams. Exclusion criteria were non-English articles and reviews, case reports, letters and guidelines.

Results: Nineteen articles were included. Long-term severe neurodevelopmental impairment (NDI) was reported by seven and ranged from 4.0%-18.0% with a mean of 9.7% (95% confidence interval (CI): 7.8-11.5). The prevalence of cerebral palsy ranged from 1.6%-18.2%, with a mean of 5.1% (95% CI: 4.1-6.2). The mean prevalence of minor impairment was 13.7% (95% *CI*: 11.4-16.0). However, only 78.9% (15/19) studies used a validated neurodevelopmental test. As studies lack uniform definitions of primary outcome, timing of follow-up, inclusion criteria and methods, adequate comparison is hampered.

Conclusion: The prevalence of severe NDI and cerebral palsy after fetoscopic laser surgery for TTTS in the last decade remains stable around 9.7% and 5.1%, respectively. International agreements on primary outcomes, methods, and follow-up are necessary to improve the knowledge of NDI in TTTS-survivors.

INTRODUCTION

Twin-twin transfusion syndrome (TTTS) is a severe complication in monochorionic (MC) twin pregnancies, for which fetoscopic laser surgery is the preferred treatment. TTTS occurs in approximately 10% of MC pregnancies. [1] Without treatment this condition is lethal in 73%-100% of cases. [2] TTTS is characterized by a net transfer of blood between twins through vascular anastomoses on the shared placenta. As a result, one fetus, the recipient, presents with a polyhydramnios while the other fetus, the donor, is often "stuck" behind the intertwin membranes due to oligohydramnios. Fetoscopic laser surgery is the preferred treatment in TTTS and is associated with an increased survival rate and a reduced risk of cerebral injury compared to twins treated with amnioreduction. [3-5]

This improving survival rate and decrease in perinatal complications have led to a shift in attention towards the long-term outcome of survivors of TTTS, especially the impact on neurodevelopment later in life. Neurodevelopment is an important outcome measure as it has a great influence on overall quality of life and academic achievement of children, burden on the family and on society.

The improved outcome in TTTS is a result of growing expertise and improved techniques, including the use of a selective sequential method and the Solomon laser technique. [6] Therefore, discussing studies from several decades ago gives an unreliable perspective on current outcome. This review focuses on the long-term neurodevelopmental outcome after fetoscopic laser surgery for TTTS reported by studies from the last decade, 2009 to 2019.

METHODS

A systematic literature search was performed to obtain all relevant articles. We searched PubMed, Embase, Emcare, Web of Science, Cochrane library and Academic Search Premier using the following search (mesh) terms: fetofetal transfusion, fetoscopy, laser therapy, lasers, neurodevelopmental disorders, human development, cognition, cognition disorders, motor skills, cerebral palsy (CP), patient health questionnaire, neuropsychological tests and neurobehavioral manifestations. For the complete search strategy see Supplemental Digital Content 1. Inclusion criteria were articles published between January 2009 and April 2019 about neurodevelopmental outcome in TTTS-survivors treated with fetoscopic laser surgery and assessed after the neonatal period using neurologic exams and cognitive developmental tests. Exclusion criteria were publications in other languages than English, reviews, case reports, guidelines, and letters. Reference lists of eligible studies were searched for relevant articles which were possibly missed by our search strategy. Eligibility and methodological quality of each study were assessed independently by two reviewers (P.K. and J.v.K.).

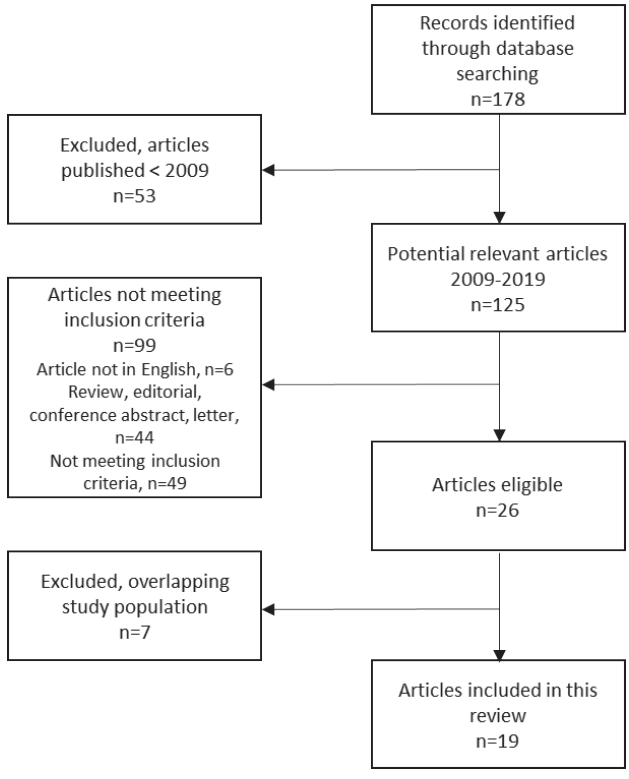

Figure 1. Flowchart showing the selection of studies

We searched eligible articles on neurodevelopmental primary and secondary outcomes, including CP, cognitive delay, blindness and deafness. We registered lost to follow-up rates, reported risk factors and the tests used to determine cognitive delay and CP. Severe cognitive delay was defined as either a score below -2 standard deviations (SD) on a developmental test or was based on the description of severe cognitive delay by the authors when no validated test was used. CP was classified as grade I-V on the Gross Motor Function Classification System (GMFCS) or was based on other tests and reports of CP by the authors when GMFCS was not used. [7]

The primary outcome for this study was severe neurodevelopmental impairment (NDI), a composite of CP, severe motor and/or cognitive delay (< -2SD), bilateral blindness and/or bilateral deafness requiring amplification with hearing aids.

A secondary outcome was used to record adverse neurodevelopmental outcome as reported according to the various definitions in the included studies.

Data are reported as mean ± SD or median (interquartile range), as appropriate.

RESULTS

Our search yielded 178 articles, 125 published between January 2009 and April 2019 (Figure 1). In total, 26 articles met our inclusion criteria. We excluded seven articles because the same cohort was more fully described in later, larger or more detailed series by the same authors. [8-14] We included three articles written by the Leiden University Medical Center, which describe patients from three different cohorts (2000 to 2005, 2008 to 2012 and 2011 to 2014). [15-17] We report the main findings in the following sections and discuss advantages and limitations.

Long-term neurodevelopmental outcome in TTTS treated with laser surgery

From 1999 to 2009 only five long-term follow-up studies were published, compared to nineteen follow-up studies in the last decade, 2009 to 2019. Table 1 summarizes the long-term neurodevelopmental outcome stated as the prevalence of CP and NDI reported by these follow-up studies.

Cerebral palsy

The majority of studies (17/19) reported CP as a primary outcome or part of a composite outcome. The mean prevalence of CP was 5.1% (87/1700, 95% confidence interval [CI]: 4.1-6.2). Several tests were used to determine CP, including Amiel-Tison neurodevelopmental examination and other standard neurologic examinations. The GMFCS was used to classify CP by 4/19 (21.1%) studies. [7]

Cognitive outcome

To assess cognitive outcome, 6/18 (33.3%) studies used the Ages Stages Questionnaire (ASQ), a developmental questionnaire for children aged 1 to 66 months and to be completed by parents. [18-23] In all studies, which used the ASQ, scores below -2SD ranged between 6.0% and 42.4%. Salomon et al. (2010) followed-up a cohort from six months to six years of age and used both the ASQ at 12, 24, 48 and 60 months and the Wechsler Intelligence Scale for Children IV at six years to evaluate cognitive development. [19] Mean ASQ-score at 60 months was 261 ± 53.7 and mean total IQ on Wechsler Intelligence Scale for Children IV was 90.6 ± 19.9. However, the proportion of children with scores below -2SD was not reported. Korsakissok et al. (2018) and Schou et al. (2019) assessed 53.4% (31/58) and 68.0% of their cohorts with an ASQ. [22, 23] In the others outcome was based on recent hospital records, telephone interviews with parents or International Classification of Disease-10 codes. Schou et al. (2019) reported a mean ASQ-score of 176.4 ± 51.5 at a median age of 27 months.

In TTTS-survivors with a similar age (median 24 months), Lenclen et al. (2009) reported a mean ASQ-score of 216.3 ± 54. [18]

In 5/18 (27.7%) studies the Bayley scales second or third edition (Bayley II or III) was used to assess neurodevelopment. [15-17, 24, 25] Scores below -2SD ranged from 3.2% to 15.8%, though only 3/5 studies presented these data. [15, 16, 24] Lopriore et al. (2009) conducted an international multicenter study in the Netherlands, Belgium and Spain, the largest cohort in this review (*n* = 278). [15] Campos et al. (2016) evaluated their TTTS-survivors twice, first at 1 to 6 months followed by a second assessment at 7-12 months of age. [25] Because the Bayley screening test is not validated in Brazil, the authors included a comparison group of 22 'normal' children. Inappropriate performance at both evaluations, defined as 'the child requires subsequent reviews or should be referred for diagnostic assessment', for the TTTS group was 18% for the cognitive domain, 9% for receptive communication, 21% for expressive communication, 24% for fine motor and 24% for gross motor skills. In a cohort with a similar follow-up range (at age 12 months), Chang et al. (2012) reported cognitive impairment in 6.8% (4/59) using Bayley scales with a cut-off point of <70. [24] For both studies, follow-up was too early (≤ 12 months) to assess 'long-term' outcome in a reliable way, in particular CP.

Table 1. Neurodevelopmental outcome in TTTS-survivors treated with laser therapy

Author, year	Definition reported impairment	Outcome measure	Age in months (range)	CP % (n/N)	Reported impairment % (n/N)	Lost to FUP % (n/N)
1. Lenclen, 2009 [18]	CP with neurologic abnormalities leading to permanent disability, bilateral blindness, deafness	Neuro exam, ASQ	Mean 23	10.2 (9/88)	11.4 (10/88)	12.9 (13/101)
2. Lopriore, 2009 [15]	CP, Bayley < 70, bilateral blindness, deafness requiring hearing aids	Neuro exam, Bayley-II	Mean 24	6.1 (17/278)	18.0 (50/278)	5.8 (17/295)
3. Salomon, 2010 [19]	CP with neurological abnormalities including hemiparesis, spastic quadriplegia, blindness	Amiel-Tison, ASQ, WISC, Good-enough draw a man test	Mean 6 - 72	13.0 (9/69)	13.0 (9/69)	5.5 (4/73)
4. Gray, 2011 [26]	CP, Griffiths' or Bayley < 70, bilateral blindness or deafness requiring hearing aids	Neuro exam, Griffiths' scale, Bayley-II/III, GMFCS	Median 25 (21– 46)	2.7 (5/113)	12.3 (14/113)	2.6 (3/116)
5. Chang, 2012 [24]	CP, Bayley < 70	Neuro exam, Bayley, MRI	Mean 12	5.1 (3/59)	6.8 (4/59)	3.3 (2/61)
6. Graeve, 2012 [27]	CP, K-ABC < -2SD	Neuro exam, K-ABC, GNSE, questionnaire	Median 77 (59-124)	NA	8.9 (17/190)	25.2 (64/254)
7. Kowitt, 2012 [30]	CP, seizures, hydrocephalus requiring shunt, IVH, PVL, developmental delay and visual, hearing impairment	Physical exam and questionnaire	Median 52 (24-120)	2.6 (1/38)	7.9 (3/38)	28.3 (15/53)
8. Swiatkowska, 2012 [33]	CP	Pediatric check-up	Mean 6	7.0 (7/100)	NA	6.6 (6/91) PR
9. McIntosh, 2014 [28]	CP, WPPSI < 70 or other developmental test < 2SD	WPPSI-III, Bayley-III, Griffiths' scale, questionnaire	Mean 48 (30-69)	2.0 (1/50)	4.0 (2/50)	16.1 (10/62)
10. Tosello, 2014 [20]	ASQ scores < -2SD	Clinical exam, ASQ	Median 37 (4-60)	5.7 (2/35)	31.4 (11/35)	20.5 (9/44)
11. Vanderbilt, 2014 [29]	CP, BDI scores < 70, bilateral blindness (unable to fix and track), deafness requiring hearing aids	Amiel-Tison, BDI	Mean 24	3.0 (3/100)	4.0 (4/100)	51.5 (106/206)

Author, year	Definition reported impairment	Outcome measure	Age in months (range)	CP % (n/N)	Reported impairment % (n/N)	Lost to FUP % (n/N)
12. Mullers, 2015 [31]	CP, speech and language delay, behavioral concerns including autism, mild motor delay	Pediatric review and patient correspondence	Median 48 (6 – 84)	3.8 (4/106)	14.2 (15/106)	10.1 (7/69) PR
13. Campos, 2016 [25]	CP, Bayley-III scores	Neuro exam, Bayley-III	Mean 6 (1-6) and 10 (7-12)	18.2 (6/33)	NA	NA
14. Sananès, 2016 [21]	ASQ scores < -2 SD	ASQ	Mean 43 (24-60)	NA	13.5 (17/126)	43.6 (109/250)
15. Van Klink, 2016 [16]	CP, Bayley < 70, bilateral blindness, deafness	Neuro exam, Bayley-III, GMFCS	Mean 24	2.8 (6/216)	5.6 (12/216)	6.0 (14/235)
16. Korsakissok, 2018 [22]	CP, severe motor or cognitive delay, bilateral blindness, deafness requiring aids	Neuro exam, ASQ, interview parents and pediatrician about learning deficiencies, and rehabilitation needs	Mean 59 (24-95)	5.2 (3/58)	12.1 (7/58)	44.8 (47/105)
17. Sommer, 2018 [32]	CP, vision impairment, hearing impairment with or without hearing aids	GMFCS, hearing and visual evaluation	Mean 18	15.4 (2/13)	NA	60.6 (20/33)
18. Schou, 2019 [23]	CP, ASQ scores < -2SD, bilateral blindness, deafness (ICD-10)	ASQ, telephone interviews, ICD-10 codes	Median 27 (11-60)	5.8 (5/86)	10.5 (9/86)	18.0 (22/122)
19. Spruijt, 2019 [17]	CP, Bayley < 70, blindness, deafness	Bayley-III, GMFCS	Mean 24	1.6 (4/258)	4.1 (10/241)	15.4 (47/305)
Total % (n/N) 95% CI				**5.1 (87/1700) 4.1-6.2**	**10.5 (194/1853) 9.1-11.9**	**20.8 (515/2475) 19.2-22.4**

Seven follow-up studies (Arias et al; 2015; Chmait et al; 2016; Chmait et al; 2019; Chon et al; 2018; van Klink et al; 2014; Ortibus et al; 2009; Peralta et al; 2013) in TTTS after laser are not included in this table because the included children are more fully described in the multi-center follow-up of this studies (Campos et al; 2016; van Klink et al; 2016; Lopriore et al; 2009; Vanderbilt et al; 2014.) Legends: CP = cerebral palsy; FUP = follow-up; n = number of children that match the description; N = number of children available for study; ASQ = Ages and Stages Questionnaire, Bayley=Bayley Scale of Infant and Toddler, WISC = Wechsler Intelligence scale for Children, Griffiths' scale = Griffiths Mental Development Scales, GMFCS = Gross Motor Function Classification System, K-ABC = Kaufman-Assessment Battery for Children, GNSE = German National Screening Examination, NA = no answer, IVH = intraventricular hemorrhage, PVL = periventricular leukomalacia, WPPSI-III = Wechsler Preschool and Primary Scale of Intelligence 3rd Edition, BDI = Battelle Developmental Inventory, PR = number is per pregnancy; CI = confidence interval.

In 4/18 studies several tests were used according to the age range of their TTTS cohort. Gray et al. (2011) used both Griffith Mental Development Scales (Griffiths' scales) (71.7%) and Bayley II and III (13.3% and 15.0%) to assess neurodevelopment and detected scores below -2SD in 13 (11.5%) TTTS-survivors. [26] Graeve et al. (2012) used the Kaufman-Assessment Battery for Children and the German national screening examination to assess cognitive and motor development in TTTS-survivors at a median age of six years and five months. [27] This cohort has the longest follow-up period of all studies included in this review. Normal test scores were achieved by 151 (79.5%) children. McIntosh et al. (2014) used the Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) in 41 children, in four (8.0%) children other tests were used, in five (10.0%) children neurodevelopment was considered normal based on parental reports. [28] Scores below -2SD were detected in one child (2.0%). Vanderbilt et al. (2014) used the Battelle Developmental Inventory scores (BDI) in two-year-old TTTS-survivors and detected cognitive scores below -2SD in one child (1.0%). [29]

In four studies, no validated test was used to assess neurodevelopment. Information on long-term outcome was obtained from parents, patient records, questionnaires, check-ups or the child's pediatrician. [30-33] Mullers et al. (2015) described 'neurodevelopmental concerns' in 14.1% (15/106) based on pediatric review and correspondence with parents. [31] These neurodevelopmental concerns were specified as speech and language delay in seven children, behavioral concerns in two children, mild motor delay in two children and CP in four children.

Neurodevelopmental impairment

A wide variety of definitions was used to report neurodevelopmental outcome. The composite outcome 'severe NDI' as defined in our Methods section was used in only 7/19 (36.8%) studies. [15-17, 22, 23, 26, 29] These studies reported NDI in 4.0% to 18.0%, with a mean of 9.7% (106/1092, 95% *CI*: 7.8-11.5).

The majority of other follow-up studies used a different definition for NDI. Three studies reported a composite outcome including CP and a score below -2SD on a developmental test, though lacking deafness and blindness. [24, 27, 28] Five studies did not define a composite outcome; two studies reported only a proportion of children with ASQ scores below -2SD and four reported CP. [20, 21, 25, 32, 33] Four studies reported a composite outcome without cognitive impairment based on validated developmental tests and used other definitions (see table 1). [18, 19, 30, 31] The prevalence of the reported adverse neurodevelopmental outcome when combining these different definitions is 10.5% [194/1853, 95% *CI*: 9.1-11.9]. Seven studies also included minor impairment defined as 'borderline' scores or scores below -1SD on developmental tests, minor neurological impairments or temporary and treatable impairments with no significant impact on daily life (Table 2). The prevalence of minor impairment ranges between 0%-25.9% with a summarized mean of 13.7% [117/853, 95% *CI*: 11.4-16.0]. [16, 17, 19, 22, 27, 28, 30]

Table 2. Minor neurodevelopmental impairment in TTTS-survivors treated with laser therapy

Author, year	Definition minor impairment	Minor impairment % (n/N)
Salomon, 2010 [19]	Neurological deficiencies with prospect to normalization, including strabismus, mildly retarded motor and speech development according to questionnaires and examination	0 (0/69)
Graeve, 2012 [27]	Either temporary and treatable neurological deficiencies including language developmental delay and strabismus or permanent deficiencies which have no prognostic significance for quality of life or life expectancy such as mild impaired fine- or gross-motor skills	11.6 (22/190)
Kowitt, 2012 [30]	Not permanent neurological morbidity	21.1 (8/38)
McIntosh, 2014 [28]	Score 70-79 on WPPSI-III	18.0 (9/50)
Van Klink, 2016 [16]	Score <-1SD on Bayley	6.0 (13/216)
Korsakissok, 2018 [22]	Moderate impairment, rehabilitation need at the time of the study, moderate learning deficiencies but class level corresponding to age, ASQ with one or two areas of difficulty, neurological examination slightly affected, no significant impact on daily life	25.9 (15/58)
Spruijt, 2019 [17]	Score <-1SD on Bayley	21.6 (50/232)
Total % (n/N) **95% CI**		**13.7 (117/853)** **11.4-16.0**

n = number of children that match the description; N = number of children available for study; ASQ = Ages and Stages Questionnaire; Bayley = Bayley Scale of Infant and Toddler; WPPSI-III = Wechsler Preschool and Primary Scale of Intelligence 3rd Edition; CP = Cerebral palsy, GMFCS = Gross Motor Function Classification System, CI = confidence interval

Control groups

Four studies compared neurodevelopmental outcome of TTTS-survivors with a control group of singletons, uncomplicated MC or dichorionic (DC)-twins. Campos et al. (2016) reported in both evaluations (1-6 and 7-12 months), more children in the TTTS group with an inadequate performance than in the control group of uncomplicated singletons. Schou et al. (2019) reported lower ASQ scores for TTTS survivors with a median age of 27 months (range 11-60) compared to a control group of uncomplicated MC-twins of 18 months (range 17-25) [–23.5 points; 95% *CI*: –44.8 to –2.2, $p = 0.03$]. [23] However, the prevalence of NDI was comparable between the TTTS-survivors and the uncomplicated MC-twins (3.1%, 3/98) when corrected for gestational age at birth, birthweight and gender ($p = 0.07$). Lenclen et al. (2009) reported comparable ASQ scores in 85 TTTS-survivors born between 24 and 34 weeks of gestational age and assessed at the corrected age of two years and 184 DC-twin controls, 216.3 ± 54 versus 225.5 ± 54 respectively (p = not significant). [18]

Sommer et al. (2018) described the outcome in TTTS-survivors born < 29 weeks of gestational age at a corrected age of eighteen months. [32] Compared to a control group of DC twins matched for gestational age, no difference in prevalence of CP, vision impairment, hearing impairment (with or without hearing aid) and growth was found. Hearing impairment was 5.7% (4/70) in DC twins versus 23.1% (3/13) in TTTS-survivors (p = 0.07).

Risk factors

An important characteristic of long-term outcome studies is the possibility to assess (perinatal) risk factors for long-term impairment. All nineteen studies included for this review assessed risk factors for their primary outcome.

The severity of TTTS, defined as Quintero stage I to V, is reported a risk factor for adverse outcome in 5/12 (41.6%) studies. [17, 19, 21, 26, 29, 34] Four studies found higher Quintero stage at laser surgery associated with adverse long-term neurodevelopmental outcome. In contrast, Sananès *et al.* (2016) reported an association between Quintero stage I, indicating less severe disease, and abnormal ASQ scores (p = 0.021). However, 63.5% (40/63) stage I cases were lost to follow-up in this study (p = 0.004), leading to possible selection bias, since lost to follow-up was 49.5% (54/109) in stage II, 38.6% (27/70) in stage III and 37.5% (3/8) in stage IV.

Prematurity and low birth weight, in particular fetal growth restriction or being small for gestational age, are well-known risk factors for adverse long-term outcome. Low gestational age at birth was reported a risk factor for adverse long-term neurodevelopmental outcome in 30.7% (4/13) studies. [15, 17, 21, 22] Additionally, Sommer et al. (2018) reported a high prevalence of CP (15.4%) in very premature infants (<29 weeks of gestational age) born after laser therapy for TTTS. [32] In the study cohort of Kowitt et al. (2012), 90.9% (10/11) children with severe neurological morbidity (see definition in table 1) were born before 32 weeks of gestation. [30] Schou et al. (2019) reported CP or ASQ-scores below -2SD in 23.1% of TTTS-survivors born before 34 weeks of gestation versus 6.6% in survivors born after a gestational age of 34 weeks. [23]

Low birth weight was reported a risk factor for long-term impairment in 44.4% (4/9) studies. [15, 17, 21, 22] Spruijt et al. (2019) reported an independent association between cognitive scores and low birth weight [Regression coefficient B 0.3; 95% *CI*: 0.1-0.6, p = 0.004] and between cognitive scores and growth restriction below the tenth percentile [Regression coefficient B -4.3; 95% *CI*: -7.9 - -0.7, p = 0.021]. [17] Sananès et al. (2016) described an association between birth weight below the fifth percentile and adverse neurodevelopmental outcome (p = 0.036): 23.1% (9/39) children with a birth weight below the fifth percentile had an abnormal ASQ. [21] Lopriore et al. (2009) found low birth weight associated with NDI [odds ratio (*OR*): 1.2 for each 100-g decrease;

95% CI*:* 1.1-1.3; *p* <0.001] though no association between NDI and growth restriction below the tenth percentile.[15]

Graeve et al. (2012) described significantly better Kaufman-Assessment Battery for Children mental processing scores in recipients compared to donors (median 106 (69-127) and 100 (70-124) respectively, *p* = 0.045), though no significant difference in overall scores. [27] Campos et al. (2016) reported an association between donor status and difficulties with expressive communication (odds ratio [OR]*:* 6.8, 95% CI*:* 1.0-44.6). [25] Altogether 11/12 (91.7%) studies did not report a difference in long-term impairment between donor and recipient twins.

In one study, cranial magnetic resonance imaging (MRI) was routinely performed in the whole study population. Chang et al*.* (2012) described impairment in one child with no cerebral injury on MRI and two children with cerebral injury on MRI and normal neurologic exams. [24] Spruijt et al. (2019) reported an association between decreased Bayley motor scores and severe cerebral injury (regression coefficient B -14.1; 95% CI: -25.0 to -3.2, *p* = 0.012), although 58.8% (10/17) of children with NDI had no severe cerebral injury on cranial ultrasound. [17]

Maternal education was associated with scores on the Battelle Developmental Inventory by Vanderbilt et al (2014). [29] Education level defined as high school or less was associated with lower scores. Lower maternal education level had a higher impact on NDI (β level 0.60, *p* < 0.001) than lower gestational age at birth (β level 0.3, *p* < 0.01) and advanced Quintero stage (β level -0.4, *p* < 0.01). In contrast, Campos et al*.* (2016) reported no association between impairment and maternal education, although they did find an association between impairment and economic class, defined according to the Brazilian Association of Research Companies, (each point decreased the risk of abnormality with 16%). [25]

DISCUSSION

In the past decade, fetal medicine centers all over the world increasingly reported on the long-term neurodevelopmental outcome after fetoscopic laser surgery for TTTS. Overall, in the last 10 years, 19 studies evaluated the long-term neurodevelopmental outcome. Severe NDI was reported in seven studies and the prevalence of severe NDI was 9.7% (range 4.0%-18.0%). The prevalence of adverse neurodevelopmental outcome (our secondary outcome) was 10.5% (table 1) and the prevalence of CP was 5.1%. Minor impairment was reported in 13.7%.

Important risk factors for adverse long-term neurodevelopmental outcome include prematurity, low birth weight and advanced Quintero stage. The association between Quintero stage and long-term impairment suggests that increasing disease severity may not only lead to increased perinatal mortality but also to increased long-term morbidity. Recipient or donor status of the fetus was not associated with adverse neurodevelopmental outcome in most studies, although two studies found lower scores on one domain. The prognostic value of severe antenatal or postnatal cerebral injury for long-term impairment remains a subject of debate. Conclusions on long-term neurodevelopmental outcome based on cerebral injury are difficult to make as cerebral injury does not directly correlate with long-term neurodevelopment. The prevalence of minor impairment implies that, even in children without obvious NDI, subtle problems may occur, including mild CP and neurocognitive impairments. These "subtle" problems can have a significant impact on the care and educational requirements of children throughout life.

The prevalence of NDI and CP in this review is equivalent to the prevalence described in a recent review by Hecher *et al*. (2018), reporting NDI in 6%-18% and CP in 3%-11% of TTTS-survivors. [35] Previous reviews of Rossi *et al*. (2011) and van Klink *et al*. (2016) reported mean NDI in 11.1% and 9.8% and CP in 4.8% and 6.1% respectively. [36, 37] In this review, though a broad range of studies was included, a similar mean prevalence was found. This indicates that since the introduction of laser therapy, severe NDI after laser surgery for TTTS has a relatively stable prevalence of about 9.7%. [37] However, this mean prevalence must be interpreted with caution as the range of reported impairment and CP is broad and most studies did not use the composite outcome NDI. Low gestational age at birth and low birth weight are well-recognized risk factors for long-term impairment: severe NDI in children born preterm is very frequent and is inversely related with gestational age and birth weight.

In several studies bias may have occurred, the majority due to an unequal distribution of Quintero stages in the follow-up group, as no Quintero stage I cases were included or a higher proportion of low or high Quintero stages were lost to follow-up. [21, 26, 28, 29] In addition, lost to follow-up was relatively high in several cohorts,

included significantly more children with low birth weights and less or more severe neonatal morbidity or the study included only very premature children (21, 29, 32).[21, 22, 29, 32] Control groups were sometimes not accurately matched in age to the TTTS-survivors. [23] Furthermore, in several studies not all children were examined by researchers and conclusions on neurological development were solely based on information from parents, treating physicians or pediatricians or medical records.

An important limitation for comparison between studies is the substantial difference in the timing of follow-up (age range from one month to ten years), their definition of the primary outcome, inclusion criteria and the methods and materials to assess outcome. The majority of studies performed their assessments at an adjusted age of two years. At this age, it is possible to discover severe developmental abnormalities that require and benefit from early intervention. However, developmental outcomes assessed during early childhood are only moderate predictors of long-term neurodevelopment, particularly for scores on cognitive tests and academic performance. Although some studies followed their cohort until a mean of five years of age, some developmental problems, including learning difficulties, speech and language deficits and communication disorders, cannot be detected until later on, once the children start becoming more socially and academically challenged at school age. In addition, definitions of primary outcome ranged widely from CP to impaired cognitive function, sometimes including blindness and hearing impairment. The aforementioned composite outcome, NDI, was unfortunately used in less than half of the included studies. Therefore, the mean prevalence of NDI must be interpreted with caution as it is based on a minority of the reported impairment. In these studies, different neurodevelopmental tests were used, like Bayley II and III, ASQ, as well as non-validated questionnaires and neurologic exams. Results were either reported as mean scores per domain of the developmental test, the proportion of children with abnormal results per domain or only overall scores, which makes it difficult to compare results between studies.

Longer follow-up of TTTS-survivors is required to understand the clinical relevance of milder forms of impairments diagnosed in early childhood and to follow speech and language development, for instance at the age of two, five and eight years. Studies reporting on long-term neurodevelopment should use a uniform definition of NDI that is, scores on neurodevelopmental tests below -2SD, CP GMFCS grade II or higher, bilateral blindness and/or severe hearing impairment. In this review, we had to include all grades of CP in the composite outcome NDI since most studies did not report or grade CP according to GMFCS. To reliably compare study results, it is important that diagnoses of individual cases are reported and in particular when there are comorbidities. Only TTTS-survivors treated with laser surgery should be included in follow-up along with an appropriate control group. When

other groups are included in follow-up, presentation of separate results on primary and secondary outcomes are recommended. Validated neurodevelopmental tests are of uttermost importance to assess neurodevelopment. Methods sections should contain a detailed description of the used definitions and methods. In the results section authors should report both mean scores, including standard deviations, per domain and on the overall test, and the proportion of children with scores below -2 SD. Consensus on these terms is necessary to allow valid comparison of cohorts, which would improve the quality of research and lead to more accurate knowledge on TTTS. Accordingly, development of a core outcome set to allow comparison of study data would be beneficial in improving the quality of research. [38, 39]

Moreover, large prospective multicenter studies with stringent neuroimaging and long-term follow-up protocols could provide more clarity around the association between cerebral injury and NDI.

In conclusion, TTTS-survivors are at increased risk for NDI and close fetal monitoring and long-term follow-up remains required. Continuing follow-up until at least school age is recommended. International collaboration in long-term follow-up of TTTS-survivors to form universal inclusion criteria, developmental tests, ages at assessment, and outcome measures are of great importance to improve knowledge on long-term neurodevelopmental outcome and allow adequate parental counseling.

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Supplemental Content 1. Methods

Search strategy (PubMed-version)
(("twin-twin transfusion syndrome"[tw] OR "twin to twin transfusion syndrome"[tw] OR "twin transfusion syndrome"[tw] OR "TTTS"[tw] OR "Fetofetal Transfusion"[Mesh] OR "fetofetal transfusion"[tw] OR "twin transfusion"[tw] OR "twin transfusions"[tw]) AND ("fetoscopic laser surgery"[tw] OR "fetoscopic laser"[tw] OR (("Fetoscopy"[mesh] OR "Fetoscopes"[mesh] OR fetoscop*[tw] OR foetoscop*[tw] OR amnioscop*[tw] OR embryoscop*[tw]) AND ("Laser Therapy"[Mesh] OR "Lasers"[mesh] OR laser*[tw])) OR "Laser Therapy"[mesh] OR "laser therapy"[tw] OR "laser surgery"[tw] OR "laser coagulation"[tw] OR "Lasers"[mesh] OR laser*[tw]) AND ("Neurodevelopmental Disorders"[Mesh] OR "neurodevelopmental disorders"[tw] OR "neurodevelopmental disorder"[tw] OR neurodevelop*[tw] OR neuro-develop*[tw] OR "Human Development"[Mesh] OR "Human Development"[tw] OR "Adolescent Development"[tw] OR "Child Development"[tw] OR "Language Development"[tw] OR "Child Language"[tw] OR "Cognition"[Mesh] OR "cognition"[tw] OR "cognitive"[tw] OR "Cognition Disorders"[Mesh] OR "motor development"[tw] OR "Motor Skills"[Mesh] OR "Motor Skills"[tw] OR "Motor Skill"[tw] OR "Motor Performance"[tw] OR "neurological outcome"[tw] OR "neurological outcomes"[tw] OR "neurologic outcome"[tw] OR "neurologic outcomes"[tw] OR "Cerebral Palsy"[Mesh] OR "Cerebral Palsy"[tw] OR bayley*[tw] OR "BSID"[tw] OR "ages and stages"[tw] OR "ASQ"[tw] OR "Surveys and Questionnaires"[mesh:noexp] OR "Patient Health Questionnaire"[Mesh] OR questionnair*[tw] OR "scale"[tw] OR "scales"[tw] OR "Neuropsychological Tests"[mesh] OR "Motor Activity"[mesh] OR "long-term morbidity"[tw] OR "Neurobehavioral Manifestations"[Mesh] OR "Neurobehavioral Manifestations"[tw] OR "Neurobehavioral Manifestation"[tw] OR Neurobehav*[tw] OR neuro-behav*[tw]))

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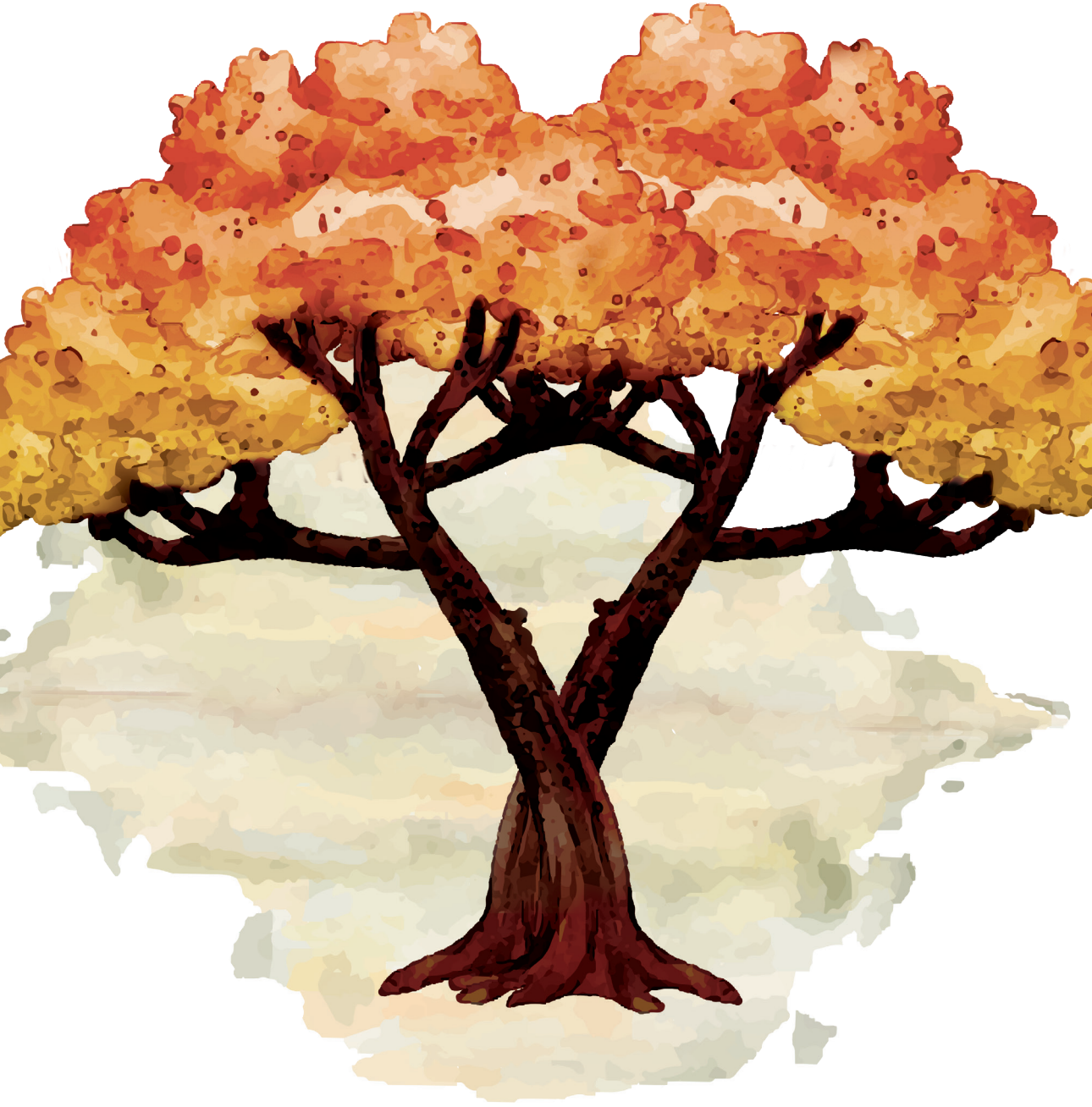

7

Chapter 7

Neurodevelopmental trajectories of preterm born twin-twin transfusion syndrome survivors: from birth to five years of age

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ABSTRACT

Objective: To investigate the neurodevelopmental outcome at two and five years of age in survivors of twin-twin transfusion syndrome (TTTS) treated with fetoscopic laser surgery and born premature- and/or small for gestational age.

Study design: At two and five years of age, standardized neurologic, motor and cognitive assessments were performed by a neonatologist, a pediatric physical therapist and psychologist. Behavior was assessed using a validated questionnaire completed by parents.

Results: Neurodevelopmental assessment at both time points was available for 73 survivors of TTTS. Mild to moderate neurodevelopmental impairment (NDI) was detected in 34% of survivors (25 of 73) at five years, compared with 25% (18 of 73) at two years ($p = 0.178$). Severe NDI was observed in 12% (9 of 73) at five years and in 3% (2 of 73) at two years ($p = 0.035$). Mean cognitive score was lower at the five-year follow-up (90.7 ± 12.3 versus 95.6 ± 13.1 at two years; $p = 0.001$), and more children were diagnosed with mild cognitive impairment at five years (29% versus 11% at two years; $p = 0.007$). When comparing individual outcomes at both time points, 35% (25 of 71) moved from a normal outcome or mild to moderate impairment at two years toward more severe impairment at five years.

Conclusions: A high rate of mild to moderate cognitive impairment and severe NDI at five years was not identified at age two years. Our data highlight the importance of longitudinal follow-up of survivors of TTTS beyond age two years and emphasize the precautions that should be taken when diagnosing an absence of impairment before school age.

INTRODUCTION

Twin-twin transfusion syndrome (TTTS) is a complication in monochorionic twin pregnancies caused by an imbalance in blood flow through the anastomoses on the shared placenta. It usually occurs between 16 and 26 weeks of pregnancy. Without timely intervention, TTTS is lethal in 73-100% of cases.[1] Fetoscopic laser coagulation of the intertwin anastomoses is the preferred treatment.[2] Although intervention has increased the survival rates of both twins from 50% to 70% and survival of at least one twin from 81% to 92%, TTTS is associated with high mortality and morbidity in survivors.[3] One important aspect of morbidity is long-term neurodevelopmental impairment (NDI). The reported prevalence of severe NDI is approximately 10%, and minor NDI is detected in an additional 14%.[4] However, these outcomes are based primarily on studies in toddlers and preschoolers, using different outcome measures and often without validated tests.[5-11] Favorable outcomes at an early age do not always reflect a child's abilities later in life. With increasing age and additional demands on the child's functioning, particularly at school age, the presence of developmental impairments is likely to become more visible.[12] Knowledge of neurodevelopmental outcome beyond the age of two years and at least until school age is important as it will benefit the counseling of parents of twins with TTTS and support early intervention strategies to improve outcomes. The aims of the present study were to investigate the rate of NDI in survivors of TTTS treated with fetoscopic laser surgery and born before 30 weeks of gestation and/or small for gestational age (SGA; <P10) at two and five years of age and to compare individual outcomes between the two time points.

METHODS

All survivors of TTTS treated with fetoscopic laser surgery and born between 2009 and 2014 at the Leiden University Medical Center were eligible if they were born before 30 weeks of gestational age and/or at SGA (ie, < 10th percentile Perined [Hoftiezer]) growth chart of 2008) with a birth weight < 1500 grams. [13] In the Netherlands, all children born at < 30 weeks of gestational age and/or SGA with a birth weight < 1500 grams undergo a standardized neurodevelopmental assessment at two and at five years of age, according to the national guideline of the Dutch Neonatal Working Group on Follow-Up. If only one of the twins is born SGA, the appropriate grown co-twin is tested as well. For this study, only survivors of TTTS with completed follow-up data at both time points were included. Children who could not be assessed due to severe motor, neurosensory, or cognitive impairments were assigned the corresponding lowest score. Some of the children had been included in a previous study reporting neurodevelopmental outcome at two years of age. [11]

The Medical Ethics Committee Leiden-The Hague-Delft reviewed the protocol of this anonymized retrospective study with prospectively gathered follow-up data and issued a statement of no objection (G20.010).

Baseline characteristics of the study population

Perinatal data were collected from patient records, including TTTS stage according to internationally accepted staging criteria (I to V) [14], donor or recipient status, gestational age at fetoscopic laser surgery (in weeks), fetal demise, gestational age at birth (in weeks), birth weight, sex, neonatal mortality (within 28 days after birth), and severe cerebral injury. Severe cerebral injury was defined as the presence of at least one of the following: cystic periventricular leukomalacia grade ≥ 2, intraventricular hemorrhage grade ≥ 3, ventricular dilatation > 97th percentile, porencephalic or parenchymal cysts, and arterial or venous infarction or other severe cerebral lesions associated with adverse neurological outcome.[15-17] Maternal education was classified into three categories: primary and general secondary education, intermediate, and higher vocational education and university.

Outcome assessment and measures: Children and their parents were invited for follow-up visits at our outpatient clinic at corrected ages (for prematurity) of two and at five years. All children were seen by our dedicated neonatal follow-up team of pediatric psychologists, pediatric physical therapists and neonatologists. At two years of age, cognitive and motor development was assessed with the Bayley Scales of Infant and Toddler Development third Dutch edition (Bayley-III-NL). [18] At five years of age, cognitive development was assessed using the Wechsler Preschool and Primary Scale of Intelligence third Dutch edition (WPPSI-III-NL).[19] Results of both tests were interpreted according to the Dutch norms. The Bayley-III-NL cognitive and motor composite scores and WPPSI-III-NL verbal, performance and total IQ scores follow a normal distribution with a normed mean of 100 and an SD of 15. Children had mild to moderate cognitive or motor impairment with scores of 70 to 84 (between -1 and -2 SD) or severe impairment with scores below 70 (-2 SD). Motor development at five years of age was examined with the Movement Assessment Battery for Children second Dutch edition (M-ABC-II-NL).[20] According to the M-ABC-II-NL, children had either mild to moderate motor impairment with scores between the 5th and 15th percentiles or severe motor impairment with scores below the 5th percentile. At both time points, a neurologic examination was performed by a neonatologist. Cerebral palsy (CP) was classified grade I-V according to the Gross Motor Function Classification System (GMFCS).[21]

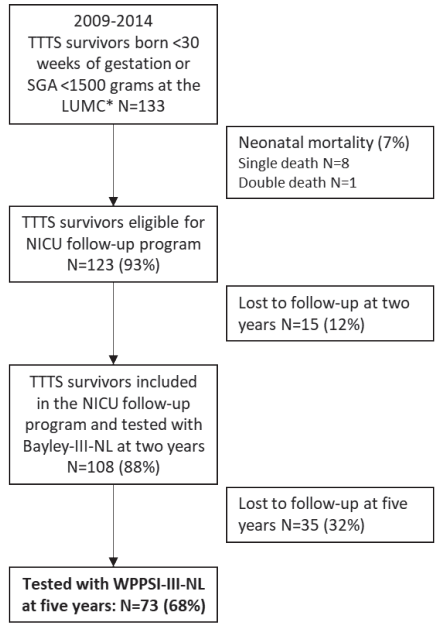
Parents reported on behavioral problems at both time points using the Child Behavior Checklist (CBCL).[22] Age standardized t-scores were obtained for internalizing (withdrawal, somatic complaints, anxiety/depression), externalizing (delinquent or

rule-breaking and aggressive behavior) and total problem behavior, with higher scores indicating higher levels of problem behavior. Children were classified as having mild to moderate behavioral problems with t-scores in the borderline clinical range (≥ 84th percentile), or severe behavioral problems with t-scores in the clinical range (≥ 90th percentile).

Severe NDI, a composite outcome score for both time points, was defined as at least one of the following: Bayley-III-NL cognitive and/or motor score < 70, WPPSI-III-NL full scale, verbal or performance score < 70, M-ABC-II score ≤ the 5th percentile, CP GMFCS ≥ grade 2, blindness or severe visual impairment and/or severe hearing impairment (ie, bilateral deafness, treatment in an audiologic center, severe neurosensory hearing loss or hearing loss requiring amplification). Mild to moderate NDI was defined as Bayley-III-NL cognitive and/or motor score < 85 or WPPSI-III-NL full scale, verbal or performance scores < 85, M-ABC-II scores between the 5th and 15th percentiles, CP GMFCS grade 1, mild hearing loss (up to 30 dB) and/or mild visual impairment (defined as needing correction with > +4 or < -4 optical amplification). If a child already had been tested for follow-up elsewhere, the test results were requested with written permission from the parents.

Statistical analysis

Results are presented as number of cases and percentage, mean ± SD or median (interquartile range (IQR)), depending on the distribution of the variable. Perinatal factors of survivors of TTTS with and without follow-up at both time points were compared to assess whether selective loss to follow-up occurred. Proportions were compared using a χ^2 test or Fisher exact test. Continuous variables were calculated using the independent *t*-test or Mann-Whitney-*U* test. To account for the fact that observations between co-twins are not independent, these analyses were performed using generalized estimating equations. To assess for a difference in the group distribution of the composite NDI (mild-moderate and severe) score and for each developmental domain (CP, cognitive scores, vision, hearing, and behavior) separately, the marginal homogeneity test was conducted (to adjust for the effect of paired testing). In the event of a significant difference ($p < 0.05$), the McNemar tests was conducted post-hoc. Characteristics of the group with NDI (mild-moderate or severe) and the group without NDI were compared using a χ2 test, Fisher exact test, or independent *t*-test. All statistical analyses were performed using SPSS version 25.0 (IBM).



*= fetal demise N=36 (16 double and 4 single demise); LUMC = Leiden University Medical Center

Figure 1. Flowchart of the study population

RESULTS

Study group

Between 2009 and 2014, 133 survivors of TTTS were born preterm at < 30 weeks or SGA with a birth weight <1500 g at our center after treatment with fetoscopic laser surgery for TTTS. The neonatal mortality rate was 7% in liveborn children (Figure 1). Overall, 123 survivors of TTTS were eligible for long-term follow-up according to the Dutch Guideline for Neonatal Follow-Up. Follow-up assessment at two years with Bayley-III-NL was available for 88% (108/123) of survivors of TTTS and follow-up at both time points for 68% (73 of 108) of survivors. The perinatal characteristics of the group tested at both time points and the group tested only at two years were comparable (Table 1).

Table 1. Perinatal characteristics and neonatal outcome and follow-up assessment at two years of the TTTS survivors tested at both timepoints versus TTTS survivors tested at two years of age only

	Two- and five year group (n = 73)	**Two year group (n = 35)**	***p*-value**
Gestational age at laser in weeks, median (IQR)	20.0 (17.5-23.0)	19.0 (17.0-24.0)	0.70
TTTS staging, n (%)			
stage 1	14 (19)	4 (11)	0.49
stage 2	27 (37)	14 (40)	0.94
stage 3	28 (38)	17 (49)	0.41
stage 4	4 (6)	0 (0)	-
Donor, n (%)	38 (52)	17 (49)	0.30
Female, n (%)	50 (69)	18 (51)	0.19
Gestational age at birth in weeks, median (IQR)	29.9 (28.3-32.1)	30.0 (28.6-31.9)	0.84
GA < 28 weeks	16 (22)	4 (11)	0.31
GA < 32 weeks	55 (75)	27 (77)	0.55
Birth weight in grams, median (IQR)	1280 (990-1600)	1330 (1205-1400)	0.36
Small for gestational age (p < 10), n (%)	24 (33)	11 (31)	0.32
Single survivor, n (%)	5 (7)	1 (3)	0.40
Maternal education, n (%)			
primary, general secondary education	4 (6)	7 (20)	0.13
intermediate	32 (50)	15 (43)	0.55
higher vocational education, university	32 (44)	13 (37)	0.75
Severe cerebral injury, n (%)	7 (10)	3 (9)	0.86
Neonatal morbidity[a], n (%)	30 (41)	11 (31)	0.33
Bayley cognitive index, mean ± SD	95.64 ± 13.1	97.3 ± 18.2	0.59
Cognitive scale score	8.97 ± 2.7	9.57 ± 3.23	0.31
Bayley motor index, mean ± SD	**97.4 ± 12.7**	**103.4 ± 13.6**	**0.039**
Fine motor scale score	**10.14 ± 2.85**	**11.4 ± 2.39**	**0.044**
Gross motor scale score	8.63 ± 2.8	9.57 ± 3.1	0.14
Mild to moderate NDI, n (%)	**18 (25)**	**1 (3)**	**0.022**
Severe NDI, n (%)	2 (3)	4 (11)	0.09
Cerebral Palsy, n (%)	3 (4)	1 (3)	0.75
GMFCS grade I	3 (4)	-	-
GMFCS grade II-V	-	1 (3)	-

Data presented as n (%), median (IQR = interquartile range) or mean ± SD.

Neonatal outcome and follow-up assessment at two years

Table 1 presents the neonatal outcome and follow-up data at two years for both groups. Bayley-III-NL motor index scores were significantly lower for the group tested at both time-points compared with the group tested at two years (mean 97.4 ± 12.7 vs 103.4 ± 13.6; $p = 0.039$). More children were diagnosed with mild NDI in the group tested at both time points compared with the group tested only at two years (25% [18 of 73] vs 3% [1 of 35]; $p = 0.022$). CP (GMFCS grade I) was diagnosed in 4% of children (3 of 73) tested at both timepoints and in 3% of children (1 of 35, GMFCS grade II) tested tested at age two years only.

Neurodevelopmental outcomes in TTTS survivors from two to five years of age

Table 2 presents the results of the cognitive, motor, behavioral and neurologic assessments of the survivors of TTTS tested at both time points. Cognitive scores were significantly lower at age five years compared with age two years (mean, 90.8 ± 12.3 vs 95.6 ± 13.1; $p = 0.001$). The percentage of children with cognitive scores within the normal range dropped from 88% (64 of 73) at age two years to 64% (47 of 73) at reassessment ($p = 0.000$). Significantly more children were diagnosed with a mild-moderate cognitive impairment at age five years than at age two years (29% [21 of 73] vs 11% [8 of 73]; $p = 0.007$). Severe cognitive impairment was present in 7% of the children (5 of 73) at age five years.

At the five year reassessment, fewer children were diagnosed with a mild -moderate motor impairment than were seen at two years (6% [4 of 68] vs 17% [12 of 73]). Significantly more children had a severe motor impairment at five years (7% [5 of 68] vs 1% [1 of 73]). The individual CP diagnoses did not change from two to five years, with 4% (3 of 73) with GMFCS grade I. Neither blindness nor deafness was observed; one child had a mild visual impairment at both time points. At age five years, 14% of the children (10 of 70) had borderline to clinical behavioral problems compared with 9% (6 of 70) at two years ($p = 0.527$). Only two children had borderline to clinical behavioral problems at both time points.

Rate and course of neurodevelopmental impairment

The rate of NDI was significantly different between the two time points ($p = 0.005$), owing to an increase in the number of children with severe NDI at five years, from 3% (2 of 73) at two years to 12% (9 of 73) at five year reassessment ($p = 0.035$). There was a decrease in the number of children with a normal neurodevelopmental outcome, from 73% (53 of 73) at two years to 53% (39 of 73) at five years ($p = 0.004$). Mild-moderate NDI was present in 34% of the children (25 of 73) at five years.

Table 2. Neurodevelopmental outcome of the 73 TTTS survivors at two to five years of age

	Two year assessment n = 73	**Five year assessment n = 73**	***p*-value**
Age in months, median (IQR)	26 (25-27)	69 (67-71)	
Cognitive development, mean ± SD	*Bayley-III-NL*	*WPPSI-III-NL*	**<0.001**
Cognitive index/ Full scale IQ	**95.64 ± 13.1**	**90.75 ± 12.3**	**0.001**
Verbal IQ		94.4 ± 13.9	
Performance IQ		90.7 ± 11.7	
Normal range, n (%)[a]	**64 (88)**	**47 (64)**	**<0.001**
Mild - moderate impairment[a]	**8 (11)**	**21 (29)**	**0.007**
Severe cognitive impairment[a]	1 (1)	5 (7)	0.10
Motor development, n (%)	*Bayley-III-NL*	*M-ABC-II-NL (n = 68)*	0.88
Normal range	60 (82)	59 (87)	0.32
Mild - moderate impairment	**12 (17)**	**4 (6)**	**0.021**
Severe motor impairment	1 (1)	5 (7)	0.10
Behavior, borderline to clinical, n (%)	*CBCL (n = 70)*	*CBCL (n = 70)*	0.86
Internalizing problems	8 (11)	12 (17)	0.32
Externalizing problems	9 (13)	9 (13)	0.48
Total behavior problems	6 (9)	10 (14)	0.53
Cerebral Palsy, GMFCS grade I, n (%)	3 (4)	3 (4)	-
Neurodevelopment, composite, n (%)			**0.005**
Normal	**53 (73)**	**39 (53)**	**0.004**
Mild – moderate impairment	18 (25)	25 (34)	0.18
Severe impairment	**2 (3)**	**9 (12)**	**0.035**

Data are presented as n (%) or mean ± SD or median (IQR); [a] = cognitive outcome at five years is based on WPPSI-III-NL Total IQ, Verbal IQ and Performance IQ-scores; Bayley-III-NL = Bayley Scales of Infant and Toddler development 3rd Dutch Edition; WPPSI-III-NL = Wechsler Preschool and Primary Scale of Intelligence 3rd Dutch edition; M-ABC-NL = Movement Assessment Battery for Children 2nd Dutch edition; CBCL = Child Behavior Checklist; GMFCS = Gross Motor Functioning Classification System.

Neurodevelopmental trajectories

Figure 2 shows the individual neurodevelopmental trajectories and change in severity of NDI from age two to five years. Of the 53 children with a normal outcome at two years, 34 (64%) also had a normal outcome at five years (Figure 2), 16 (30%) moved from a normal neurodevelopmental outcome to mild NDI at five year reassessment and 3 (6%) from normal neurodevelopment at two years to severe NDI at five years. Of the 18 children with mild-moderate NDI at two years, 8 (44%) remained in the mild NDI group, 4 (22%) improved to a normal outcome, and 6 (33%) deteriorated to severe NDI. One child diagnosed with a severe motor developmental delay at age two years

(Bayley-III-NL motor score of 69) had normal motor development at age five years. This was due to the fact that the child could not walk at age two years but started walking after that point.

			Five-year assessment		
			Normal	Mild impairment	Severe impairment
Two-year assessment	Cognitive		47 (64%)	21 (29%)	5 (7%)
		Normal N=64 (88%)	46 (72%)	17 (27%)	1 (20%)
		Mild impairment N=8 (11%)	1 (13%)	3 (38%)	4 (50%)
		Severe impairment N=1 (1%)	0 (0%)	1 (100%)	0 (0%)
	Motor		59 (87%)	4 (6%)	5 (7%)
		Normal N=60 (82%)	49 (89%)	2 (4%)	4 (7%)
		Mild impairment N=12 (17%)	9 (75%)	2 (17%)	1 (8%)
		Severe impairment N=1 (1%)	1 (100%)	0 (0%)	0 (0%)
	Composite		39 (54%)	25 (34%)	9 (12%)
		Normal N=53 (72%)	34 (64%)	16 (30%)	3 (6%)
		Mild NDI N=18 (25%)	4 (22%)	8 (44%)	6 (33%)
		Severe NDI N=2 (3%)	1 (50%)	1 (50%)	0 (0%)

Figure 2. Change in neurodevelopmental outcome from two to five years of age
NDI = neurodevelopmental impairment

Overall, at a group level, neurodevelopment was normal at both time points in 47% of the children (34 of 73). In 8% (6 of 73), neurodevelopmental outcome at five years improved from mild-moderate NDI to normal development in 5% (4 of 73) and from severe to normal development in one child. In 34% (25 of 73), neurodevelopment at five years deteriorated from normal to mild in 22% (16 of 73), from mild to severe NDI in 8% (6 of 73), and from normal development to severe NDI in 4% (3 of 73). Only 58% of children (42 of 73) remained in the same neurodevelopmental category at both time points.

The 34 children with mild-moderate or severe NDI at age five years did not differ from the 39 children without NDI at five years with respect to possible risk factors for adverse outcome, including gestational age at birth, donor status, SGA, being a single survivor, severe cerebral injury, and maternal education (p >0.05) (Table 3). Significantly more male survivors had mild or severe NDI at the five year assessment (p = 0.033).

Table 3. Characteristics of children with and without NDI

		With mild to moderate or severe NDI n = 34	**Without NDI n = 39**	***p*-value**
TTTS stage	1	9 (23)	5 (15)	-
	2	13 (33)	14 (41)	0.69
	3	14 (36)	14 (41)	0.34
	4	3 (8)	1 (3)	0.37
Gestational age at birth in weeks		30.0 (25.6-35.3)	29.7 (25.9-36.4)	0.74
Donor		17 (50)	21 (54)	0.74
Female		**19 (56)**	**31 (79)**	**0.030**
Small for gestational age		14 (41)	10 (26)	0.16
Single survivor		1 (3)	4 (10)	0.22
Severe cerebral injury		5 (15)	2 (5)	0.24
Maternal educational level; higher vocational education, university		11 (32)	21 (54)	0.07

Data is presented as n (%) or mean ± standard deviation or median (min-max NDI= neurodevelopmental impairment, composite outcome.

DISCUSSION

Principle findings

This study found relatively high rates of mild-moderate (34%) and severe (12%) NDI in school-aged survivors of TTTS that were not detected when the same children were examined as toddlers. Our findings indicate that neurodevelopment examined at age two years changed in the following years in 42% of children. Therefore assessment at age two years might reliably predict neurodevelopmental outcome in the future. In addition, behavioral problems observed at age two years can be completely resolved at age five years and new or other problems may occur. Our findings highlight the importance of ongoing follow-up, as early termination could possibly lead to unnecessary delay in detecting neurodevelopmental problems in this high risk group. At the five year reassessment, we observed significantly lower cognitive scores and more children with severe NDI compared with the assessment at age two years. Overall, 36% moved from normal neurodevelopment at two years to mild-moderate or severe NDI at five years. Only 58% of the children were in the same neurodevelopmental outcome category at both time points.

The reported 12% rate of severe NDI at five years is comparable to NDI rates reported in other studies, although most studies included survivors of TTTS born at >30 weeks of gestation and with a birth weight appropriate for gestational age.[4] Sananès et al. and Mullers et al. reported NDI in 13% and 14% of survivors of TTTS at a 43- and 48-month assessment, respectively.[23, 24] The mean gestational age at birth in these studies was 33.0 and 29.7 weeks, respectively, and in the first study, SGA was reported in 13% (< 5th percentile) of the children. Graeve et al. examined survivors of TTTS at two years and at six years and reported severe NDI in 9%.[5] In this group, 23% of the survivors of TTTS were born before 32 weeks of gestation. Concordant with our findings, these authors reported more children with NDI at age six years compared with the two-year assessment (11% [21 of 190] vs 4% [8 of 190]); however, unlike in our study, this difference was not statistically significant.

The rate of mild-moderate NDI (34%) at the five-year assessment in our study is higher than the rates reported in other studies, which ranged from 0 to 26% based on a variety of definitions and in most cases measured at age two years.[4-11] McIntosh et al. reported 'borderline cognitive impairment', defined as a WPPSI full-scale IQ score of 70-79, in 18% of survivors of TTTS born at a mean gestational age of 32 weeks with 39% born SGA (<P10).[8] In our study, a substantially wider spectrum of criteria was used to classify mild-moderate NDI, that is, WPPSI-III-NL verbal, performance, and/or full scale IQ of 70-84, M-ABC-II-NL scores between the 5th and 15th percentiles, CP GMFCS grade 1 and/or minor visual/hearing impairment. We also tested the children

at a mean age of five years and nine months, whereas the children in the study of McIntosh et al. were tested at age four years.

A comparable course of neurodevelopment is reported in studies of preterm born children without TTTS. A follow-up study from Sweden assessed 91 children born before 32 weeks of gestation at age 2.5 years and 6.5 years, using the Bayley-III, WPPSI-III, and Wechsler Intelligence Scale for Children 4th edition. [25] They reported cognitive impairments at the 6.5-year assessment in 22% of children (19 of 88) with normal results on the Bayley at the 2.5-years assessment. A German study in two-, five- and ten-year-old preterm-born children, born before 28 weeks of gestation, reported similar large variations in neurodevelopment between age two and five years, respectively, and 9% and 25% of the children scored in a lower category on cognitive and motor development, respectively, at age five years. [26] Variations between age five and ten years were smaller. In addition, a similar shift in individual behavioral outcomes was described as in our study. Between age five and ten years, 43% of children had a change in behavioral category; 15% went from borderline and clinical range to normal behavior scores and 21% changed from normal behavior scores to scores in the borderline to clinical range. A previous study by our center reported a similar rate of behavioral problems in survivors of TTTTS as in the normal population.[27] The rate of behavioral problems in this study is consistent with these results.

At a younger age, impairment can potentially remain concealed due to low test sensitivity (i.e., Bayley scales vs Wechsler scales). The previously mentioned study from Sweden reported the sensitivity and specificity of Bayley-III cognitive scores in predicting scores on Wechsler scales. [25] The specificity of Bayley scores below 2 SD in predicting WPPSI scores below 2 SD was high (99%), although sensitivity was low (20%). Only 44% with scores below -1 SD at age 2.5 years, still scored below -1 SD. At 6.5 years, 22% of the children with scores below -1 SD had average scores at 2.5 years. Another possible explanation is that some problems may only arise as children age with increasing demands on the child's functioning, especially their academic, cognitive and social-emotional functioning. In that case, children do not 'deteriorate' but instead 'grow into' seemingly new deficits as they fail to make age-appropriate developmental gains. [28]

Strengths and limitations

The scientific literature contains only a few studies on neurodevelopment beyond age two years in survivors of TTTS treated with laser therapy and most studies did not use a validated neurodevelopmental test in all their subjects. One of the strengths of this study is the follow-up of patients until age five years using internationally accepted and validated tests.

Follow-up assessment of all treated survivors of TTTS at the age of two years is standard of care in our center since 2015. Before 2015, not all children treated with fetal therapy were included in long-term follow-up, only those born premature or SGA. The group of children included in this study likely represents a more at-risk group compared with survivors of TTTS in general, because our study group was born more premature or SGA, which is associated with a higher rate of neonatal and long-term morbidity. This might have led to an overestimation of the overall rate of NDI. However, the 34 survivors of TTTS with mild-moderate or severe NDI at age five years did not differ from the 39 children without NDI at five years with respect to important risk factors for long-term NDI, including severe cerebral injury, gestational age at birth and birth weight. Only female sex was associated with better neurodevelopmental results at five years; however, this study was not designed to distinguish outcomes by sex, owing to the unequal distribution of females (69%) and males (31%) in our follow-up group. The study was not powered to demonstrate associations with known risk factors for NDI, such as prematurity and birth weight. In addition, the design of this study was not suited to distinguish between the influence of TTTS and prematurity on the trajectories. The discrepancies in NDI at age two years and five years could be due to TTTS, prematurity, or a combination.

Conclusions

In this study, we observed 34% mild and 12% severe NDI in five year-old survivors of TTTS who were born premature (< 30 weeks) and/or SGA (< 1500 grams and <P10). Between the two time points, we observed a change in neurodevelopmental outcome, particularly concerning cognitive and behavioral scores. We conclude that in the future, predictions of neurodevelopmental outcome should not be based solely on the examination at age two years. Follow-up of survivors of TTTS at five years and preferably also at eight years and during adolescence with standardized developmental tests can provide more insight into the neurodevelopmental trajectory of survivors of TTTS. Accurate and timely detection of NDI is important to offer appropriate developmental support and to help caregivers in the counseling of future parents and survivors of TTTS.

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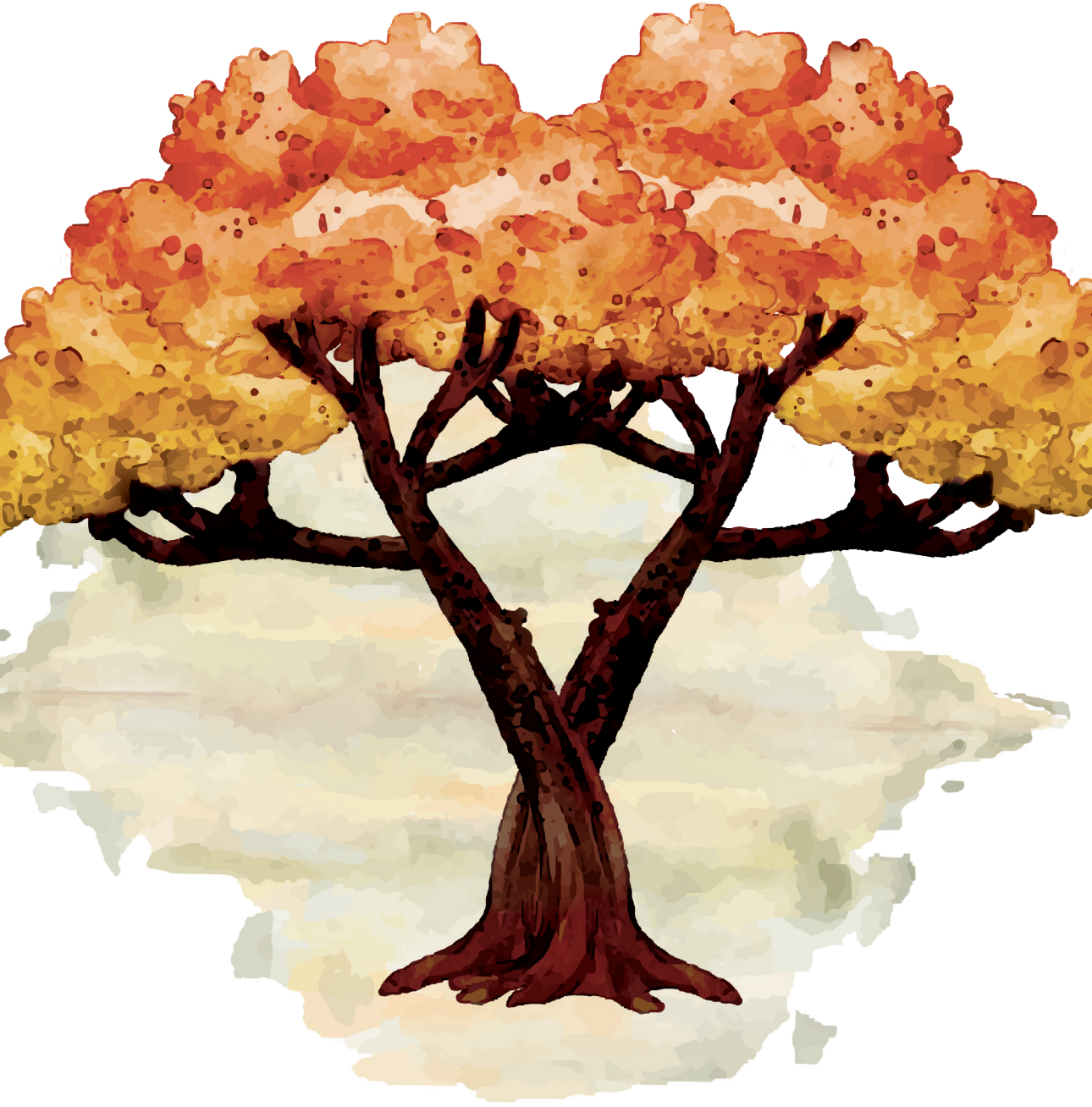
Discussion and summary



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Chapter 8

General Discussion

GENERAL DISCUSSION

Twin-twin transfusion syndrome (TTTS) is a complication affecting 10% of all monochorionic twin pregnancies.[1] Without treatment TTTS is generally lethal.[2] Fetoscopic laser surgery is the preferred and only causal treatment. The aim of fetoscopic laser surgery is dichorionization of the fetal blood circulations by coagulating all connecting vascular anastomoses. This procedure improves survival rates dramatically but is not without risks.

The aim of this thesis was to study antenatal complications of TTTS pregnancies treated with fetoscopic laser surgery and to explore postnatal and long-term neurodevelopmental outcomes in TTTS survivors.

ANTENATAL COMPLICATIONS

Residual anastomoses and placental studies

Separating the fetal blood circulations by coagulating all intertwin anastomoses nullifies the intertwin transfusion, thereby curing the TTTS. However, during surgery anastomoses might be missed or may be technically unreachable. These residual anastomoses can cause TTTS to persist or can reverse it, where the former donor becomes the recipient and the former recipient the donor.[3, 4] Residual anastomoses can also cause post-laser twin anemia polycythemia sequence (TAPS).[5] Rates of residual anastomoses vary widely between studies from 3.5% up to 75% and are frequently not reported. [6-11] Unfortunately, placental examination and injection with colored dye is not part of the routine follow-up in every fetal therapy center. Importantly, (miniscule) residual anastomoses can only be detected with thorough and systematic placental examination. By massaging color dye in the placental vessels even miniscule anastomoses can be visualized. Placental examination enables detailed documentation of residual anastomoses and facilitates retrospective evaluation of the laser procedure. In this way fetal surgeons receive direct feedback on the performed procedure and can learn from possible errors, positively influencing their learning curves. In addition, placental examination is fundamental in understanding the angioarchitecture in TTTS, TAPS and other complicated monochorionic twin pregnancies.

Placental examination with color dye is standard care for all treated TTTS placentas in our center since 2002. [12] In this thesis (chapter 2) residual anastomoses after laser surgery for TTTS were detected in 21% (68/371) of examined placentas.[13] In placentas treated with the Solomon technique residual anastomoses were detected less frequently compared to when the Selective technique was used. Documentation

of residual anastomoses for more than two decades provides an overview on the rate of residual anastomoses over time (Figure 1).

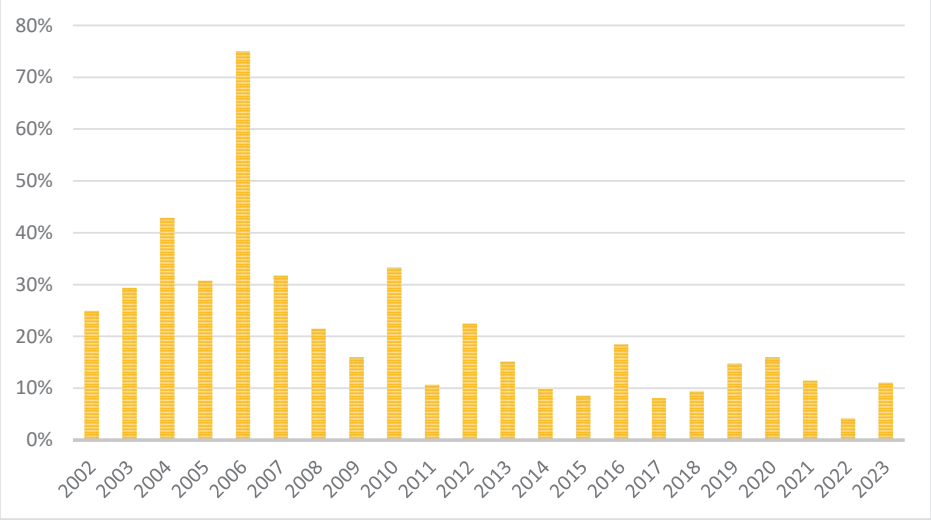


Figure 1. Percentage of residual anastomoses over time

Of note, in 2006 lost to follow-up of placentas was high due to logistic reasons and only 8 placentas were injected, of which 6 with residual anastomoses. The rate of residual anastomoses has declined significantly. This decrease could partly be attributed to the introduction of the Solomon technique in 2007. However, awareness of the dangers of residual anastomoses and a learning curve effect of the fetal surgeons are likely additional components of the declined rate. Despite this decrease in residual anastomoses, fetal therapy centers should closely monitor pregnancies after laser therapy as almost half of these cases with residual anastomoses developed recurrent TTTS or post-laser TAPS. We also discovered that prediction of residual anastomoses during or directly after fetoscopy laser surgery is deceitful. Even after the fetal surgeon considered the procedure successful, residual anastomoses were still found in almost 1 in 6 placentas. Therefore regular screening is imperative even after laser surgery. We suggest at least fortnightly ultrasound examinations, followed by postnatal placental examination. Without accurate placental examinations, completeness of laser therapy cannot be determined.

Post-procedural amniotic band syndrome

Post-procedural amniotic band syndrome was detected in 2% of the pregnancies after fetoscopic laser therapy for TTTS.[14] While the prevalence of spontaneous amniotic band syndrome ranges between 0.007% and 0.08%.[15] The etiology of spontaneous amniotic band syndrome is not yet fully understood. Multiple theories

exist and various additional comorbidities are described in medical literature.[16] Post-procedural amniotic band syndrome is considered a rare complication resulting from damage to the fetal membranes and probably differs in etiology from spontaneous amniotic band syndrome. In chapter 3 we detected a relation between amniotic bands and chorion amnion separation which strengthens this hypothesis. Although spontaneous amniotic band syndrome is also associated with limb-body-wall-complex and severe congenital malformations, we detected predominantly amputations of distal digits as fingers and toes.[16] The etiology of spontaneous amniotic band syndrome presumably lies earlier in embryogenesis. In one case in this thesis the amniotic band constricted the umbilical cord, leading to fetal demise. Mortality rates are high when amniotic band syndrome involves the umbilical cord.[17] In this thesis, amniotic bands were not reported in antenatal ultrasound records. The bands were probably not detected because they were small and primarily encircled toes. Nevertheless, perinatologists should be aware of amniotic bands as consequences can be quite severe and even lethal. Monitoring of TTTS pregnancies after fetoscopic laser therapy and screening for amniotic bands is crucial, especially when chorion amnion separation is detected. In some fetal therapy centers, fetoscopic salvation of these bands have proven successful.[18] Particularly if amniotic bands are limited to an extremity or the umbilical cord, salvation can be feasible and in some cases lifesaving, although the risks of (another) fetal surgery should be taken into account. [19]

Timing is everything

Most fetoscopic laser surgeries are performed around 20 weeks of gestation. Occasionally TTTS occurs very early or late in gestation. The severity of TTTS often does not permit an expectant approach and laser surgery is performed sometimes as early as 14 weeks or as late as 30 weeks of gestation. [20] Early intervention can be difficult as the small size of the uterus limits options for insertion of the fetoscope, especially if the placenta is located anterior. Late intervention can be challenging as the size of the placenta hampers complete visualization of the vascular equator, coagulation of larger anastomoses is more difficult with a higher risk of bleeding, the larger fetuses may block the view or instruments may be undersized. We observed higher rates of residual anastomoses in interventions performed before 18 weeks and after 22 weeks of gestation.[13] In addition, the risk of post-procedural amniotic band syndrome appeared higher when laser therapy was performed earlier in gestation.[14] Some studies reported an association between laser therapy at an early gestation and amnion chorion separation.[21, 22] Other small studies reported similar outcomes between laser therapy early and later in pregnancy. [20, 23] The amnion and chorion fuse between 14 and 16 weeks of gestation and are possibly more vulnerable

for separation, membrane damage and premature rupture of membranes (PPROM) when surgery takes place early in gestation.[21] Increased awareness of the risks in early interventions may be beneficial to prevent severe complications in these pregnancies. Close monitoring after fetoscopic laser surgery remains imperative to screen for signs of recurrent TTTS or post-laser TAPS, amniotic bands and membrane damage, especially if treatment occurred early or late in gestation. More studies including surgical techniques and procedure related data as energy use, laser power and scope size can aid in determining the optimal treatment according to gestation. Knowledge on risks specific for either early or late treatment enables a more personalized approach to the care for this group and may eventually lead to increased survival rates and decreased rates of morbidity. Therefore future research should focus on complications and outcomes in early and late interventions by presenting results for different gestational age groups. As the amount of early (<18 weeks) and late (>22 weeks) procedures is much smaller, multicenter studies may be required to achieve sufficient power.

Optimal management in iatrogenic monoamniotic twin pregnancies?

Iatrogenic monoamniotic twin (iMAT) pregnancies differ from spontaneous monoamniotic twin pregnancies in etiology. Nonetheless, management of iMAT pregnancies is often extrapolated from the strict management strategy in spontaneous monoamniotic twin pregnancies. This management strategy usually includes frequent (daily) fetal monitoring after 28 weeks and an elective preterm cesarean section between 32 and 33 weeks of gestation.[24, 25] To enable frequent monitoring, the pregnant woman is often hospitalized for weeks. The purpose of this strict management is to prevent cord accidents, subsequent fetal demise and severe cerebral injury. However, in this thesis we found cord entanglement in only one in five of iMAT pregnancies.[26] This means that the majority of iMAT pregnancies does not benefit from this management, but does suffer the harmful effects of iatrogenic preterm birth and the burden of prolonged hospitalization of the mother. Therefore iMAT pregnancies should be managed differently, based on data of iMAT pregnancies instead of spontaneous monoamniotic twin pregnancies.

In this thesis, we investigated a large group of TTTS pregnancies with and without iMAT. Most iMAT with cord entanglement were identified on antenatal ultrasound, underlining once more the value of routine ultrasound follow-up. Our data suggests an expectant approach may be beneficial in iMAT cases without sonographic cord entanglement. However, possible risks of extending pregnancy should be weighed against comorbidities associated with premature birth and future parents should be counseled extensively. For iMAT pregnancies with sonographically confirmed cord

entanglement the prevention of cord accidents presumably justifies an preterm elective caesarean section and the risks of preterm birth. Although we did not detect significant differences in outcome of TTTS-survivors with and without cord entanglement, very preterm delivery is a known risk factor for increased mortality and morbidity rates and poorer long-term neurodevelopmental outcomes.[27, 28]. The lack of adverse outcome in our cohort may be attributed to adequate surveillance and treatment of iMAT pregnancies with cord entanglement. Some studies in spontaneous monoamniotic gestations demonstrate that monoamnionicity and cord entanglement in themselves are not associated with increased perinatal morbidity and mortality but can be attributed to increased rates of congenital anomalies and large placental anastomoses.[29-33] As iMAT pregnancies are 'dichorionized' during laser surgery and division of embryos happened earlier after fertilization, risks of adverse outcome may be lower compared to spontaneous monoamniotic twin pregnancies.

This thesis warrants a critical review of the established management of iMAT pregnancies. Future research should focus on the best strategy for iMAT pregnancies with and without sonographically detected cord entanglement. A possible approach includes a multicenter randomized controlled trial for iMAT without sonographic cord entanglement with different follow-up schedules, including inpatient and outpatient screenings. Postponing the elective caesarean section to approximately 36 weeks of gestation in pregnancies without cord entanglement or other complications can be considered. A simultaneous trial is aimed at the best management protocol for iMAT pregnancies with sonographic cord entanglement and includes a control group of spontaneous monoamniotic twin pregnancies. As prevalence of spontaneous monoamniotic twin pregnancies is scarce, a multicenter approach is necessary. The primary outcome in both studies should be intact survival; survival without long-term neurodevelopmental impairment.

Increased risk of placental abruption after laser surgery?

Placental abruption occurs in 2.7% of pregnancies treated with fetoscopic laser therapy for TTTS.[34] This percentage is somewhat higher than the rate reported in uncomplicated multiple gestations of 1.2-1.6%.[35] Fetal therapy centers in Italy and in Japan observed a higher rate of placental abruption when the Solomon technique was used and suggested a causal relation.[36, 37] A review including data of 9 centers reports an association between the Solomon technique and placental abruption.[33] Of note, despite the higher rates of placental abruption, all groups report higher survival rates in the Solomon group. We did not find an association between placental abruption and the Solomon technique in a large group of TTTS pregnancies treated with the Solomon or Selective technique. We did observe an increase in placental abruption over time. If a causal relation exists between TTTS

or fetoscopic laser surgery and placental abruption remains unclear. The increasing rate of placental abruption can also be attributed to an enhancing population risk as some studies report a simultaneous rise in rates of placental abruption in the population.[38, 39] In addition, rates of placental abruption could have been underestimated in the past while technical developments have improved detailed documentation in electronic patient records in the more recent years. We were not able to find risk factors for placental abruption. However, some aspects that could possibly influence the placenta are worth exploring in future research. Laser surgery evidently damages the placental surface, although its effect on the deeper layers of the placenta is unknown. Akkermans et al proposed a scoring system for placental damage and described a relation between more placental damage, premature birth and premature rupture of membranes (PPROM). [40] Placental damage increased with higher energy use during laser surgery. The energy used during procedures varies widely between fetal therapy centers and ranges in available literature from 4 to 12 kiloJoules (kJ). [37, 41] One fetal therapy center reported 10% placental abruption in 168 TTTS pregnancies treated with the Solomon technique with a median energy use of 12kJ. The rate of placental abruption in the Solomon group in this thesis was 3% and the median energy use 5kJ. As higher energy use damages the placenta it may influence the risk of placental abruption. Placental damage in relation to placental abruption has never been studied. Similarly, during fetoscopy amniotic fluid of the recipients' sac is routinely drained causing a decrease in uterus size. As a consequence the available surface area of decidua underneath the placenta shrinks. In addition, double survival rates are rising since the introduction of fetoscopic laser surgery. As the fetuses grow larger the demand on the placenta intensifies. Better short term survival rates directly after laser surgery could therefore lead to an increased prevalence of later complications. All aforementioned events impact the placenta, although a relation to the risk of placental abruption remains uncertain. More placenta histology studies are crucial to assess placental damage after laser surgery in relation to complications and technical procedure related details as deep vertical pocket before and after surgery. Assessment of placental damage can be determined according to the scorings system proposed in an earlier manuscript form our center.[40]

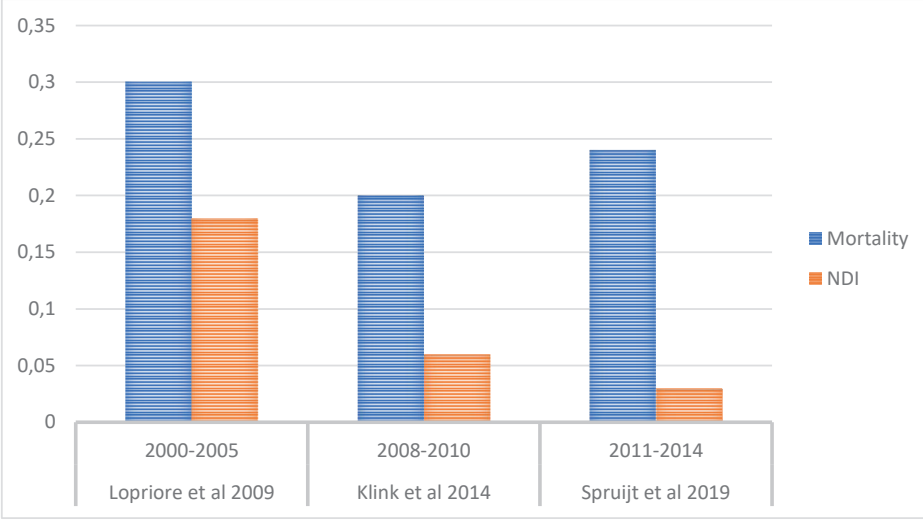
POSTNATAL OUTCOME AFTER FETOSCOPIC LASER SURGERY

As survival rates of TTTS are gradually improving, attention shifts toward quality of life and neurodevelopmental outcome. Several fetal therapy centers conduct follow-up programs of TTTS survivors and report neurodevelopmental outcomes.[27, 28, 42-65] The reported rates of cerebral palsy (CP) range between 2% and 18% with a mean

of 5%. The prevalence of severe neurodevelopmental impairment (NDI) ranges from 4% to 18% with a mean of 9 to 10%. Few studies investigated mild NDI, defined as scores < 1SD on a developmental test or neurological deficiencies with prospect to normalization or with no significant impact on quality of life. Rates of mild NDI vary from 0 to 34%.[27, 48, 51, 53, 58, 59, 62, 65]

Similar to the increasing survival rates and the decrease in residual anastomoses, the prevalence of neurodevelopmental impairment at two years in our center is gradually declining (Figure 2). Technical improvements, advances in neonatal care and learning curves of the perinatal team have probably led to less complications and better long-term survival.

Figure 2. Rates of perinatal mortality and NDI at two years of age over time



Although the timing of follow-up assessment of TTTS survivors ranges from 6 months to 6 years of age, the majority of studies (11/26, 42%) report neurodevelopmental outcome at two years of age. Substantiated knowledge on neurodevelopment in TTTS survivors later in life is lacking. Therefore assessment of TTTS survivors at age 5 was part of the research for this thesis.

Neurodevelopmental impairment at school age

We detected more neurodevelopmental impairment at the age of 5 years in a group TTTS survivors who were also assessed at the age of 2.[66] The rate of mild to moderate NDI at age 5 appeared to be 34% and the rate of severe NDI 12% in a group of TTTS survivors born premature and/or small for gestational age. The neurodevelopment at age 2 changed for 42% of TTTS survivors at the age of 5. A similar course of

increasing rates of neurodevelopmental impairment with age is described by German and Swedish studies in premature born children without TTTS. [67, 68]

This indicates that there still is room for improvement and underlines the importance of long-term follow-up. Although children may achieve certain milestones as a toddler, problems can arise when demands on the child's functioning increase with age. Learning difficulties and behavioral problems could manifest later in childhood when the child is more challenged at school and in social relationships.

Future predictions of neurodevelopmental outcome should not be based on the examination at two years alone. Follow-up of TTTS survivors at 5 years and preferably again at 8 years and during adolescence with standardized developmental tests, can provide more insight in the neurodevelopmental trajectory of TTTS survivors. Accurate and early detection of NDI is important to offer timely and appropriate developmental support, to improve the counseling of future parents and survivors of TTTS and to validate the optimal treatment strategy for complications, such as iMAT and post-procedural amniotic band syndrome.

Bayley scales, Wechsler Preschool and Primary scale of intelligence (WPPSI) and Wechsler intelligence scale for children (WISC) are appropriate validated test for assessing TTTS survivors at different ages. Centers with minimal resources available for follow-up can consider using the Ages and Stages Questionnaire (ASQ) or the Parent Report of Children's Abilities (PARCA) instead of Bayley scales. Both ASQ and PARCA are questionnaires for parents validated against the Bayley scales. At school age and in adolescence academic functioning e.g. grade repetition, special needs education and, eventually, the level of social and community participation can be used as a measure for 'intact survival' if no resources are available for developmental testing. In addition, the Adaptive Behavior Assessment System (ABAS) can be used to assess adaptive behavior from birth up to 89 years. ABAS includes (online) questionnaires for parents, teachers and a self-report for adults. However, evaluation by school results or ABAS is not comparable to assessment by validated tests or evaluation by a team of specialists.

Outcome measures

In chapter 5 we reviewed the available literature on neurodevelopmental outcome in TTTS-survivors.[69] In chapter 6 we reviewed available literature on neurodevelopmental outcome in complicated monochorionic twin pregnancies, including TAPS, sFGR, acute peripartum TTTS and acute perimortem TTTS.[70] Both chapters illustrate the lack of uniformity in the approach of follow-up. Children are assessed at different ages, often before school age. Various methods are used to determine NDI, including non-validated tests and questionnaires and definitions of NDI differ between studies. This heterogeneous approach hampers comparability

and the forming of substantiated conclusions. The mean rates of NDI and CP of respectively 9 to 10% and 5% should therefore be interpreted with caution. To improve comparability fetal therapy centers should determine a guideline for follow-up including ages at follow-up and definitions of NDI and CP. We propose assessment of TTTS survivors at predetermined ages of 2, 5, 8 years and adolescence.

Data collection

The chapters in this thesis entail cohort studies with prospectively and retrospectively collected data. This data is derived form a large cohort that spans multiple years. Most studies include much smaller sample sizes, impeding the formation of substantiated conclusions, especially in subgroups with rare complications. Disadvantages of retrospective data collection include incomplete patient records and absent data due to lost to follow-up. As aforementioned, outcome measures lacking an uniform approved definition can hamper comparability between studies. For instance: placental abruption is a clinical diagnosis without internationally established criteria. To determine placental abruption in retrospect may be difficult if clinical details in patient records are incomplete. Therefore definitions should be uniform and internationally approved. Fetoscopy centers should exert a systematic data collection including complications and outcomes to prevent loss of data. Data collection is important for every fetal therapy center to affirm the treatment benefits outweigh the risks and to counsel future TTTS parents on outcomes and possible complications of treatment.

It takes two to tango

An important step in achieving uniform outcome measures and systematic data collection is international collaboration between fetal therapy centers. Perry et al proposed a core outcome set to ensure comparability between studies.[71] Although documentation of the same outcome data by every fetal therapy center is an important step in the right direction, this core outcome set includes only 13 outcome parameters. It lacks complications such as iMAT, premature rupture of membranes, placental abruption and long-term outcomes. Despite the fact that collection of more data than the 'core outcomes' is time consuming and costly, it is crucial to the development of better treatment strategies. Multiple fetal therapy centers already collaborate in the TAPS registry and TAPS trial to optimize the care for TAPS.[72] Despite the larger quantity of data due to the higher prevalence of TTTS, this alliance could consider a similar approach in optimizing the care for TTTS. Especially studies on rare complications are difficult to empower for a single center. International collaboration can achieve substantiated conclusions on the best management strategies must faster, enabling fetal therapy centers to offer more personalized care.

Future research

Even as survival rates improve in TTTS, rates of complications and neurodevelopmental impairment are not negligible. Research in TTTS pregnancies is still of great value. As aforementioned, future research should focus on prevention and management of complications after fetoscopic laser surgery and long-term neurodevelopmental outcome and quality of life in TTTS survivors beyond the age of 2 years. Definitions and outcome measures should be uniformly defined and internationally approved. Fetoscopy centers should exert a systematic data collection including complications and outcomes to validate its treatments. International collaboration is necessary, especially to develop management strategies for more rare complications. Follow-up should not end after birth but continue at least until survivors reach adolescence.

FINAL CONCLUSIONS

This thesis has provided novel insights in short and long term outcomes after fetoscopic laser surgery in TTTS. It warrants critical review of the current management in some subgroups with rare complications and underlines the importance of continued research and follow-up in this vulnerable patient group. To further improve the care for TTTS pregnancies, critical revision of the management of iMAT pregnancies is imperative to reduce the amount of preterm deliveries and avoid associated neonatal comorbidities. A possible association between TTTS and placental abruption should be explored in further research. Use of less energy during laser can possibly lead to less placental damage and a lower risk of placental abruption. This thesis highlights the value of placental examination in detecting residual anastomoses to evaluate the successfulness and improve the quality of laser surgery. Gestational age at laser surgery should be considered when screening for complications as residual anastomoses and amniotic band syndrome. Postnatal follow-up using validated neurodevelopmental tests should continue until adulthood because certain deficits can surface later in life. International collaboration and systematic registry of complications and outcome is essential in improving knowledge and care for TTTS.

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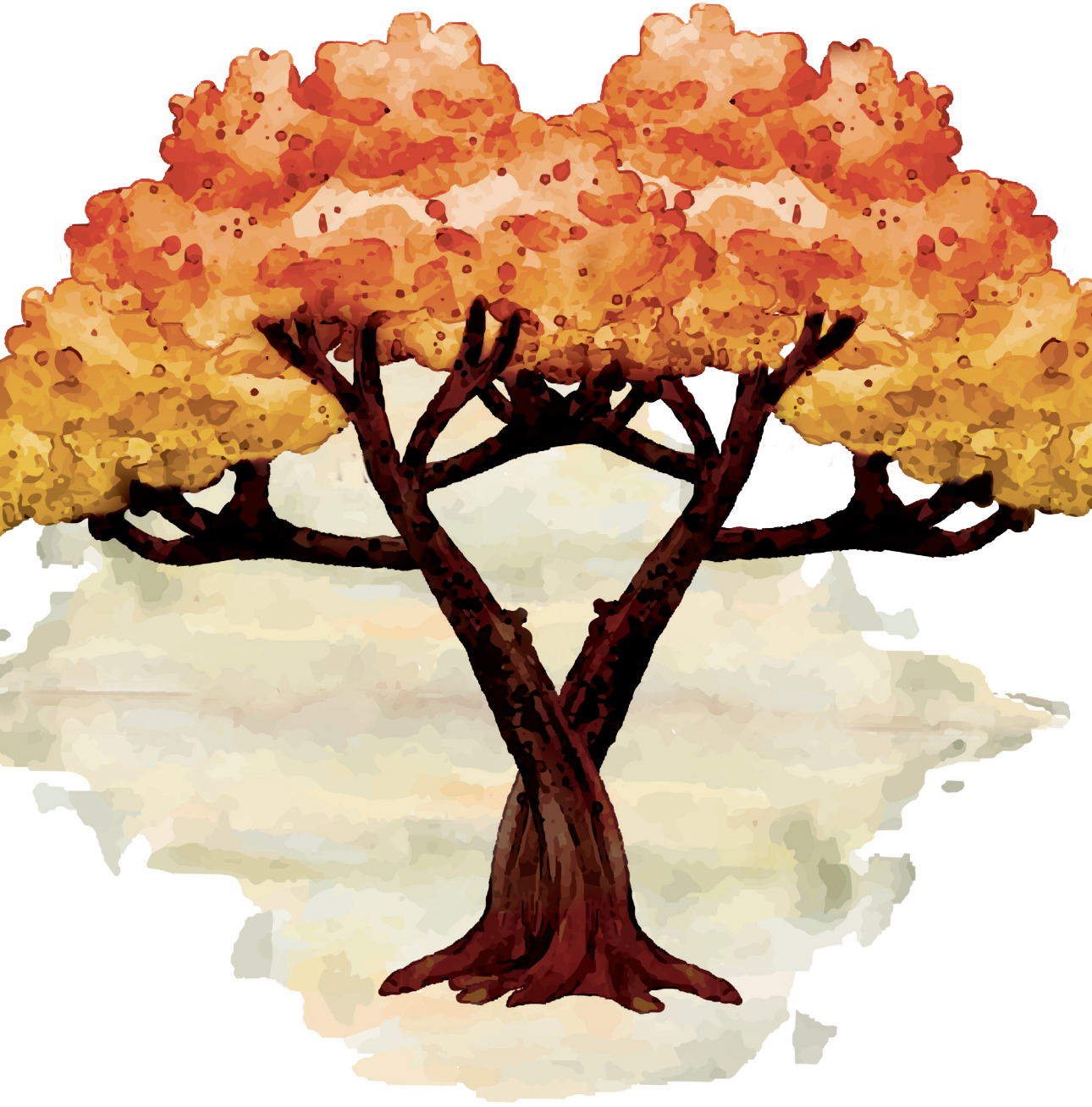

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Chapter 9

Summary

SUMMARY

This thesis consists of studies of complications and outcomes of fetoscopic laser therapy for twin-twin transfusion syndrome.

Monochorionic twin pregnancies

Approximately 1 in 200 pregnancies is a monozygotic twin pregnancy. Monozygotic twin pregnancies arise from the splitting of a single fertilized oocyte into two embryos. When this happens within 3 to 8 days after fertilization a monochorionic twin pregnancy arises, where the fetuses share a placenta. If the fertilized oocyte splits after 8 days the twins are not only monochorionic but also monoamniotic, which means that they share the amniotic sac. A spontaneous monoamniotic twin pregnancy is rare and occurs in approximately 1% of the twin pregnancies. See also figure 1 in de introduction of this thesis.

Twin-twin transfusion syndrome

The blood circulations of monochorionic twins are connected through vascular anastomoses on the shared placenta. In most monochorionic twin pregnancies the blood flow from the placenta to the twins is in balance. However, in about 10% of the monochorionic twin pregnancies, one child receives more blood than the other child. This situation is called twin-twin transfusion syndrome (TTTS). The child receiving more blood is called the recipient. The recipient has hypervolemia, polyuria and a polyhydramnion. The donor has hypovolemia, oliguria and an anhydramnion. On ultrasound examinations an empty bladder and a “stuck” twin appearance are typical signs of the TTTS donor, ie the donor is surrounded by amnion membrane and no amniotic fluid is visible. Without treatment, this condition is often lethal for both twins.

Fetoscopic laser therapy

Fetoscopic laser therapy is the preferred and only causal treatment for TTTS. During fetoscopic laser therapy the vascular anastomoses are visualized and coagulated with a laser. The aim of this procedure is to ‘dechorionize’ the placenta and thereby separating the blood circulations of the twins. Fetoscopic laser therapy is performed since the 90’s and has improved survival rates from 65 to 90%. However, fetoscopic laser therapy is not always successful and residual anastomoses can persist, which can cause recurrence of TTTS or TAPS. In addition, fetoscopic laser therapy can induce pregnancy complications. Until recently, rates and risk factors of these complications were unknown. Data on health and neurodevelopment of TTTS twins was rare and limited to short-term outcomes. In this thesis complications, risk factors and outcomes of fetoscopic laser therapy for TTTS are investigated.

Antenatal complications

In **Chapter 1** we studied the rate of residual anastomoses after fetoscopic laser therapy over a period of 15 years. Placentas were examined after birth using colored dye. Residual anastomoses were discovered in 21% of the placentas. We observed a higher rate of residual anastomoses in the early years (39%) compared to the more recent years (12%). The introduction of a new laser technique in 2012, the Solomon technique, was associated with a lower rate of residual anastomoses. The Solomon technique includes lasering a line over the vascular equator after every individual anastomosis has been coagulated (see the introduction of this thesis for more information). The aim is to coagulate miniscule anastomoses that could potentially be missed. In this chapter we confirmed the decrease in residual anastomoses when this technique was used. A learning curve of the fetal therapist may have played an additional role. Nevertheless, routine ultrasound assessments remain imperative as residual anastomoses could be found in 15% of the procedures considered complete by the fetal surgeon.

In **Chapter 2** we studied a possible relation between fetoscopic laser therapy and the prevalence of placental abruption. Placental abruption is the premature complete or partial separation of the placenta from the uterus wall. As the placenta is responsible for oxygenation and nutrient supply of the children, the consequences can be severe. A few studies suggested a possible relation between placental abruption and the use of the Solomon laser technique. In this thesis we could not find a significant association in more than 750 TTTS pregnancies. However, the prevalence of placental abruption in TTTS is higher compared to other pregnancies.

Amniotic band syndrome is a rare condition which can occur during pregnancy. Strands of amniotic membrane, the inner membrane of the amniotic sac, circle around the body of the unborn child. These strands can cause severe malformations and can lead to fetal demise in some cases. Amniotic band syndrome occurs spontaneously in approximately 1 in 1200 to 15000 pregnancies or can occur after a procedure as an amniotic fluid punction or fetal therapy. In **Chapter 3** we determined the prevalence of amniotic band syndrome in TTTS and explored possible risk factors. Post-procedural amniotic band syndrome occurred in 2% of the TTTS pregnancies treated with laser therapy. The amniotic bands primarily affected toes and fingers, but caused fetal demise in one pregnancy were the strand constricted the umbilical cord. Post-procedural amniotic band syndrome occurred more frequently when fetoscopic laser therapy treatment transpired relatively early in the pregnancy. A possible explanation could be that the amniotic membranes are more delicate and vulnerable early in pregnancy. Additionally, in 93% of the pregnancies with amniotic band syndrome, separation of the amnion and chorion membrane was observed on ultrasound examinations.

A part of the amniotic membrane separates the amniotic sacs of the twins. During fetoscopic laser therapy the intertwin membrane may rupture causing an iatrogenic monoamniotic twin pregnancy. In spontaneous monoamniotic twin pregnancies, the umbilical cords of the twins are always entangled. Entanglement can lead to strangulation and interruption of the blood flow to one or both twins. To prevent intrauterine demise, monoamniotic twin pregnancies are generally terminated at approximately 32 weeks with an elective cesarean section. In **Chapter 4** we investigated the prevalence of iatrogenic monoamniotic twins and the rate of cord entanglement. We observed intertwin membrane rupture in approximately 16% of TTTS pregnancies treated with fetoscopic laser therapy. The risk of intertwin membrane rupture increased when more fetal surgeries were performed, such as a second laser therapy procedure or a intrauterine transfusion. In addition, we observed an association between an increased risk of iatrogenic monoamnionicity and higher maximum laser power used during fetoscopic laser surgery. In 21% of the iatrogenic monoamniotic pregnancies cord entanglement was detected. Survival rates, rates of cerebral injury and neurodevelopmental impairment at age two years of children with cord entanglement were equal to children without cord entanglement. However, we did observe an association between iatrogenic monoamniotic twins and prematurity and severe cerebral injury, compared to diamniotic TTTS twins. These findings demand a critical evaluation of the current management of these pregnancies.

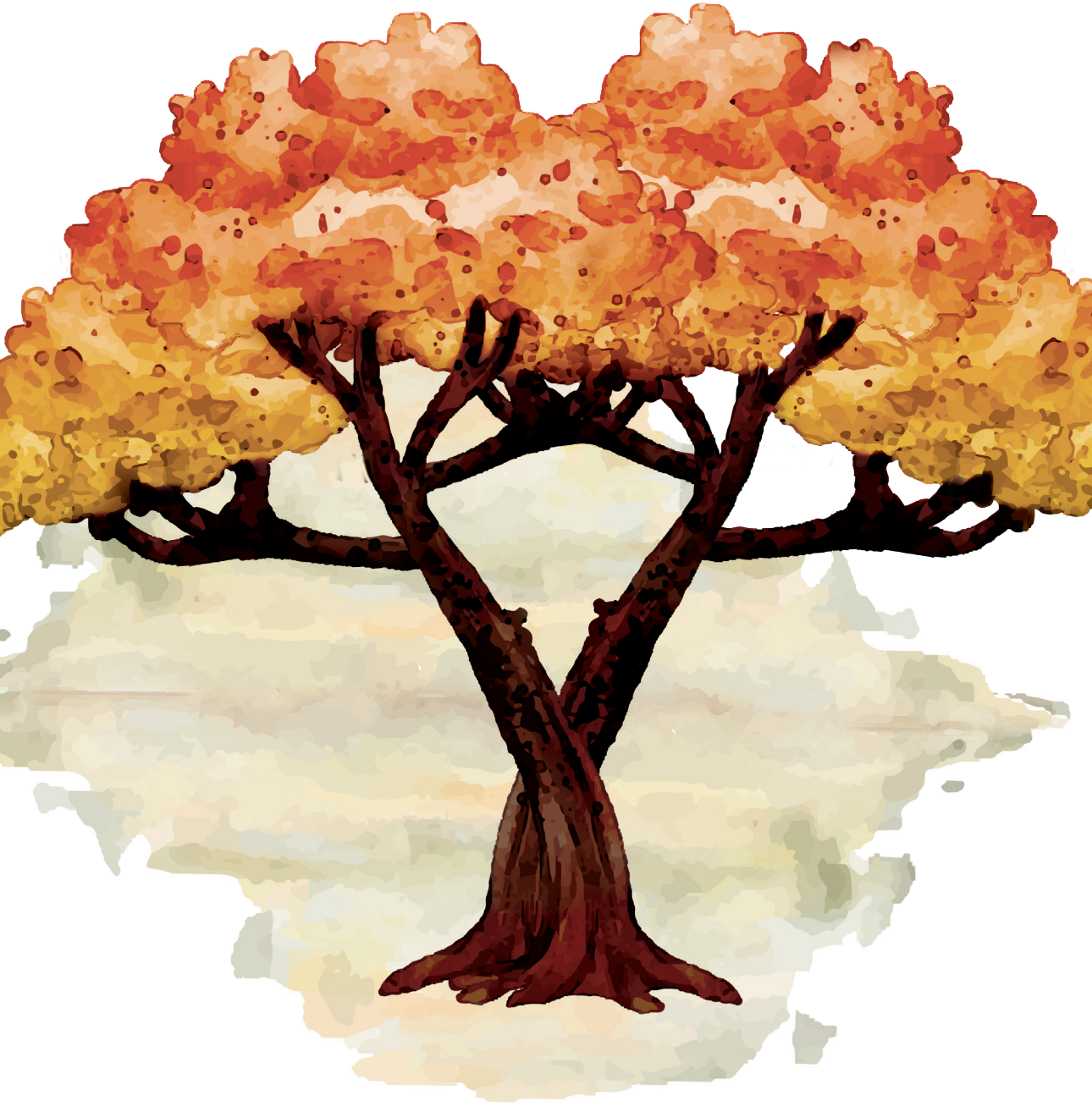
Postnatal outcome

The review in **Chapter 5** summarizes the current knowledge of the motor and cognitive development of complicated monochorionic twins. Studies on neurodevelopment in monochorionic twins with TTTS, TAPS, selective fetal growth restriction (sFGR), spontaneous monoamniotic twin pregnancies, acute perimortem TTTS and acute peripartum TTTS are evaluated. In some pregnancies a combination of these conditions can develop. Compared to studies in survivors of TTTS, even less is known about neurodevelopmental impairment in other complicated monochorionic twin pregnancies. Donors in TAPS, who have been exposed to chronic anemia, are at increased risk of deafness. In sFGR twins, the smaller twin has an increased risk of neurodevelopmental problems. The surviving twin of acute perimortem TTTS has a risk of approximately 29% to develop neurodevelopmental impairment due to severe cerebral injury caused by a drop in blood pressure after demise of the co-twin.

Chapter 6 is a review on neurodevelopmental problems in survivors of TTTS treated with fetoscopic laser surgery. Different fetal therapy centers have follow-up programs, mostly assessing survivors of TTTS at age two years. Data of neurodevelopment at

an older age is limited. Follow-up programs differ widely between centers concerning the age of follow-up, the use of validated standardized tests, physical assessments by pediatric specialists and the use of questionnaires. Both chapter 5 and 6 underline the importance of structured and uniform approach to collect neurodevelopmental outcome data of survivors of TTTS and other complicated monochorionic twins. This information is important to evaluate current treatment strategies, to improve timely support of TTTS survivors and to counsel future parents.

To provide more information about neurodevelopmental outcome in older survivors of TTTS, we conducted a retrospective study on neurodevelopmental impairment at age five years in **Chapter 7**. Survivors of TTTS who were born premature or small for gestational age were included in this follow-up study. The same children had an assessment at age two years. We detected more mild to moderate neurodevelopmental impairment in survivors of TTTS at age five years compared to two years. In addition, the neurodevelopmental impairment we observed in children at age two years could improve or even resolve at age five years. This study underlines the importance of long-term follow-up of survivors of TTTS. Problems can surface later, when children are more socially and academically challenged. We therefore recommend long-term follow-up with assessments at the age of two, five and eight years and during adolescence.



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Chapter 10

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Dit proefschrift bestaat uit studies naar complicaties en uitkomsten na behandeling van het tweeling transfusiesyndroom met foetoscopische laser therapie.

Monochoriale tweelingen

Ongeveer 1 op de 200 zwangerschappen betreft een eeneiige tweeling. Eeneiige tweelingen zijn ontstaan uit een bevruchte eicel die zich vroeg in de zwangerschap splitst. Twee derde van deze eeneiige tweelingen deelt een placenta. We noemen deze tweelingen “monochoriaal”. Of een eeneiige tweeling ook een monochoriale tweeling is, hangt af van het moment waarop de bevruchte eicel zich splitst. Als dit binnen 3 dagen na bevruchting gebeurt, hebben eeneiige tweelingen net als alle twee-eiige tweelingen een eigen placenta. Als dit tussen 3 en 8 dagen na bevruchting gebeurt, delen de kinderen een placenta maar hebben een eigen vruchtzak (amnion). Als dit na 8 dagen gebeurt ontstaat een monoamniotische tweeling, die samen zowel de placenta als de vruchtzak delen. Een spontane monoamniotische zwangerschap komt heel weinig voor, ongeveer 1% van alle monochoriale tweeling deelt ook de vruchtzak. Zie ook Figuur 1 in de introductie van dit proefschrift.

Tweeling transfusie syndroom

Door middel van vaatverbindingen op de gezamenlijke placenta staan de bloedsomlopen van monochoriale tweelingen met elkaar in verbinding. Soms is de stroming van het bloed niet in evenwicht en krijgt het ene kind meer bloed van de placenta dan het andere kind. Bij ongeveer 10% van de monochoriale tweelingen treedt zo een disbalans op, wat we het tweelingtransfusie syndroom (TTTS) noemen. Het ene kind, de ontvanger of recipient, heeft heel veel bloed in het lichaam (hypervolemie), gaat veel plassen (polyurie) en heeft veel vruchtwater in de vruchtzak (polyhydramnion). Het andere kind, de donor, heeft weinig bloed in de bloedsomloop (hypovolemie), heeft een lege blaas (anurie) en heel weinig of geen vruchtwater (oligo- of anhydramnion). Zonder behandeling is er een grote kans dat beide kinderen overlijden.

Foetoscopische laser therapie

Om overlijden van de ongeboren kinderen te voorkomen kan een laserbehandeling worden uitgevoerd. Deze behandeling is te vergelijken met een kijkoperatie in de baarmoeder. De foetaal chirurg, een gespecialiseerde gynaecoloog-perinatoloog, brengt een foetoscoop (camera) met een laserdraad in, door de buikwand van de moeder, in de vruchtzak van de ontvanger. De vaatverbindingen op de placenta worden opgespoord en met de laser dicht gebrand. Zo wordt de bloedsomloop

van de kinderen gescheiden en de oorzaak voor de TTTS weggenomen. Deze laserbehandeling wordt uitgevoerd sinds de jaren 90' en sindsdien is de overleving van tweelingen met TTTS toegenomen van 65% naar 90%. De laserbehandeling kan technisch moeilijk en uitdagend zijn waardoor er helaas soms na de behandeling nog 'rest' vaatverbindingen zijn. Door de 'rest' verbindingen kan TTTS blijven bestaan of kan tweeling anemie polycythemie sequentie (TAPS) ontstaan. Ook kunnen door de laserbehandeling complicaties in de zwangerschap optreden zoals een perforatie van het vlies tussen de vruchtzakken, amnion streng syndroom of het vroegtijdig breken van de vliezen, wat tot vroeggeboorte kan leiden. Tot op heden was van deze complicaties niet goed bekend hoe vaak ze voorkomen en of er risicofactoren voor zijn aan te wijzen. Daarnaast is er beperkt onderzoek naar de gezondheid en ontwikkeling van TTTS tweelingen na de geboorte. In de studies in dit proefschrift worden complicaties, risicofactoren en uitkomsten van laserbehandeling voor TTTS verder onderzocht.

Antenatale complicaties

In **Hoofdstuk 1** hebben we de onderzocht hoe vaak er 'rest' vaatverbindingen aanwezig waren na laser therapie. Om dit te bepalen werden de placenta's na geboorte met verf opgespoten. In 21% van de placenta's werden 'rest' vaatverbindingen gevonden. Over de onderzoeksperiode van 15 jaar was dit percentage echter het hoogst in de beginjaren (39%) en daalde naar 12% in de meest recente jaren. De introductie van een nieuwe lasertechniek, de Solomon techniek, in 2012 heeft ervoor gezorgd dat laserbehandelingen vaker compleet waren. Bij de Solomon techniek wordt nadat alle vaatverbindingen zijn opgespoord en dicht gebrand, een streep over het placentaoppervlak gelaserd, van de ene rand naar de andere, die alle brandpunten verbind. De gedachte hierachter is dat hele kleine verbindingen die mogelijk niet goed te zien zijn op die manier ook dicht gebrand worden. In dit hoofdstuk bevestigen we dat met deze techniek inderdaad minder 'rest' vaatverbindingen zijn. Daarnaast speelt de leercurve van de operateurs zeer waarschijnlijk een rol. Het blijft belangrijk om ook na laser therapie de zwangerschap middels regelmatige echocontroles te vervolgen omdat in 15% van de behandelingen die de operateur als compleet had beoordeeld, er toch 'rest' vaatverbindingen werden gevonden.

In **Hoofdstuk 2** evalueerden we de relatie tussen laser therapie en de prevalentie van placenta abruptie. Bij een placenta abruptie of solutio raakt de placenta geheel of gedeeltelijk los van de placentawand voordat de kinderen geboren zijn. Omdat de placenta de kinderen in de baarmoeder voorziet van zuurstof en voedingstoffen kan dit ernstige gevolgen hebben. Een aantal studies zagen aanwijzingen voor een relatie tussen de Solomon techniek en de prevalentie van placenta abruptie. In ruim

750 TTTS zwangerschappen die wij onderzochten werd deze relatie niet aangetoond. Wel lijkt placenta abruptie vaker voor te komen in TTTS zwangerschappen dan in andere zwangerschappen.

Een zeldzame aandoening die in de zwangerschap kan voorkomen is amnion streng syndroom. Bij dit syndroom wikkelen strengen van amnionvlies, het binnenste vlies van de vruchtzak, om het lichaam van het ongeboren kind. Deze strengen kunnen ernstige verminkingen en soms zelfs overlijden veroorzaken. Dit syndroom kan spontaan ontstaan in 1 op 1200 tot 15000 zwangerschappen of kan ontstaan na een ingreep zoals een vruchtwaterpunctie of foetale therapie. Het lijkt ook vaker voor te komen na laser therapie voor TTTS. In **Hoofdstuk 3** onderzochten we de prevalentie van amnion streng syndroom in TTTS en eventuele risicofactoren voor het ontwikkelen hiervan. We ontdekten dat amnion streng syndroom bij 2% van de met laser therapie behandelde TTTS zwangerschappen voor kwam en dus niet erg zeldzaam is. De amnion strengen werden met name gevonden rond tenen en vingers, maar leidden in één zwangerschap tot overlijden van één van de kinderen door een streng die de navelstreng afklemde. Amnion streng syndroom bleek vaker voor te komen als de laser therapie relatief vroeg in de zwangerschap had plaats gevonden. De hypothese hiervoor is dat de amnionvliezen van de vruchtzak vroeg in de zwangerschap kwetsbaarder zijn dan later in de zwangerschap. Daarbij werd bij 93% van de zwangerschappen met een amnion streng op eerdere echocontroles gezien dat het amnion en het chorion, het buitenste vlies, van elkaar gescheiden waren.

De vruchtzakken van beide kinderen wordt gescheiden door een deel van het amnion. Soms kan dit tussenschot scheuren tijdens een laserbehandeling. Er ontstaat dan een iatrogene (niet-spontane) monoamniotische tweelingzwangerschap. Van spontane monoamniotische tweelingzwangerschappen is bekend dat er altijd verstrengeling van de navelstrengen optreedt, wat soms tot een beknelling van de bloedtoevoer kan leiden. Daarom wordt bij monoamniotische tweelingen de zwangerschap vaak rond 32 weken beëindigd middels een keizersnede. In **Hoofdstuk 4** hebben we onderzocht hoe vaak iatrogene monoamniotische tweelingzwangerschappen optreden en hoe vaak er verstrengeling van de navelstreng plaats vindt. In ongeveer 16% van de laserbehandelingen ontstaat een scheur in het tussenschot. Het risico hierop was hoger wanneer er meerdere foetale behandelingen tijdens de zwangerschap werden uitgevoerd, zoals een tweede laserbehandeling of een intra-uterine bloedtransfusie. Ook was het risico hoger wanneer er een hoger maximaal wattage gebruikt werd tijdens de laser therapie. Bij slechts 21% van de iatrogene monoamniotische tweelingzwangerschappen werd vervolgens een knoop in de navelstrengen gezien. Tussen de kinderen met en zonder een knoop in de navelstreng observeerden we geen verschil in overleving, hersenschade na geboorte of ontwikkelingsproblemen

op tweejarige leeftijd. Wel constateerden we dat in iatrogene monoamniotische zwangerschappen kinderen significant vaker prematuur geboren werden en vaker ernstige hersenschade hadden na geboorte in vergelijking met kinderen die voor TTTS met laser behandeld waren maar geen tussenschotperforatie hadden. Deze bevindingen maken een kritische herbeoordeling van het huidige beleid noodzakelijk.

Postnatale uitkomsten

In de review in **Hoofdstuk 5** wordt de huidige kennis over de motorische en cognitieve ontwikkeling van gecompliceerde monochoriale tweelingen samengevat. Naast kinderen die behandeld zijn voor TTTS worden ook studies naar ontwikkelingsproblemen bij kinderen met TAPS, selectieve foetale groeirestrictie (sFGR), spontane monoamniotische zwangerschappen, acute perimortem TTTS en acute peripartum TTTS in kaart gebracht. Deze aandoeningen kunnen ook gecombineerd voorkomen. Naar de ontwikkeling van deze subgroepen is over het algemeen minder onderzoek gedaan dan naar tweelingen die TTTS hebben gehad. TAPS donoren, die blootgesteld zijn aan chronische anemie, hebben een grotere kans op gehoorproblemen. Bij een sFGR heeft het kleinere kind meer kans op ontwikkelingsproblemen. Het overlevende kind bij acute perimortem TTTS heeft een kans van 29% op ontwikkelingsproblemen doordat bij het overlijden van de tweelingbroer of -zus de bloeddruk plots wegvalt en ernstige hersenschade kan ontstaan.

In aansluiting hierop betreft **Hoofdstuk 6** een review naar ontwikkelingsproblematiek bij kinderen die behandeld zijn voor TTTS. Opvallend is dat de studies die door verschillende foetale therapie centra verricht zijn, voornamelijk tweejarige kinderen onderzocht hebben. Over de ontwikkeling op basisschoolleeftijd en middelbare schoolleeftijd is erg weinig bekend. Daarnaast is er geen uniform beleid omtrent het vervolg van deze kinderen. Sommige centra gebruiken gevalideerde testen en laten de kinderen terugkomen voor beoordeling door een kinderarts of fysiotherapeut, terwijl andere centra vragenlijsten opsturen of alleen telefonisch contact met ouders hebben. Zowel hoofdstuk 5 als hoofdstuk 6 tonen aan dat een gestructureerd en uniform beleid belangrijk is om betrouwbare informatie te kunnen verzamelen over de ontwikkeling van kinderen die TTTS hebben gehad. Deze informatie is nodig om de huidige behandeling te kunnen evalueren, om kinderen zo vroeg en gericht mogelijk te kunnen begeleiden en ondersteunen en om toekomstige ouders betrouwbare informatie te kunnen geven.

Om die reden hebben wij in **Hoofdstuk 7** een studie verricht naar de motorische en cognitieve ontwikkeling op twee en vijfjarige leeftijd van een groep kinderen die TTTS hebben gehad en prematuur en/of dysmatuur geboren zijn. We signaleerden dat op vijfjarige leeftijd meer kinderen mild tot matige ontwikkelingsproblemen hadden

dan op tweejarige leeftijd was vastgesteld. Ook constateerden wij dat kinderen die op tweejarige leeftijd ontwikkelingsproblemen hadden, daar op vijfjarige leeftijd soms minder of geen last meer van hadden. Deze studie toont aan dat het vervolgen van de ontwikkeling van kinderen die TTTS hebben gehad voor een langere termijn waardevol kan zijn. Soms komen problemen pas later aan het licht, als er meer van kinderen wordt gevraagd op school, sport en het aangaan van vriendschappen. Controles zouden dan ook moeten worden verricht op twee-, vijf- en achtjarige leeftijd en gedurende adolescentie.

Appendices

ABBREVIATIONS

ABAS	Adaptive Behavior Assessment System
ASQ	Ages and Stages Questionnaire
Bayley-III-NL	Bayley Scales of Infant and Toddler Development third Dutch edition
BDI	Battelle Developmental Inventory
CBCL	Child Behavior Checklist
CI	confidence interval
CP	cerebral palsy
DC	dichorionic
GA	gestational age
GEE	generalized estimating equation
GMFCS	Gross Motor Functioning Classification Scale
GNSE	German National Screening Examination
ICD	international classification of diseases
iMAT	iatrogenic monoamniotic twin
IQ	intelligence quotient
IQR	interquartile range
IUFD	intrauterine fetal demise
IVH	intraventricular hemorrhage
K-ABC	Kaufman-Assessment Battery for Children
LUMC	Leiden University Medical Center
M-ABC-II-NL	Movement Assessment Battery for Children second Dutch edition
MA	monoamniotic
MC	monochorionic
MCA-PSV	middle cerebral artery peak systolic velocity
MoM	Multiples of the Median
NDI	neurodevelopmental impairment
NICU	neonatal intensive care unit
OR	odds ratio
PABS	postprocedural amniotic band syndrome
PARCA	Parent Report of Children's Abilities
PPROM	preterm premature rupture of membranes
PVL	periventricular leukomalacia
RA	residual anastomoses

SD	standard deviation
sFGR	selective fetal growth restriction
SFMIH	Shanghai First Maternity and Infant Hospital
SGA	small for gestational age
TAPS	twin anemia polycythemia sequence
TTTS	twin-twin transfusion syndrome
WISC	Wechsler intelligence scale for children
WPPSI-III-NL	Wechsler Preschool and Primary Scale of Intelligence third Dutch edition

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CURRICULUM VITAE

Patricia Knijnenburg werd op 24 oktober 1991 geboren in De Lier. Zij groeide hier op met haar twee jongere broers en ging naar basisschool de Achtsprong. In 2010 behaalde zij haar gymnasium diploma cum laude aan het Sint Stanislascollege in Delft. In datzelfde jaar begon zij aan de studie geneeskunde aan de Universiteit Leiden. Tijdens haar bachelor werkte zij als onderzoeksassistente op de afdeling reumatologie en is zij voor een klinische stage naar Kaapstad, Zuid-Afrika, gegaan. Na het behalen van de Bachelor graad in 2013 heeft zij een jaar lang de rol van secretaris vervuld in het bestuur van de Medische Faculteit der Leidse Studenten. Gedurende de master heeft zij naast de reguliere coschappen in Nederland, een coschap keel- neus en oorheelkunde gedaan in Suriname. In 2016 startte zij met een wetenschappelijke stage op de afdeling Neonatologie onder begeleiding van prof. dr. Enrico Lopriore. Het onderwerp van deze stage betrof een onderzoek naar residuele anastomosen na laser therapie voor het tweelingtransfusie syndroom en zou later het eerste hoofdstuk van dit proefschrift worden. In 2017 behaalde zij de Master graad, waar na zij als arts-assistent kindergeneeskunde ging werken in het Haaglanden Medisch Centrum. In 2018 is zij naast haar werk als arts-assistent begonnen aan een PhD-traject onder begeleiding van prof. dr. Enrico Lopriore (neonatologie), dr. Jeanine van Klink (kinderpsychologie), prof. dr. Dick Oepkes en dr. Femke Slaghekke (verloskunde). Van oktober 2018 tot april 2019 heeft zij naast het PhD-traject als arts-assistent op de kinderneurologie in het Hagaziekenhuis gewerkt. Van mei 2020 tot februari 2021 heeft zij tevens als arts-assistent kindergeneeskunde in het Reinier de Graaf gasthuis gewerkt. Vanaf februari 2021 is zij werkzaam in het Amsterdam Universitair Medisch Centrum op de afdeling Humane Genetica, waar zij in januari 2022 aan de opleiding tot klinisch geneticus is begonnen.

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