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Brain matters in twin-twin transfusion syndrome

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Citation
Spruijt, M. S. (2025, January 15). *Brain matters in twin-twin transfusion syndrome*. Retrieved from https://hdl.handle.net/1887/4175821

Version:	Publisher's Version
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Downloaded from:	https://hdl.handle.net/1887/4175821

Note: To cite this publication please use the final published version (if applicable).

General discussion & future directions

Twin-twin transfusion syndrome (TTTS) was first described by the German obstetrician Friedrich Schatz in 1875 as a complication specific to identical twins, caused by a shared circulation between the two fetuses.(1) He demonstrated intertwin anastomoses by injecting placental vessels with colored solutions and was the first to realize their potentially harmful effects.

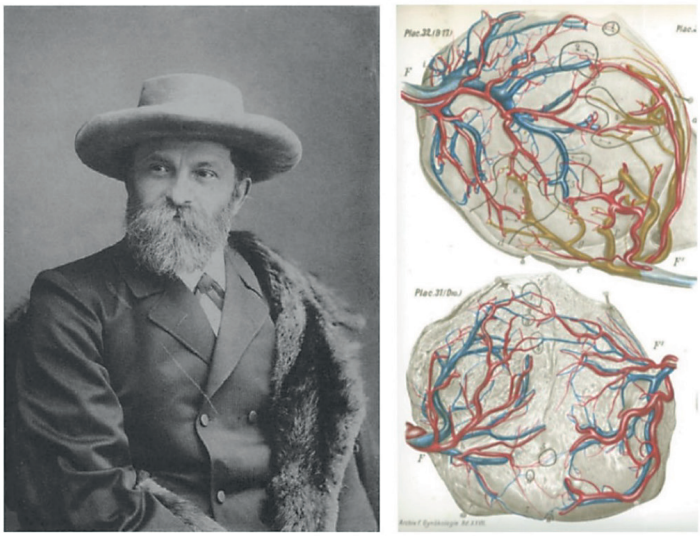

Figure 1. *Left:* Friedrich Schatz, late 19th century (2) *Right:* Schatz's drawings of placental vascular anastomoses in monochorionic twin placentas, injected with colored solutions (3)

For a long time, TTTS was a diagnosis with very little hope of a favorable outcome. A revolutionary new therapy was developed in the late 20th century and fetoscopic laser coagulation of the vascular anastomoses has become the preferred treatment for TTTS.(4) Fetoscopic laser surgery has been demonstrated to be the best available therapy in terms of perinatal survival rate, gestational age at delivery, and the risk of brain injury and long-term neurodevelopmental impairment (NDI).(5-8) Perinatal survival rates have continued to improve in recent decades, possibly related to the ongoing refinement of laser techniques, as well as the growing experience and awareness within the fields of fetal therapy and neonatology.(9) Consequently, the majority of fetuses now survive TTTS and go on to lead full lives. That does not mean that those lives are not influenced by their prenatal history,

as TTTS infants remain susceptible to complications. Fetal and neonatal morbidities due to TTTS are not fully prevented by laser surgery and include cerebral, cardiovascular, renal, intestinal and hematologic disease, as well as rare occurrences such as in utero acquired limb ischemia and amniotic band syndrome.(10) Brain injury may be caused by prematurity, TTTS, or both, increasing the risk of long-term NDI. The primary objective in every TTTS pregnancy should be survival of both twins without the occurrence of long-term NDI.

The aim of this thesis was to provide insight into the risks of fetal and neonatal brain injury, along with the long-term neurodevelopmental outcomes of survivors of TTTS in the contemporary era of fetoscopic laser surgery. To achieve this aim, we conducted a series of studies examining fetal, neonatal, and pediatric follow-up data from the Leiden University Medical Center (LUMC).

Brain injury

Incidence

The ever-growing experience in the management of monochorionic pregnancies in general and TTTS in particular have led to a slow but steady decline in the incidence of brain injury in this potentially catastrophic disease. While the introduction of laser surgery as the primary treatment for TTTS clearly marks the beginning of the fall in brain injury incidence, further developments in the management of TTTS pregnancies and in neonatology have likely contributed to its further decrease.(9) Reported rates of brain injury after treatment with laser surgery vary between studies due to inconsistencies in definitions and screening regimens, and range from 3 to 16%.(7, 11) Our cerebral injury study outlined in *chapter 2* was performed in the largest cohort of TTTS survivors treated with laser surgery to date and we uniquely used a control group of dichorionic twins matched for gestational age. We compared the incidence of severe cerebral injury on neonatal cranial ultrasound scans and found that the risk of brain injury was 9% in the TTTS neonates after laser surgery performed between 2004 and 2011, which was not different from the 7% incidence found in the dichorionic twins. Compared to an earlier cohort from our center however, the incidence had clearly dropped, being 14% in TTTS neonates treated between 2002 and 2005.(12) This trend continued in our latest study which evaluated brain injury and detected an overall incidence of brain injury of 6% in liveborn neonates with known neuroimaging results

(*chapter 3*). These numbers are in line with other more recent reports.(13, 14) Some authors have looked exclusively at fetal brain injury, eliminating the influence of prematurity on perinatal brain damage. The results from our *chapter 3* study align with a recent systematic review, both showing a 2% incidence of fetal brain lesions.(15) Most studies in this review, as well as our own study, rely predominantly on the use of ultrasound and only partly on MRI. Therefore the true incidence of fetal brain injury in TTTS is probably underestimated, as MRI has been shown to have additional value in determining fetal brain abnormalities, including subtle injuries and disturbed brain growth.(16) Studies using MRI exclusively have reported antenatal brain injury in TTTS fetuses treated with laser surgery in 2-11% of fetuses.(17-19)

Risk factors and proposed mechanisms

Brain lesions in TTTS patients can be acquired both antenatally and postnatally. The most important risk factor for fetal and neonatal brain injury is to not be treated with laser surgery.(7) This information may seem irrelevant in the current era because laser surgery is now the primary treatment performed for TTTS. However, it is important for neonatologists to realize that laser treatment is not always available or possible for several potential reasons, including late presentation, technical impossibility to perform the procedure or fetal distress requiring prompt cesarean section. Preterm TTTS infants not treated with laser surgery have a significantly higher risk of mortality and severe neonatal morbidity, including severe cerebral injury.(20) Fetuses not treated with laser are exposed to hemodynamic imbalance, anemia or polycythemia for a longer period of time and they are born while still in an unstable hemodynamic state. A principal factor contributing to preterm brain injury in general is the inadequate cerebral autoregulation present in the immature brain. Severe hemodynamic instability is therefore very likely to result in perinatal brain injury in these babies. This thesis deals with TTTS patients who were treated with laser surgery. Other authors have found increased rates of fetal brain injury in cases with recurrent TTTS or TAPS after laser surgery, both complications seen as a result of residual anastomoses.(17) We were able to confirm this finding in *chapter 3*. In this study, we analyzed both fetal and neonatal brain injury and aimed to identify risk factors for brain injury. Recurrent TTTS or post-laser TAPS resulted in a three-fold higher brain injury risk in this large cohort of over 900 TTTS fetuses. Our findings emphasize the need for ultrasonographic follow-up after laser surgery.

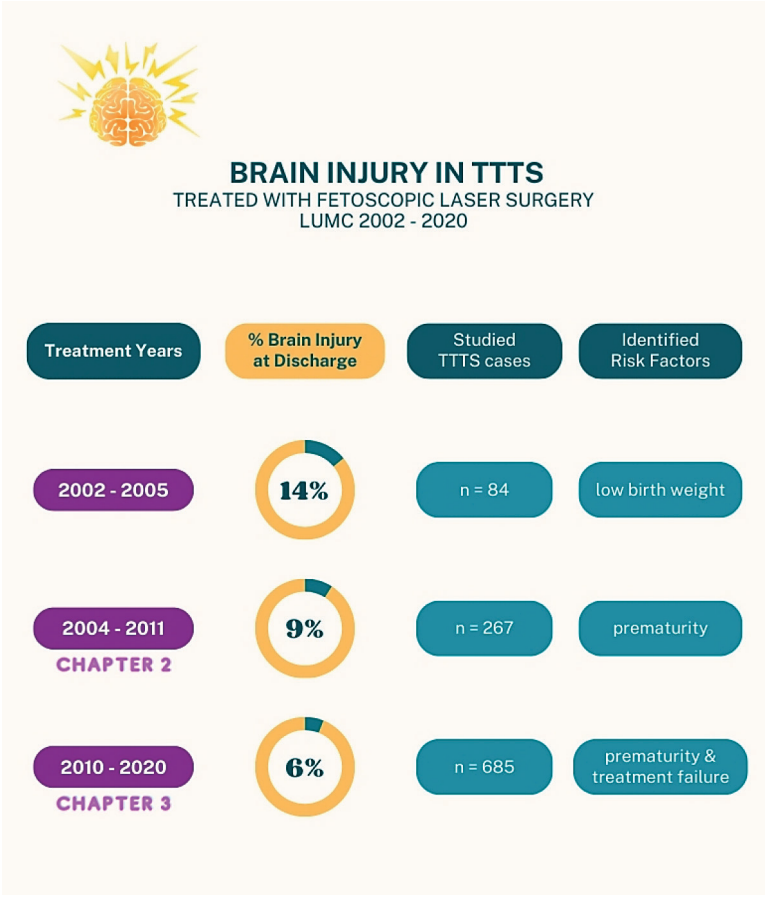

Figure 2. Overview of the incidence of brain injury at discharge in liveborn TTTS infants treated at the LUMC in the past two decades.(12, 21, 22)

Treatment failure: recurrent TTTS or post-laser TAPS

As the majority of TTTS survivors are born preterm, their risk for prematurity-related cerebral injury is also increased. Of the factors identified to have an association with brain injury in TTTS survivors, prematurity is indeed the most important one.(11, 14) The findings presented in *chapters 2 and 3* confirm prematurity as the most important factor associated with neonatal brain injury. Other factors that could potentially be related to the risk of brain injury, including donor or recipient status, TTTS stage and gestational age at laser surgery, were not related to the risk of cerebral injury. The fact that prematurity

is the principal factor related to brain injury in TTTS survivors does not mean that all brain injury is prevented if we can just get these pregnancies to last until term. A proportion of brain injury that is diagnosed after birth, actually has its origin in the fetal period. This statement is based on the observations in *chapter 2* that, although the incidence of cerebral injury in TTTS survivors treated with laser was comparable to the dichorionic twin control group, TTTS neonates were eight times more likely to already have these lesions on their first cranial ultrasound scan performed within 24 hours after birth. A similar observation was made in an earlier report from our center, in which the control group consisted of monochorionic twins without TTTS.(12) Also, several cases with brain injury diagnosed after birth, presented in *chapter 3*, were consistent with ischemic events that occurred during the fetal period, based on the type and timing of injuries.

Types of brain injury

Although many previous authors have described brain injury occurring in the context of TTTS, the pathophysiologic mechanisms behind most injuries have still not been fully elucidated. Most studies have only reported severe intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) as outcome measures in TTTS infants.(5, 23, 24) In fetal neuroimaging studies, reported brain lesions include diffuse lesions linked to early in utero hypoxia-ischemia, like multicystic encephalomalacia, cystic PVL, cerebral atrophy and even migrational and gyrational disorders.(25) Focal lesions, including IVH and focal infarctions are also described. More recent studies using MRI have reported additional brain abnormalities in TTTS, including sinovenous thrombosis, milder forms of white matter injury and significant differences in biometric measurements of different brain areas in TTTS fetuses.(17-19, 26-29) Details about types and timing of different brain injuries can give us more insight into the mechanisms behind their occurrence, but the way we plan, assess and report on neuroimaging results is crucial for the interpretation of the data we acquire. In *chapter 2* of this thesis, a remarkable finding was that four former recipients in the TTTS group suffered middle cerebral artery (MCA) strokes, whereas this abnormality was not detected in donors or in infants from the dichorionic control group. In *chapter 3*, we detected two additional cases of MCA stroke in recipients and again, none in donors. The diagnosis was made on fetal imaging in one of these cases and in the other case, cranial ultrasound on the first day of life showed a large area of tissue loss in the left MCA territory, implying that an MCA stroke must have occurred weeks earlier when the patient was still in the womb. Although Benders et al. had previously established that TTTS is an important risk factor for arterial

stroke in preterm infants, no details about mode of treatment for TTTS nor donor/recipient status were given for the stroke cases in their study.(30) In their large fetal MRI study, Stirnemann et al. also found two cases of MCA stroke in recipients, and none in donors.(17) Furthermore, an earlier fetal brain imaging study by Quarello reported one recipient to have a 'unilateral clastic brain lesion', which is probably an arterial stroke too.(26) After the completion of our neuroimaging study, we found another similar patient: Rosie, who was also a former recipient and whose injury, based on the timing of detected abnormalities, probably originated before or around laser surgery. Although a widening of her left lateral ventricle had been noted on ultrasonography nine days after laser surgery, it was not clear at that point how serious Rosie's injury really was. Her case demonstrates the importance of repeated neuroimaging in TTTS fetuses throughout the pregnancy in order to timely diagnose potentially devastating injuries. In the literature about cerebral injury in TTTS, we did not find any cases of arterial stroke in donor twins. Thus, specifically recipient twins appear to be at risk for this type of brain injury in TTTS. The exact mechanism of arterial ischemic stroke in recipient twins remains uncertain, but we hypothesize that it may be related to vascular sludging due to polycythemia and hyperviscosity. Another possibility is that fetal volume overload and hypertension due to TTTS lead to endovascular changes that increase the risk for stroke. Others have suggested that thrombo-embolic phenomena resulting from the TTTS disease process or fetoscopic laser surgery may be responsible for focal ischemic damage in TTTS fetuses.(31)

When we investigated the types of brain injury in TTTS fetuses and neonates treated with laser surgery in *chapter 3*, one other type of injury stood out. We detected four antenatal and four postnatal cases with cerebellar hemorrhage (CBH), while only one other report in the literature had previously described a single fetal TTTS case with this type of injury.(27) An association between CBH and fetal anemia with intrauterine blood transfusions (IUT) has been reported in two small case series.(32, 33) We suspect that the increased recognition of CBH is due to advancements in prenatal and postnatal neuroimaging techniques. Our findings implicate that the cerebellum deserves special attention in TTTS patients both antenatally and postnatally.

We attempted to improve our understanding of the mechanisms behind brain injury in TTTS by dividing the types of brain injury into two groups: 'diffuse' and 'focal' types of brain injury. The reason behind this division was that cerebral hypoperfusion and anemia probably cause diffuse, symmetrical brain injury such as multicystic encephalomalacia and cystic PVL, whereas hyperviscosity due to polycythemia and possibly thrombo-emboli would most likely lead to focal brain injury. This division is of course somewhat

artificial and far from perfect, as for instance IVH and CBH are characterized as focal injury types, while it is well-known that fluctuations in cerebral blood flow combined with impaired cerebral autoregulation are an important underlying mechanism for the occurrence of IVH and CBH in preterm infants. Although diffuse injury types were more common prenatally and in donors, the numbers of patients with brain injury were too small to detect any certain risk profiles for specific injury types.

Use of magnetic resonance imaging

In our institution, brain MRI is not routinely performed in TTTS fetuses or (preterm) neonates. In our fetal and neonatal neuroimaging study described in *chapter 3*, we established that fetal brain MRI was performed in 3% of TTTS pregnancies between 2010 and 2020. In the same period, just 4% of surviving TTTS neonates underwent brain MRI in the neonatal period or at term-equivalent age (TEA). While recent MRI studies have demonstrated the potential additional value of fetal MRI over neurosonography alone, the question remains whether routine fetal MRI in TTTS is warranted, especially in cases with seemingly uncomplicated, successful laser treatment and normal fetal neurosonography findings.(34) An important consideration here is that the ideal timing of MRI for the detection of fetal brain injury is often in the late second or early third trimester. This is because laser surgery is generally performed in the second trimester and there should be an interval of several weeks between surgery and MRI to allow for the optimal detection of cystic lesions following ischemic events. In the Netherlands, legal restrictions limit the possibility of termination of pregnancy or selective fetal reduction after 24 weeks of gestation. Consequently, conducting an MRI at this stage would typically be too late to contribute to informed decisions regarding the (dis-) continuation of the pregnancy. However, even in these cases, a fetal brain MRI can provide professionals and parents with more certainty about the type and suspected severity of brain injury in the fetus, allowing for more detailed counseling and sometimes, reassurance. In our neuroimaging study, we identified an ex-donor who was diagnosed with bilateral perisylvian polymicrogyria on a postnatal MRI scan. This MRI was made after suspicions of abnormal gyration seen on postnatal, but not prenatal, cerebral ultrasound. This case exemplifies a scenario in which a fetal MRI scan would likely have detected the abnormality, allowing for informed preparation of the parents regarding this severe brain abnormality. Furthermore, this diagnosis at an earlier stage might have influenced decisions regarding delivery and NICU management. The same holds true for Rosie's case: a fetal MRI would have led to an earlier diagnosis, better equipping her parents for the journey ahead.

Whether an earlier diagnosis would have influenced treatment decisions made by obstetricians or neonatologists in her case is unsure, given that laser surgery was performed at 21 weeks, and an MRI would likely have been scheduled after 24 weeks of gestation. In our view, the findings from our studies suggest that while we lack sufficient data to strongly recommend routine fetal brain MRI in TTTS treated with laser surgery, lowering the threshold for fetal MRI is likely wise, particularly in cases with incomplete laser surgery or when changes in fetal brain morphology are observed during repeated ultrasound examinations.

There is something else we need to consider. While ultrasound is primarily suited for the detection of overt brain lesions, image quality has significantly improved in recent years and newer ultrasound machines now offer increasingly detailed images. In postnatal neurosonography, the use of additional acoustic windows provides the opportunity to visualize areas of the neonatal brain that are difficult to assess through the anterior fontanelle, such as the posterior fossa. Owing to these advancements, more abnormalities can be detected by ultrasound than before. Similarly, the field of fetal neurosonography has been evolving. "Advanced neurosonography" involves generating images of the fetal brain in the coronal and sagittal planes, in addition to the 'basic' axial plane assessment that has been widely used in clinical practice as well as in research. This technique significantly improves the detection of fetal brain anomalies, according to a study of fetuses at risk for acquired brain lesions.(35) In our center, this technique has become standard for the evaluation of TTTS fetuses only a few years ago. Previously, fetal brain ultrasound screening was limited to the axial plane, and additional planes were only evaluated when abnormalities were suspected. The results of our neuroimaging study in *chapter 3* have to be interpreted with this in mind; had we consistently applied advanced neurosonography to all TTTS cases, as is our current practice, we might have detected more brain lesions antenatally.

Neurodevelopmental outcome

Incidence

Based on the table on the following page, it is evident that several colleagues in the field have assessed the long-term neurodevelopmental outcomes following laser treatment for TTTS. Nevertheless, inclusion criteria, follow-up rates, age at follow-up and methodologies vary among studies, complicating the interpretation and comparison of results. The organization of a structured long-term follow-up program is a challenging task, requiring financial resources,

Table 1. Studies of NDI and cerebral palsy (CP) in TTTS treated with laser surgery (8, 13, 36-49)

Reference	Country	Age (y)	Patients	NDI %	CP %
Sutcliffe 2001	UK	2	66	9	9
Banek 2003	Germany	2-3	89	11	11
Graef 2006	Germany	2-4	167	8	6
Lenclen 2009	France	2	88	11	10
Lopriore 2009	Netherlands	2	278	18	6
Salomon 2010	France	5	73	-	12
Gray 2011	Australia	2-4	113	12	4
Graeve 2012	Germany	4-10	151	9	-
Van Klink 2014	Netherlands	2	155	6	3
McIntosh 2014	Australia	1-3	50	4	2
Vanderbilt 2014	USA	2	100	4	3
Tosello 2014	France	0-5	35	-	6
Korsakissok 2018	France	2-7	58	9	5
Schou 2019	Denmark	1-4	86	10	9
Chmait 2019	USA	2	99	4	3
Spruijt 2019	Netherlands	2	258	3	2
Overall				**9% (151/1741)**	**5% (93/1695)**
Range				**3-18%**	**2-12%**

adequate space, and highly trained professionals from different professional backgrounds. Throughout the years, we have consistently emphasized the importance of long-term follow-up for all children treated with fetal therapy, however we continuously face these same challenges, much like many of our colleagues in the field. In the Netherlands, a national guideline for the long-term follow-up of various groups of NICU graduates provides recommendations for multidisciplinary follow-up assessments. These include infants born before 30 weeks gestation or with a birth weight <1000 grams, those born SGA and with a birth weight <1500 grams, infants diagnosed with hypoxic-ischemic encephalopathy treated with therapeutic hypothermia, and children who underwent fetal surgery. All children belonging to one of these groups are scheduled for follow-up appointments at 6, 12, and 24 months corrected age, as well as 5.5 and 8 years uncorrected age.(50) *Chapter 4* of this thesis describes the long-term follow-up study we performed to

determine the incidence of severe NDI among a large group of survivors after TTTS treatment with laser surgery between 2011 and 2014, comparing neurodevelopmental outcome at the corrected age of 24 months with the outcomes of a previous cohort from our center. For this study, we collected the neurodevelopmental assessments made using the Bayley Scales of Infant and Toddler Development. Despite noting that the absolute risk of severe NDI was 3% in the most recent cohort, compared to 6% in the previous one, we could not prove a significant improvement between the two time periods. Still, this may be viewed as a continuation of the positive trend observed in our center since the introduction of laser surgery.(43) Nevertheless, it is important to acknowledge that a neurodevelopmental evaluation at the age of 2 years can only partly predict (severe) impairment at a later age. This point was recently confirmed in a follow-up study from our group, which examined neurodevelopmental outcome in preterm TTTS survivors at the age of 5.5 years. This study revealed that severe NDI was present in 12% of these school-aged children, compared to only 3% when the same children were assessed at the corrected age of 2 years.(51) Although there is some overlap between the cohorts, an important distinction between the recent 5.5-year follow-up study and the study outlined in *chapter 4* lies in the composition of the cohorts. The 5.5-year follow-up cohort consisted only of preterm and/or small for gestational age (SGA) TTTS survivors, resulting in a lower mean gestational age of approximately 30 weeks and one-third of the study participants being classified as SGA. Preterm and SGA infants have consistently been invited for all follow-up visits, whereas there have been periods of time when financial and staffing constraints led to a higher loss-to-follow-up rate among (near-) term and appropriate for gestational age (AGA) TTTS survivors. In contrast, the cohort described in *chapter 4* describes a consecutive cohort of all TTTS survivors, with a mean gestational age of nearly 33 weeks and only 9% classified as SGA. This discrepancy indicates an underlying increased risk of NDI in the 5.5-year follow-up study, despite the prevalence of severe NDI at the age of two years appearing similar between both studies.

Risk factors for NDI

Fetoscopic laser treatment not only mitigates the risk of brain injury but also diminishes the risk of long-term NDI in survivors.(8, 40) Among the predictors of neurodevelopmental delay in children who underwent laser surgery for TTTS in utero are low gestational age at birth, low birth weight, higher TTTS stage and severe cerebral injury.(8, 13, 37, 40, 43-45, 48, 52) Studies into the comparative risk of NDI between donors and recipients consistently show a similar level of risk for both twins. Most studies have focused either on

assessing the risk of brain injury or on reporting long-term outcomes. As mentioned previously, there is a considerable degree of variation among studies regarding the definition of brain injury. Some studies report even minor abnormalities, while others focus solely on severe injuries associated with a high risk for long-term impairment, such as cystic PVL and high-grade IVH. Little is known about the long-term consequences of minor brain abnormalities reported in TTTS, a gap in knowledge that is particularly pronounced for prenatally detected injuries. Ideally, studies should integrate neuroimaging findings with long-term neurodevelopmental data to enable the accurate evaluation of the ramifications of specific types of brain injuries, whether minor or major. This is what we did in our neuroimaging study in *chapter 3*, where we not only established the incidence and types of brain injury but also documented the available long-term outcome data for all children affected by fetal and neonatal brain injury. Our results confirm the robust association between brain injury and subsequent NDI, with approximately one-third of children with brain injury manifesting severe NDI by the age of two years. Our study showed a very low survival rate among cases with fetal brain injury, mostly due to treatment decisions made because of fetal neuroimaging findings. The surviving children exhibited mild brain abnormalities and indeed had favorable neurodevelopmental outcomes. Nonetheless, we stress the importance of reporting the long-term outcomes of such cases—a practice lacking in the existing literature.

In *chapter 4*, we found that low birth weight and being classified as SGA are independently associated with lower cognitive scores on the Bayley Scales of Infant and Toddler Development. Moreover, severe brain injury had a significant negative effect on motor but not cognitive Bayley scores. While these risk factors demonstrated associations with neurodevelopmental outcomes, the association between gestational age at birth and cognitive Bayley scores did not reach statistical significance. This was probably caused by the fact that several children with severe NDI were born at gestational ages surpassing 32 weeks. Furthermore, although severe cerebral injury significantly increases the risk for NDI, the opposite is not always true: several children with severe NDI had had normal findings on neonatal cranial ultrasound examinations. These results once again emphasize the need for long-term follow-up for all TTTS survivors, independent of gestational age at birth and neonatal neuroimaging findings.

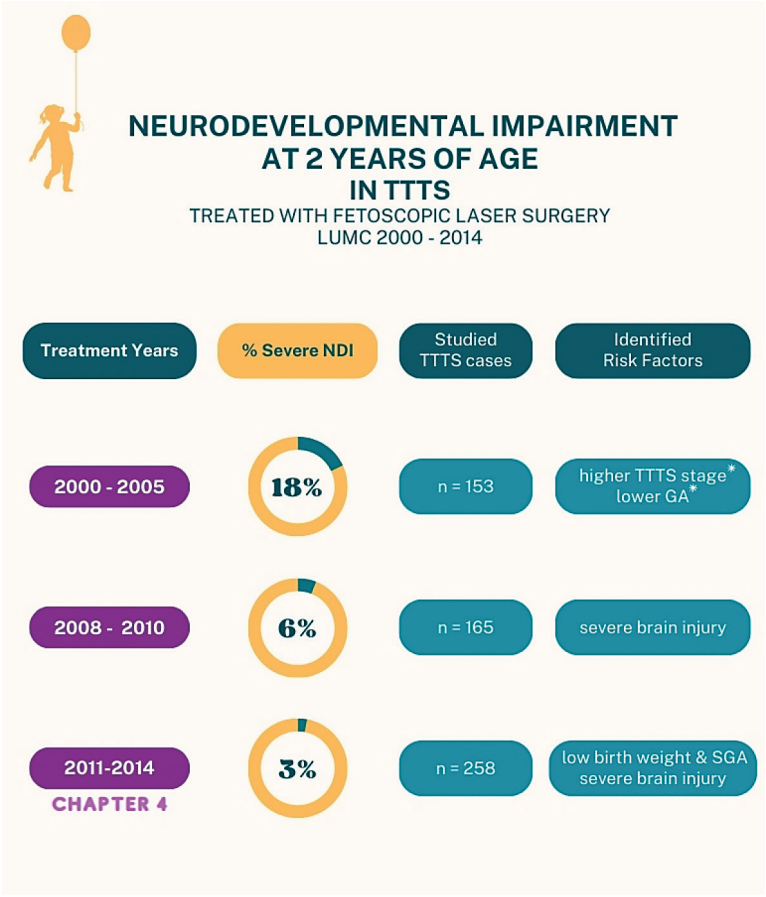

Figure 3. Overview of the incidence of severe NDI in TTTS survivors treated at the Leiden University Medical Center (43, 49)

* only trend toward an association of NDI with TTTS stage and GA (p = 0.08 for both)
GA, gestational age; SGA, small for gestational age

Mild or minor NDI

Owing to the improved survival rates and long-term neurodevelopmental outcomes observed in twins affected by TTTS, it is only logical that we delve a little deeper by examining not only severe neurological deficits, but also the incidence of mild impairments. Previous studies on the long-term outcomes after TTTS with laser surgery have reported instances of mild NDI with varying definitions and under various terminologies, including minor

neurological deficiencies, moderate impairment, or borderline development. Its incidence is reported to range between 8 and 29%.(13, 38, 42, 44) In *chapter 4* of this thesis, mild NDI was investigated in the largest cohort of TTTS survivors treated with laser surgery to date. We defined mild NDI as any of the following: cerebral palsy grade 1 according to the Gross Motor Functioning Classification System (GMFCS), or Bayley cognitive or motor composite score between 1 SD and 2 SD below the mean. The confirmed high rate of mild NDI of 23% underscores the importance of the use of standardized tests. These tests can assist in identifying the strengths and weaknesses in the development of each individual child, thereby aiding parents, teachers, and caregivers in finding the appropriate professional support, if needed.

Our study in *chapter 5* was the first-ever study to investigate behavioral outcome in TTTS survivors treated with laser surgery. Similar to those in *chapter 4*, the investigations in *chapter 5* took place when the children were 2 years old, corrected for prematurity. We demonstrated that the risk of behavioral problems at this age is comparable to the general population, but increased in children with cognitive as well as motor developmental delays. The risk of behavioral problems was mitigated by a higher level of maternal education. The 5.5-year follow-up study from our group described previously also included behavioral assessment at the school-age visit and found a higher rate of behavioral issues of 14% at the age of 5.5 years in preterm and SGA TTTS survivors.(51) Once more, these findings confirm that, while a thorough neurodevelopmental assessment around the age of two can detect the majority of children with severe impairments, the same cannot be said for mild impairments, particularly cognitive deficits, and behavioral issues.

Intentional demise

As we are well aware, TTTS is a condition characterized by significant mortality and morbidity rates, even in the era of fetoscopic laser surgery. While this surgical intervention aims to effectively eliminate the underlying cause of intertwin transfusion, it is not always feasible and may give rise to complications such as post-laser twin anemia polycythemia sequence (TAPS), preterm prelabor rupture of the membranes (PPROM), and (extremely) preterm birth. In circumstances where the prospect of a favorable outcome is limited due to severe feto-fetal transfusion at presentation, challenges in laser treatment or the emergence of post-surgery complications, discussions regarding end-of-life options become inevitable. These options may include termination of pregnancy (TOP) when prognosis is dire for both fetuses, selective fetal reduction (SFR) in cases where complications are limited to one twin or if technical challenges prevent successful laser surgery, or the decision

to withhold life-sustaining neonatal intensive care at birth, for instance when gestational age exceeds the legal termination limit. In some instances, NICU care may be withdrawn if severe complications arise in the neonatal period. While such decisions are unavoidable across fetal therapy centers and NICUs in different countries, cultural and legal factors shape the approach taken by clinicians and parents in addressing these delicate matters. End-of-life decisions during pregnancy and at the NICU impact morbidity and mortality rates, as children with the poorest prognoses do not survive when end-of-life decisions are made. We hypothesized that this phenomenon might partially explain the observed improvement in long-term neurodevelopmental outcomes over time. Are we becoming better at identifying children with unfavorable developmental trajectories, thus resulting in more frequent end-of-life decisions? In *chapter 6*, we examined the incidence of and reasons for what we termed 'intentional demise', a composite term encompassing TOP, SFR and withholding or withdrawal of NICU care. To our knowledge, no prior studies have reported rates of intentional demise in TTTS pregnancies. Our findings revealed that up to one in six women (17%) with a TTTS pregnancy experienced intentional fetal or neonatal demise, with this rate remaining consistent between 2000 and 2014. A frequent reason for intentional demise was severe brain injury, accounting for a total of 22% of cases of intentional demise. Brain injury was of antenatal origin in the majority of infants in whom NICU care was withheld or withdrawn for this reason. These findings hold significance for interpreting pregnancy outcomes and long-term neurodevelopmental trajectories following TTTS. We advocate for transparency regarding this sensitive topic in future publications on the outcome of TTTS pregnancies.

Future directions

While this thesis has shed more light on the incidence, timing, and long-term consequences of fetal and neonatal brain injury in TTTS, further questions remain to be answered, as is always the case in research.

Collaboration

To further improve outcomes for families affected by TTTS, collaboration between fetal and pediatric medicine specialists in future research endeavors is crucial. Challenges for fetal medicine primarily involve optimizing prediction and diagnosis of TTTS, along with refining technical aspects of laser surgery to minimize the risks of post-laser PPROM and residual anastomoses. Developments in fetal neuroimaging offer promise for improved detection of fetal brain injury. From a pediatric perspective, detailed neuroimaging and follow-up studies remain vital for understanding the significance of brain abnormalities diagnosed in utero or in the neonatal period. As with most things in life, timing is everything: follow-up studies should extend at least to school age in order to comprehensively assess the ongoing development in cognitive, motor, and psychosocial domains.

Neuroimaging

In many TTTS cases with brain injury, the exact timing and mechanisms of the injury remain unclear. Our research has shown that TTTS neonates are much more likely to exhibit brain injury diagnosed within 24 hours after birth (*chapter 2*), suggesting a higher incidence of antenatal injury compared to dichorionic twins. Future studies using repeated, advanced, multiplanar fetal neurosonography from the time of TTTS diagnosis until birth, along with standard third trimester fetal MRI, could greatly enhance our understanding of the mechanisms and timing of brain injury in TTTS fetuses. Ideally, advanced fetal neuroimaging should be followed by repeated neonatal cranial ultrasonography until term, as well as neonatal and/or term-equivalent MRI, to monitor the evolution of abnormalities throughout the brain's maturation process.

Given that the majority of studies investigating brain injury in TTTS to date lack specific descriptions of neuroimaging findings, discerning the true significance of such injuries across different studies poses a challenge. As established in *chapter 3* of this thesis, multiple TTTS survivors showed combinations of multiple types of injuries, making it challenging to categorize them for the sake of comparison between studies. The use of validated brain injury severity scores, such as the Kidokoro score for term-equivalent brain

MRI, could improve our comprehension of the severity of injuries in future studies on this subject.

Previous research consistently indicates that the risks of brain injury are equal for donors and recipients in TTTS. However, their intrauterine experience could be described as completely opposite from each other. Consequently, the mechanisms of brain injury likely differ for donors and recipients, especially when it occurs before or after incomplete laser surgery. In this thesis, we argue that MCA stroke appears to be a specific risk for TTTS recipients, although the exact mechanism of this injury remains uncertain. Future fetal and neonatal neuroimaging studies should prioritize investigating intertwin differences to better understand the processes underlying brain injury occurrence in TTTS donors and recipients. By unraveling these mechanisms, we may be able to develop targeted prevention strategies.

Long-term follow-up

As mentioned many times before, future neurodevelopmental follow-up studies in children born after fetal therapy for TTTS are indispensable for providing optimal care to these families. Future long-term follow-up studies focusing on children with both minor and major brain abnormalities may support the counseling of parents following the identification of brain injury through advanced fetal and neonatal neuroimaging techniques. Ensuring the inclusion of all TTTS infants in follow-up studies, rather than solely those deemed 'high risk,' is paramount.

Since the incidences of brain injury and severe NDI have notably declined over the past two decades, we have to redirect our focus and include milder forms of impairment in our follow-up studies. Particularly during school-age years and beyond, mild neurodevelopmental challenges and impaired psychosocial development, including behavioral problems, can profoundly impact children and their families.

A potential new direction of research could focus on the psychological well-being of families affected by TTTS and its effect on long-term developmental outcome in children. Studies have revealed that TTTS leads to severe anxiety and depression in the majority of mothers during and after pregnancy.(53) Moreover, perinatal anxiety has been identified as a significant predictor of adverse social-emotional development in children.(54) Future research exploring psychological support measures for families throughout pregnancy, delivery and infancy may help determine whether this effect can be alleviated.

Lastly, to establish the true effect of TTTS on fetal and neonatal brain injury as well as long-term neurodevelopmental outcomes, future research should ideally incorporate a control group of uncomplicated monochorionic twins.

Final conclusion

The findings of the studies conducted in this thesis, which investigated large consecutive cohorts of TTTS fetuses, neonates and children, indicate a decrease in the incidences of brain injury and neurodevelopmental impairment since the introduction of fetoscopic laser surgery. This decrease is accompanied by a shift towards milder forms of developmental issues. In the most recent decade, we may have reached the point where further improvement is hindered by two remaining risk factors. The first is prematurity, which we confirm as the most important factor associated with severe brain injury in infants affected by TTTS. Secondly, ongoing imbalanced intertwin transfusion through residual anastomoses after laser treatment, defined as recurrent TTTS or post-laser TAPS, poses a continued risk for the occurrence of brain injury. While prematurity is a risk factor for both severe brain injury and long-term impairment, our studies emphasize the necessity of neurodevelopmental follow-up for all TTTS survivors until at least school age, underlining that there is no such thing as a 'low risk' TTTS survivor. Much is still unknown concerning fetal and neonatal brain injury in TTTS, and we need to further increase our knowledge. It is our job to take care of the families affected by this devastating disease, and they deserve the best possible care based on the best possible research. Hopefully, for future generations, we can prevent TTTS from causing brain injury and neurodevelopmental sequelae or perhaps, even prevent TTTS altogether.

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