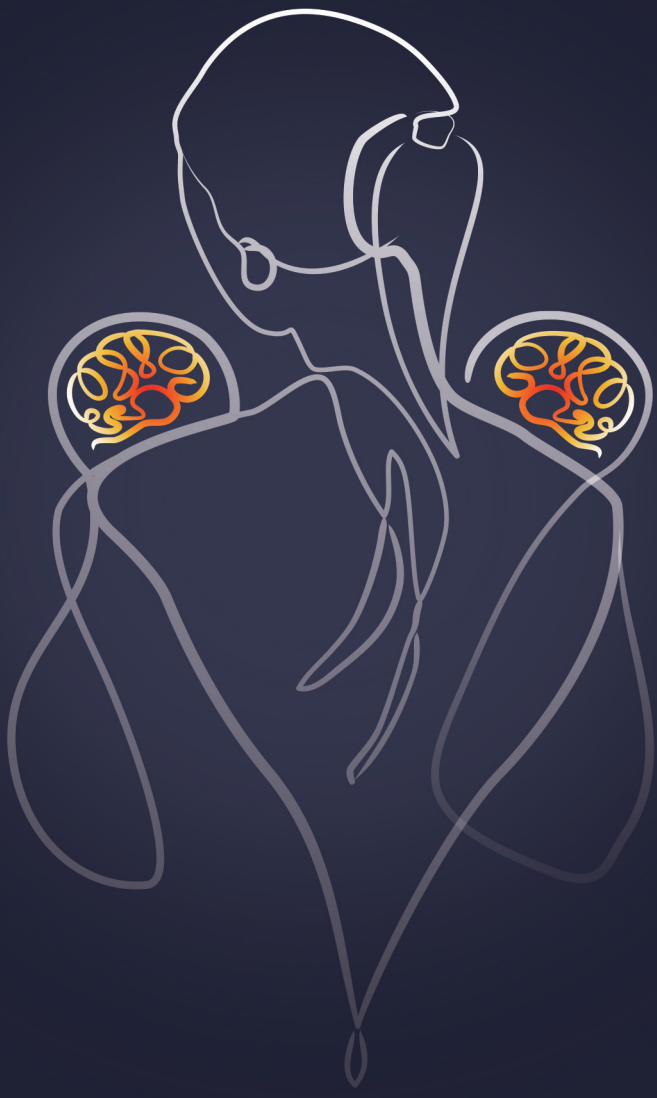
Brain matters in twin-twin transfusion syndrome

Spruijt, M.S.



Part ONE

Introduction and aim

General introduction

The story of Amy and Rosie

Mrs. de Jong was in her first pregnancy and expecting monochorionic twins. At one of her biweekly ultrasound check-ups around 16 weeks' gestation, a discordance in amniotic fluid between the twins was noted. Mrs. De Jong was referred to the Leiden University Medical Center, the national referral center for monochorionic twin complications and fetal therapy in The Netherlands. Our obstetricians confirmed the discordant amniotic fluid volumes, but criteria for twin-twin transfusion syndrome (TTTS) were not met. The future parents were counseled about the chances of progression to TTTS and Mrs. De Jong was followed with regular ultrasound examinations at our center. Indeed, progression to TTTS stage 1 was seen at 19 weeks' gestation, but in the absence of maternal symptoms, the future parents were counseled towards expectant management. After further progression to TTTS stage 2 at 21 weeks' gestation, fetoscopic laser coagulation of the placental anastomoses using the Solomon technique was performed.

Recovery from TTTS was evident in the days following laser surgery and both fetuses appeared to be in good condition. Ultrasonography of the former recipient's brain 9 days after laser surgery showed an asymmetry of the lateral ventricles, without any other clear abnormalities. The intertwin membrane could not be visualized between the twins, suggestive of iatrogenic mono-amnionicity. Reassuringly, although the asymmetry was still present, both the recipient's lateral ventricles remained within normal limits.

At 26 weeks' gestation, Mrs. De Jong's membranes ruptured, and she was admitted to the obstetric ward of our hospital. Antenatal steroids were given, and the couple was counseled about prematurity by one of our neonatologists. When labor started one week later, a primary cesarean section was performed because of monoamnionicity and the risk of cord entanglement. Two daughters were born: former donor Amy, with a birth weight of 930 grams, and former recipient Rosie, weighing 960 grams.

The placenta was examined postnatally, as is our custom, but the chorionic vessels could not be injected with colored dye to check for the presence of residual anastomoses, because the placenta was damaged and torn on the laser line. Histology of the placenta showed equal placental sharing and no signs of fetal thrombosis, nor ischemic changes.

The twins were born in good condition and admitted to our neonatal intensive care unit (NICU), requiring only non-invasive respiratory support. Both girls underwent cranial ultrasonography on the first day of life. Amy's ultrasound was unremarkable and she had an uncomplicated NICU course.

Rosie's antenatal findings were confirmed on her first postnatal cranial ultrasound, which showed a larger left lateral ventricle. Sadly, this was not the only finding, as it was clear that part of the left hemisphere was smaller and subcortical cystic changes as well as an abnormal cortical appearance were seen, especially around the left insular area (see ***Figure 1***, left panel.). Brain magnetic resonance imaging (MRI) was performed around 30 weeks post-menstrual age and showed extensive tissue loss in the territory of the left middle cerebral artery, including loss of volume in the basal ganglia and thalamus, consistent with a previous ischemic stroke.

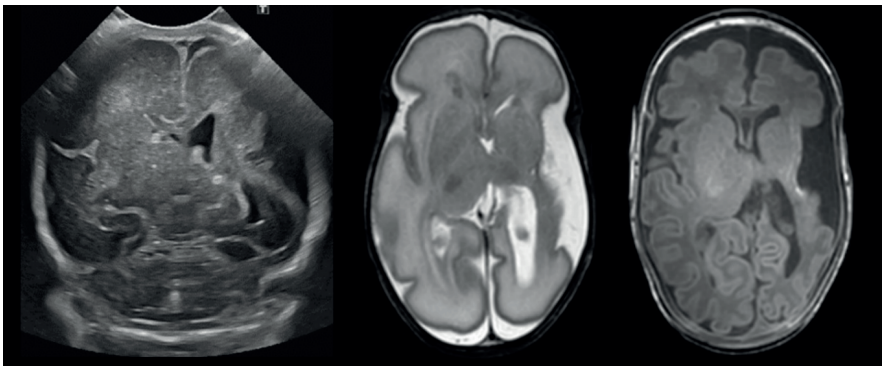


Figure 1. Postnatal neuroimaging of Rosie, the former recipient.

Left: Ultrasound in coronal plane on the first postnatal day, showing asymmetrical ventricles and a smaller left hemisphere (cystic changes were also present, not shown). Middle: MRI at 30 weeks' gestation: T2-weigthed image at the level of the basal ganglia and thalami, showing a smaller left hemisphere, basal ganglia and thalamus as well as compensatory left ventricular dilatation. Right: term-equivalent MRI: T1-weighted image at approximately the same level showing progress of gyrification in all areas of the brain and myelination of the right, but not the left posterior limb of the internal capsule (PLIC).

Rosie's further NICU course was complicated by the need for mechanical ventilation and retinopathy of prematurity. Around 35 weeks postmenstrual age, she was transferred to a local hospital together with her sister. She returned for a second MRI scan around term-equivalent age to assess the evolution of her cerebral injury and the progression of myelination. This term MRI showed a smaller left hemisphere, smaller thalamus and basal ganglia and unilateral ex vacuo ventricular dilatation, gliotic changes in the left insular area, as well as reduced myelination on the left side in the dorsal brainstem, posterior limb of the internal capsule, thalamus, globus pallidus and corona radiata (see ***Figure 1.***, right panel). We explained to Rosie's parents

that we expected Rosie to develop motor problems on the right side of her body, but that it was difficult to predict whether her cognitive and visual development would be affected as well. Therefore, long-term follow-up of her overall development would be very important.

The twins were discharged home on their due date. As expected, Rosie's motor development was progressively asymmetrical, with an early preference for use of her left hand and higher muscle tone of the right arm and leg at a corrected age of 4 months. She is under the care of a rehabilitation specialist, a physiotherapist specialized in developmental support for preterm infants, a pediatric neurologist and a general pediatrician. At the follow-up visit in the LUMC at 12 months corrected age, Rosie's motor development is delayed and asymmetrical, but she is doing well and is showing progress in all areas of development.

Rosie and Amy will return to our outpatient clinic for structured follow-up visits at the (corrected) ages of 2, 5 and 8 years. Starting at the corrected age of 2 years, the follow-up visits will include age-dependent standardized tests for cognitive as well as fine and gross motor development. Parents will be invited to complete questionnaires concerning their children's behavior and psychological well-being. In the meantime, Rosie is followed closely by medical professionals closer to home.

Figure 2. *Top left:* Rosie during her NICU stay, *Middle left:* Amy during her NICU stay, *Top right:* Kangaroo care with mom in the NICU, *Middle right:* The De Jong family: Rosie with mom, Amy with dad, *Bottom:* Amy (front) and Rosie (back) going for a drive.

Names and details about the pregnancy were modified. The parents gave permission for the publication of their story.

Twin-twin transfusion syndrome and fetoscopic laser surgery

Monochorionic twin pregnancies are threatened by several specific complications and TTTS may be the best-known, as well as the most feared one. TTTS develops in about 10% of monochorionic diamniotic twin pregnancies and its natural course is quick and more often than not, devastating. The name of the disease implies that transfusion between twins is pathological in itself. However, this is not the case. In uncomplicated monochorionic pregnancies, intertwin transfusion through deep arterio- venous placental anastomoses occurs equally in both directions or is compensated via superficial arterio-arterial (or rarely, veno-venous) anastomoses. In the case of TTTS, net blood flow from one twin to the other is unidirectional, resulting in volume depletion, oliguria and oligohydramnios in the donor fetus and volume overload with polyuria and polyhydramnios in the recipient.(1) The paradoxical exposure to different vasoactive mediators is thought to contribute to further deterioration of the disease process.(2) The major hemodynamic disturbances in TTTS, if left untreated, will result in previable or preterm delivery, or fetal demise. Because of their poor antenatal condition as well as the preterm brain's vulnerability, survivors of TTTS are at risk of brain injury and severe long-term neurodevelopmental impairment. One of the first management options for TTTS was serial amnioreduction, the repeated removal of large quantities of amniotic fluid from the amniotic sac of the recipient twin. Although this purely symptomatic treatment may be successful in terms of postponing delivery, intertwin transfusion remains unbalanced and the incidences of brain injury and neurodevelopmental consequences after serial amnioreduction remain high. The invention and further development of fetoscopic laser coagulation of placental anastomoses have had a major impact on pregnancy outcomes in TTTS.(3) Fetoscopic laser treatment aims to stop intertwin transfusion by occluding all vascular connections between the two fetuses, thus eliminating the cause of the disease. This treatment is now considered the gold standard for advanced TTTS.

Fetoscopic laser surgery in The Netherlands

Our colleagues from the obstetrics department at the Leiden University Medical Center (LUMC), many of whom contributed to this thesis, introduced fetoscopic laser surgery in our hospital in August 2000.(4) I was trained as a pediatrician and a neonatologist in the LUMC between 2011 and 2019 and

lucky enough to spend most of my time on the neonatal intensive care unit (NICU). It was during this time that I learned all about TTTS and this amazing surgical intervention the fetal surgeons could perform inside the pregnant uterus. As most babies who had undergone laser surgery for TTTS were born preterm, many were admitted to our NICU. Research from the LUMC performed in the early years after the start of the laser surgery program, had shown that short-term neonatal mortality and morbidity were still increased in survivors of TTTS treated with laser surgery, when compared to a control group of uncomplicated monochorionic twins.(5) Specifically, the incidence of cerebral injury was higher (14 versus 6%) and the majority of these injuries occurred antenatally.(6) In the earliest long-term follow-up study of TTTS survivors treated with laser surgery in Leiden between the years 2000 and 2003, the incidence of neurodevelopmental impairment was lower compared to a previous study in a conservatively treated TTTS cohort, but still remained high at 17%.(7, 8) Fortunately, the field of fetal therapy was not sitting still and major developments were ongoing. Monochorionic pregnancies were followed according to a strict national protocol, awareness for TTTS was raised among obstetricians and pediatricians across the country, and our fetal surgeons were performing more and more fetoscopic interventions.

The fetal medicine specialist versus the neonatologist

TTTS research is often performed by fetal medicine specialists, as it should be. They are obstetricians, who know all about twin pregnancies, prenatal imaging, the placenta and delivery. They make the diagnosis, perform fetal treatment, and monitor the pregnancy after laser surgery. Sometimes, they diagnose fetal complications using ultrasound or MRI. During a monochorionic pregnancy, the fetal medicine specialist manages three patients at the same time, three patients whose fates are strongly intertwined. You can imagine that at times, this means they have to make difficult decisions.

I am a neonatologist. We know about babies and a little bit about older children. When things go as planned during a TTTS pregnancy, two of the fetal medicine specialists' patients eventually become our patients. And when these babies experience complications, we make the diagnoses, treat them in the NICU and see them again in the follow-up clinic to evaluate their health and development when they are older. Much of the information that we gather during the NICU stay and follow-up visits of TTTS survivors can be of great value for our fetal medicine specialists. Because the ultimate goal of fetal

therapy in TTTS should be to ensure the healthy long-term survival of the mother and both her twins. How often are we achieving this goal? Can we find out which fetuses are at the highest risk of not achieving it? How common is fetal brain injury in TTTS and what causes it? Can we find ways to prevent it? We need research to answer these questions so that neonatologists may support some of the difficult decisions fetal medicine specialists face during TTTS pregnancies.

Back to Amy and Rosie

Without the developments in the field of fetal therapy, this family's story could have gone quite differently. Without a strict ultrasound screening protocol for monochorionic pregnancy, TTTS may not have been discovered in time to perform fetoscopic laser surgery. Without the possibility of fetoscopic laser surgery, Amy's and Rosie's chances of survival would have been very small. Without well-trained and experienced fetal surgeons, fetoscopic laser surgery may not have been as successful in treating TTTS. This being said, Rosie did not come away unscathed. We had noticed a change on prenatal ultrasound 9 days after laser surgery. Although this had us and the parents worried, we did not proceed to make a fetal MRI scan and we did not know exactly what was going on until we were able to make a postnatal brain MRI.

Amy's and Rosie's story raises many questions. In the current era of fetoscopic laser surgery, what is the incidence of brain injury in TTTS fetuses? What are the risk factors for brain injury? Is the risk of brain injury in TTTS infants decreasing with improving prenatal care and new developments in laser surgery techniques? How often is fetal or neonatal MRI used to detect brain abnormalities and what does MRI add compared to ultrasound? Did Rosie's ischemic brain injury have something to do with the fact that she was the recipient twin, with possible hyperviscosity-polycythemia? Or could it be related to the abrupt interruption of the intertwin transfusion process and sudden hemodynamic changes in brain perfusion after laser surgery? And what is the role of their prematurity? Is Rosie's brain lesion typical for TTTS and what other types of lesions may we come across? Of course, the twins' parents wonder about their future. What are the chances that they will have severe neurodevelopmental impairments (NDI), what risk factors can we identify? Based on Rosie's term-equivalent brain MRI, we predicted that she would develop unilateral cerebral palsy. To what degree does the presence of brain injury predict NDI in TTTS? Are Amy and Rosie at risk for other, milder impairments including behavioral problems?

References

1. Lewi L, Deprest J, Hecher K. The vascular anastomoses in monochorionic twin pregnancies and their clinical consequences. American journal of obstetrics and gynecology. 2013; 208(1):19-30.
2. Fisk NM, Duncombe GJ, Sullivan MH. The basic and clinical science of twin-twin transfusion syndrome. Placenta. 2009;30(5):379-90.
3. De Lia JE, Kuhlmann RS. Twin-to-twin transfusion syndrome--30 years at the front. American journal of perinatology. 2014;31 Suppl 1:S7-12.
4. Middeldorp JM, Klumper FJ, Oepkes D, Lopriore E, Kanhai HH, Vandenbussche FP. [The initial results of fetoscopic laser treatment for severe second trimester twin-to-twin transfusion syndrome in the Netherlands are comparable to international results]. Ned Tijdschr Geneeskd. 2004;148(24): 1203-8.
5. Lopriore E, Sueters M, Middeldorp JM, Oepkes D, Vandenbussche FP, Walther FJ. Neonatal outcome in twin-to-twin transfusion syndrome treated with fetoscopic laser occlusion of vascular anastomoses. J Pediatr. 2005;147(5):597-602.
6. Lopriore E, van Wezel-Meijler G, Middeldorp JM, Sueters M, Vandenbussche FP, Walther FJ. Incidence, origin, and character of cerebral injury in twin-to-twin transfusion syndrome treated with fetoscopic laser surgery. American journal of obstetrics and gynecology. 2006;194(5):1215-20.
7. Lopriore E, Nagel HT, Vandenbussche FP, Walther FJ. Long-term neurodevelopmental outcome in twin-to-twin transfusion syndrome. American journal of obstetrics and gynecology. 2003;189(5): 1314-9.
8. Lopriore E, Middeldorp JM, Sueters M, Oepkes D, Vandenbussche FP, Walther FJ. Long-term neurodevelopmental outcome in twin-to-twin transfusion syndrome treated with fetoscopic laser surgery. American journal of obstetrics and gynecology. 2007;196(3):231.e1-4.