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Brain matters in twin-twin transfusion syndrome

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Part SIX

Summary and discussion

Summary

Twin-twin transfusion syndrome or TTTS is a rare condition that complicates about 1 in 10 monochorionic twin pregnancies. Monochorionic twins share a single placenta, which nearly always contains vascular anastomoses connecting the two fetal circulations. TTTS occurs when there is a unidirectional net transfusion of blood between the twins through these anastomoses. As a result, the twin losing blood volume, known as the donor, becomes hypovolemic and oliguric. Eventually, the donor twin may become 'stuck' in the membranes due to severe oligohydramnios. Conversely, the twin receiving excessive blood flow, known as the recipient, experiences volume overload, resulting in polyuria and polyhydramnios. This presentation on prenatal ultrasound is referred to as Twin Oligohydramnios Polyhydramnios Sequence (TOPS) and it is the hallmark of TTTS diagnosis. Untreated TTTS invariably leads to serious complications for both twins, including severe brain injury, neurodevelopmental delays, and death. However, with timely diagnosis and appropriate treatment, the outcomes for TTTS are significantly improved. The appropriate treatment for TTTS is fetoscopic laser coagulation of the vascular anastomoses, a minimally invasive surgical procedure that was developed in the 1990s. In this procedure, a fetoscope, containing a tiny camera and laser fibre, is introduced into the amniotic sac of the recipient, where the connecting blood vessels between the twins are coagulated with laser to prevent further unequal blood flow. Laser surgery has improved perinatal survival rates as well as neonatal and long-term neurodevelopmental outcomes. The Leiden University Medical Center (LUMC) serves as the Dutch national referral center for fetal therapy and fetoscopic laser surgery was introduced here in the year 2000. Given the ongoing developments in the fields of monochorionic twin complications, fetal therapy, and neonatology over the last decades, the evaluation of neonatal and long-term outcomes after laser treatment for TTTS remains of utmost importance.

This thesis deals with matters of the brain in TTTS, as we investigated brain injury and neurodevelopmental outcome in TTTS fetuses, neonates and children. **Part one** of the thesis introduces the subject by providing a detailed case description of a twin pair affected by TTTS, where the recipient twin suffered severe brain injury resulting in long-term neurological sequelae. A review of the literature on TTTS with a special focus on neonatal cerebral injury and long-term neurodevelopment is described in **part two**. In **part three**, brain injury in TTTS is examined through studies exploring the incidence, types, and risk factors of brain injury in fetuses and neonates. The long-term neurodevelopmental outcomes of children affected by fetal and neonatal brain injury after TTTS are reported. Further insights into long-term outcomes are provided in **part four**, which includes two studies

using standardized tests to assess both mild and severe neurodevelopmental impairment (NDI), as well as behavioral problems in TTTS survivors. Finally, **part five** of the thesis delves into the rates of intentional fetal and neonatal demise in TTTS following the introduction of fetoscopic laser therapy at the LUMC.

Chapter 1 provides a review of the literature summarizing the latest insights regarding TTTS. It covers knowledge gained from placental injection studies, prenatal management including advancements in laser techniques, as well as fetal and neonatal complications, with extra attention given to brain injury and long-term neurodevelopmental outcome. The review concludes with suggestions for targets for further improvements in the management of the disease, emphasizing the importance of long-term follow-up for TTTS survivors, as well as the centralization of care in specialized fetal therapy centers.

In *chapter 2*, we assessed the incidence and risk factors for severe brain lesions in a case-control study of monochorionic twins with TTTS treated with fetoscopic laser surgery. We used dichorionic twins matched for gestational age as a control group and analyzed postnatal cranial ultrasonography results. We included 267 TTTS neonates treated between 2004 and 2011, matched with 267 dichorionic controls from the same period. The incidence of severe cerebral injury in the TTTS group and control group was 9% and 7%, respectively. This difference was not statistically significant. The analysis of potential risk factors revealed that only gestational age at birth was independently associated with an increased risk for severe cerebral injury. More than half of brain lesions in the TTTS group were detected within 24 hours after birth, compared to only 17% in the dichorionic control group. We report the striking finding that four recipients in our TTTS group suffered an arterial stroke in the territory of the left middle cerebral artery (MCA), whereas no donors and none of the dichorionic twins experienced this rare complication. We concluded that the risk of severe brain injury in TTTS treated with laser is comparable to a matched dichorionic control group and is independently associated with prematurity. However, compared to dichorionic twins, brain injury in TTTS is significantly more likely to occur before birth.

In *chapter 3*, our aim was to investigate brain injury in more detail by examining different types of brain injury in TTTS treated with laser surgery occurring before and after birth, the imaging modalities employed, and the long-term neurodevelopmental outcomes associated with various types of brain injuries. We again studied potential risk factors for brain injury. We categorized brain injuries into eight predefined groups, divided into 'diffuse'

and 'focal' categories. The study cohort consisted of 466 TTTS pregnancies treated between 2010 and 2020. Brain MRI was performed in only 3% of pregnancies and 4% of neonates; therefore, the majority of findings were based on fetal and neonatal brain ultrasonography. Brain injury was diagnosed in 2% of TTTS fetuses and 5% of neonates, with all predefined injury groups present. Among cases with fetal brain injury, fetal death (spontaneous or intentional) occurred in 69%. In neonates with a postnatal diagnosis of brain injury, the neonatal mortality rate was 22%. Neurodevelopmental impairment (NDI) was present in 31% of long-term survivors with brain injury. We identified two risk factors for brain injury: recurrent TTTS/post-laser twin anemia polycythemia sequence (TAPS) and lower gestational age at birth. A novel finding of this study was that cerebellar hemorrhages were a quite frequent finding, both antenatally and postnatally. We suspect that this is due to better recognition resulting from advancements in imaging techniques, as well as the increased survival of extremely preterm infants, who are at the highest risk for this complication in the neonatal period. In conclusion, based on the mix of diffuse and focal brain injuries found in fetuses and neonates, various mechanisms are likely responsible for the occurrence of brain injury in TTTS treated with laser surgery, and the presence of brain injury is associated with a high likelihood of NDI or death. Cases with recurrent TTTS or post-laser TAPS and/or lower gestational ages at birth are at increased risk of brain injury. Additionally, the true incidence of brain injury remains uncertain due to the limited use of MRI. Because of the risk of cerebellar hemorrhage in TTTS, special attention to the fossa posterior is advised.

In *chapter 4*, we examined the incidence of NDI in TTTS survivors treated with laser surgery from 2011 to 2014 and compared their outcomes to a previous cohort treated from 2008 to 2010. Neurological, cognitive, and motor development of the children were evaluated at two years of age using the Bayley Scales of Infant and Toddler Development (third edition), and risk factors associated with Bayley-III scores were determined. Our findings showed that severe NDI was observed in 3% of survivors in the new cohort compared to 6% in the previous cohort, although this difference did not reach statistical significance. Similarly, the rate of disease-free survival, defined as survival without severe NDI, did not significantly differ between the two cohorts. Mild NDI, defined as cerebral palsy GMFCS grade 1 and/or a cognitive or motor composite score between 1 standard deviations (SD) and 2 SD below the mean, was found in 23% of children in the new cohort. Low birth weight and being small for gestational age (SGA) were independently associated with lower cognitive scores, while severe cerebral injury was related to lower motor scores. Importantly, children with severe NDI were born at or after 32 weeks

of gestation in 53% of cases and had no evidence of cerebral injury on cranial ultrasound in 59% of cases. This suggests that neither gestational age above 32 weeks nor the absence of cerebral injury necessarily preclude severe NDI. We conclude that despite advancements in TTTS management, outcomes seem to have plateaued. Low birth weight, SGA, and severe cerebral injury remain significant risk factors for poor neurodevelopmental outcomes in children treated with laser surgery for TTTS. While the incidence of severe NDI has decreased, mild NDI is common in TTTS survivors. These mild problems should not be overlooked, as they can interfere with daily life across the lifespan, including school functioning, learning and everyday activities.

In *chapter 5*, we aimed to fill in part of the knowledge gap concerning the milder long-term consequences of TTTS. This study was the first to examine behavioral outcomes of twins who underwent fetoscopic laser coagulation treatment. Behavioral assessments at the corrected age of two years using the Child Behavior Checklist (CBCL) were evaluated in over 400 TTTS survivors treated at the LUMC between 2008 and 2015. The CBCL is a tool used to assess behavioral and emotional problems in children that is completed by parents or caregivers. The results of the CBCL provide scores on two broadband scales: internalizing problems (such as anxiety and depression), and externalizing problems (such as aggression and rule-breaking behavior), as well as a total problems score. Key findings from our study revealed that behavioral problems were reported in 8% of TTTS survivors, without a difference between donors and recipients. This incidence is comparable with that observed in the general population. Furthermore, the incidence of both cognitive and motor impairment was increased among children with behavioral problems. A higher level of maternal education was associated with fewer behavioral problems in their children. Since a considerable proportion of mothers in the study had a high level of education compared to the general population, and since the children included in the study had a higher birth weight and were more often born at term compared to those lost to follow-up, the incidence of behavioral problems may have been underestimated. While assessing behavioral problems at such an early age does not predict all problems that may manifest later in life, early identification and intervention for behavioral problems in TTTS survivors, particularly those with severe developmental delays, may be crucial for improving long-term outcomes.

The study outlined in *chapter 6* of this thesis aimed to assess the incidence and reasons behind intentional fetal and neonatal demise in TTTS managed at the LUMC between 2000 and 2014. The rationale for this study was the hypothesis that the observed improvement in long-term neurodevelopmental outcomes could be attributed, at least in part, to heightened awareness and

detection of cerebral injury due to growing expertise in TTTS management, potentially leading to an increase in intentional demise over time. Intentional demise was defined as termination of pregnancy, selective fetal reduction, or withdrawal of neonatal intensive care. Our findings indicated that a considerable portion of TTTS families were affected by some form of intentional demise, occurring in 17% of TTTS pregnancies and affecting 10% of fetuses/neonates. Comparison across three consecutive 5-year sub-cohorts failed to reveal a difference in the rates of intentional demise over time. The main reasons for intentional demise were complications or technical challenges during the laser procedure, severe fetal abnormalities, and significant neonatal complications arising from TTTS and/or prematurity. Severe brain injury was the reason for intentional demise in 22% (24/110) of fetuses and neonates. In essence, the decisions surrounding intentional demise were driven by poor prognoses, underscoring their potential impact on long-term neurodevelopmental outcome. Overall, this study sheds light on the determinants of intentional fetal and neonatal demise in TTTS cases in The Netherlands.