Next steps towards improved care for twin anemia polycythemia sequence

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PART 1

patient journey

Patient Journey

Pregnant

Dutch couple, Alexandra and Jan Marten are the proud parents of Rosalie and Sarah (fraternal twin girls) and Charlotte and they are expecting again. Their first ultrasound appointment at 8 weeks in the Leiden University Medical Center (LUMC) shows that for the second time, they are having twins! This time, the babies share a placenta (monochorionic) and blood circulation through placental vascular connections between the twins. This type of pregnancy is known to have increased risk of complications, and therefore follow-up care will be continued at the LUMC, a tertiary care center specialized in complicated twin pregnancies and fetal therapy.

Growth problems

As early as 13 weeks' gestation, doctors discover that one of the babies is substantially smaller than the other. A repeat ultrasound at 15 weeks confirms a diagnosis of selective fetal growth restriction (sFGR), with normal blood flow (Gratacos type 1). Their MFM specialist explains the source of the problem: the smaller baby probably is not growing well due to unequal placental sharing. A critically ill, or poorly growing fetus is a dangerous situation for monochorionic twins due to the shared circulation in their placenta. If one fetus dies, the co-twin may suddenly exsanguinate through the vascular anastomoses, with a high risk for subsequent demise or severe brain damage. There are basically two possible scenarios: (1) both babies will continue to grow sufficiently and be delivered between 34-36 weeks, or (2) the smaller twin will stop growing and/or will show signs of decompensation (abnormal blood flow) and intervention would need to be considered to prevent single or dual fetal demise. The news that there is a risk that Alexandra and Jan Marten will lose one or even both babies is devastating. Not too long ago, they lost their daughter Charlotte who was diagnosed prenatally with severe kidney abnormalities and died shortly after she was born.

Stressful weeks

During the following ultrasound examinations at 17, 19 and 21 weeks of gestation, the parents receive good news: although the smaller baby remains small, it shows adequate interval growth. In addition, the blood flow remains normal,

showing that the babies are doing fine. Unfortunately, at 23 weeks things seem to change for the worse, as the smaller baby seems to have almost stopped growing since the last check-up. There is also a large difference in middle cerebral artery peak systolic velocity (MCA-PSV) – blood flow in the brain that is used to diagnose fetal anemia – that is seen, with a decreased measure for the bigger baby (0.8 multiples of the median (MoM)) and an increased measure for the smaller baby (1.4 MoM), but as the latter value does not cross the 1.5 MoM line that indicates fetal anemia, this observation is not clinically relevant now. It is also possible that the increased MCA-PSV in the smaller baby could be related to its growth restriction.

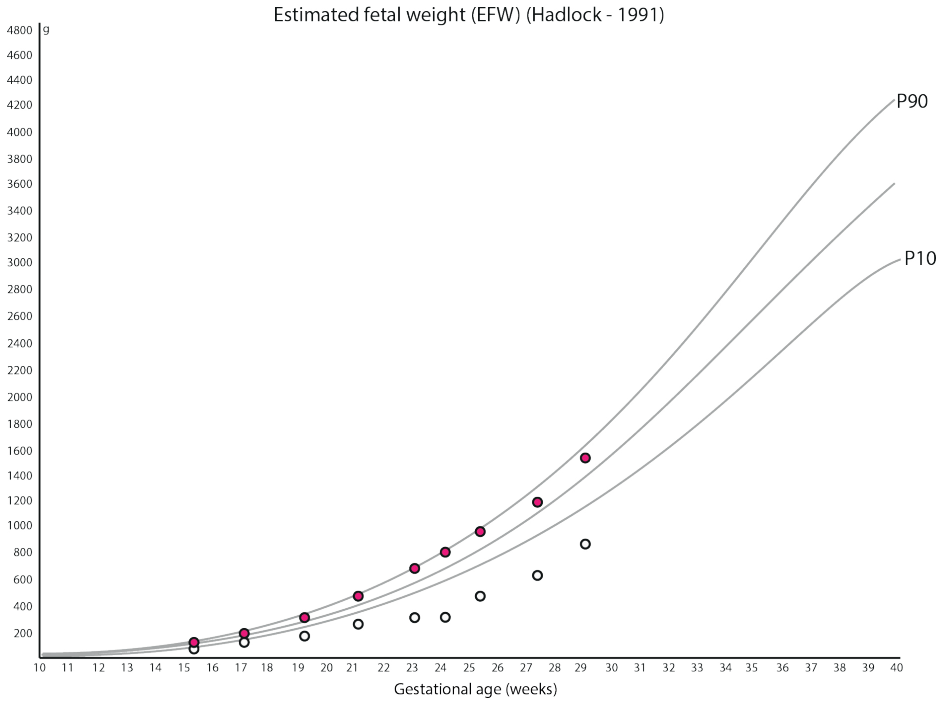

Figure 1. Estimated fetal weight for the twins (red dots: bigger baby; white dots: smaller baby)

The parents are counseled again in regard to the different treatment scenarios and "learn words they don't want to learn", such as *cord coagulation*, a procedure during which the umbilical cord of their smaller baby is clamped causing it to die, thereby precluding the damage of acute exsanguination in the co-twin. After discussing all possibilities with the parents, they elect expectant management for the interim. The parents are instructed to be conscious of decreased fetal movements and to visit our out-patient clinic again at 24 weeks.

A week later the smaller baby is still not growing well. His prognosis is unsure and the situation seems very precarious.

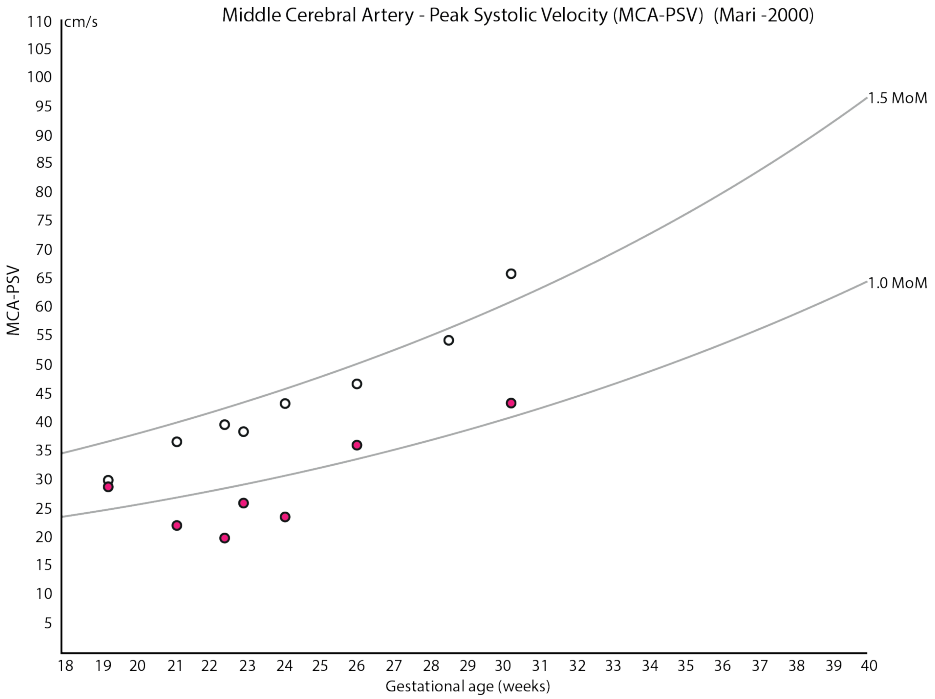

Figure 2. MCA-PSV values for both babies (red dots: bigger baby, white dots: smaller baby) .

At 25 weeks, after two very emotional and stressful weeks, there is finally some good news: the smaller baby is catching up in growth again. Ultrasound check-ups are continued weekly, and the smaller baby keeps showing satisfactory interval growth at 26, 27 and 28 weeks. The inter-twin MCA-PSV difference persists and fluctuates in wideness during the weeks. At 29 weeks, the parents receive counseling from one of the neonatalogists who explains what to expect when the boys are delivered prematurely. For now, it does not seem like the babies will be born anytime soon since the situation is stable. At 30 weeks, Alexandra and Jan Marten are again at the hospital for their routine check-up for their twins. The ultrasound reveals some unexpected bad news: the smaller baby is not doing well. It shows no fetal movements on ultrasound and the heart is enlarged. In addition, the MCA-PSV flow is increased (1.7 MoM) and now crosses the 1.5 MoM line. Furthermore, the sonographer sees that the placental share of the smaller baby is brighter on the ultrasound, and is significantly enlarged. Alexandra confirms that she indeed does not feel movements from

the smaller baby anymore and to further check the condition of the babies, a cardiotocography (CTG) registration is made. This shows that the smaller baby is in serious distress. The doctors explain to the parents that it is no longer safe for the babies to be inside the womb and that they need to be delivered as soon as possible. An emergency cesarean section is performed.

The birth of Daan and Max

A few moments later, Alexandra and Jan Marten become the parents of twin boys. Daan (bigger baby) is born first, and has a relatively good start (Apgar scores (AS): 7/10/10), and leaves for the neonatal intensive care unit (NICU) without any respiratory support. When his brother Max (small baby) is born, he is extremely pale, limp, and has a slow heartbeat (AS: 1/7/7). Resuscitation with continuous positive airway pressure (CPAP) is not sufficient to reach adequate oxygen saturation levels and intubation and mechanical ventilation is needed. During resuscitation, Alexandra is cared for in the operating room and Jan Marten is with the boys.

Figure 3. Max (left) and Daan (right) directly after birth.

New diagnosis

In the NICU, the boys are weighed and their blood is checked. As anticipated, they differ greatly in weight: Daan is 1423 grams and Max only 843 grams (weight discordancy = 44%). But there is also a striking difference in skin color: Max is very pale and Daan is red. A full blood count reveals that Max is severely anemic with a hemoglobin value of 3.0 g/dL and reticulocyte counts of 363‰ (indicating that Max was anemic for a longer time). Daan has a significantly higher hemoglobin value of 19.3 g/dL and substantially lower reticulocytes, 73‰. The large difference in hemoglobin and reticulocytes, plus their pale and red appearance indicates that something else has been going on during pregnancy, aside from the selective growth restriction.

According to routine care in the LUMC, the placenta is examined using color dye injection of the vessels. At first, a striking color difference on the maternal side of the placenta is observed with a dark red placental share for Daan and a pale placental share for Max, in analogy to their skin color at birth. Color dye injection of the placental vessels reveals the presence of only a few minuscule arterio-venous anastomoses. Inspection of the placenta yields an interesting observation: while Max is the smaller infant, his placental share is substantially larger than Daan's placental share. This contradicts the pathogenesis of sFGR, in which growth restriction is a result of a significantly smaller placental share.

Based on the large inter-twin hemoglobin difference (19.3-3.0 = 16.3 g/dL), a high reticulocyte count ratio (363/73 = 5.0) and the presence of only minuscule placental anastomoses, the medical team reaches the diagnosis of **twin anemia polycythemia sequence (TAPS),** with Max being the anemic TAPS donor and Daan the polycythemic TAPS recipient.

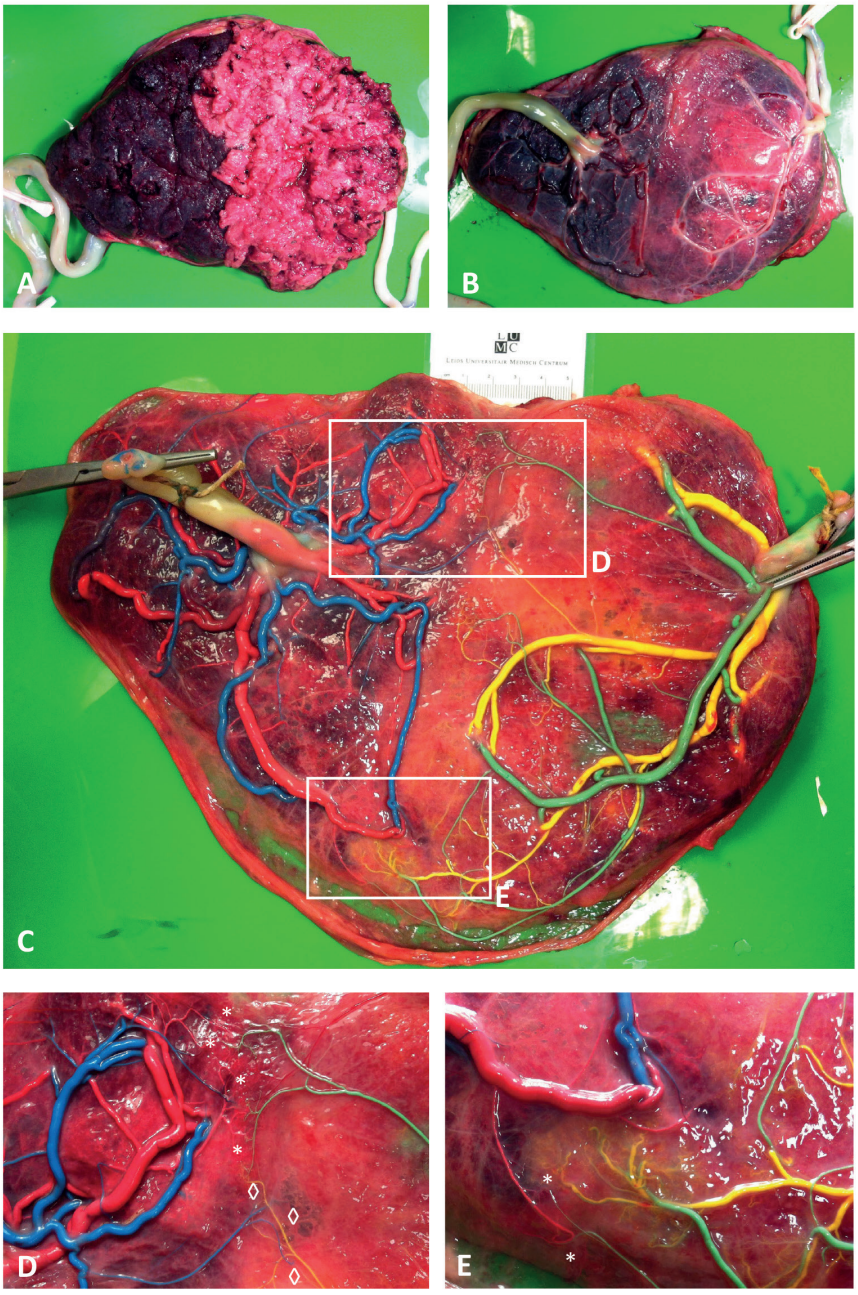

Figure 4. Pictures of the examination of the placenta of Daan and Max. **A.** Maternal side of the placenta showing a plethoric share for Daan and a pale share for Max. **B.** Fetal side of the placenta, demonstrating congested vessels for Daan and empty slender vessels for Max. **C.** Placenta injected with color dye. **D.** Close-ups of the minuscule anastomoses between Daan and Max. Stars (*) indicate VA anastomoses (Daan → Max), diamonds indicate AV anastomoses (Daan ← Max).

The first days

In the first two days, both Daan and Max are in critical condition, leaving the medical team and the parents worried about their prognosis. Although Daan had a good start, both his lungs collapse (bilateral pneumothorax) shortly after birth, for which he needs an intensified form of ventilation (high-frequency oscillation; HFO) and treatment with thoracic drains. Max, on the other hand, is diagnosed with persistent pulmonary hypertension for which nitric oxide and also HFO ventilation is required. In addition, two blood transfusions on day 1 are performed to treat his severe anemia. After two days, the condition of the boys is still worrisome, but more stable, giving the parents time to catch their breath after a very stressful and emotional 48 hours. On day 5, the parents again receive bad news: a cranial ultrasound shows that Daan has a severe brain bleed (intraventricular hemorrhage grade 3 (left) and grade 2 (right)). This is very difficult news for the family to take, especially after they just had a little hope after the boys survived their first days. The neonatologists explain that it is not clear how Daan's brain bleed will progress, but treatment with a ventricular drain in the brain might be needed if his situation worsens. In the upcoming days, his ventricles enlarge (post-hemorrhagic ventricular dilatation), but fortunately they stabilize and no further intervention is required.

Time at the hospital

In the first month after birth, both boys take small steps forward. Alexandra and Jan Marten grow quickly used to the doctors and nurses, other parents, and to all of the different and continuous NICU alarm bells.

After a week, Daan and Max switch from mechanical ventilation to less invasive respiratory support, CPAP. But both boys still have many hurdles to take. Daan battles a staphylococcus aureus sepsis, and Max develops neonatal chronic lung disease (bronchopulmonary dysplasia) due to long-term exposure to mechanical ventilation and oxygen. After 4 intensive weeks on the NICU, Daan (with no respiratory support) and Max (on CPAP) are in sufficient enough shape to be transferred to a secondary care center. The new hospital with different people with different mentality, and with no familiarity with the sensitive history of their boys, feels like a cold shower compared to the warm, nurturing care they had received before. Luckily, after 47 days of hospital admission, and even before his term date, Daan is ready to go home.

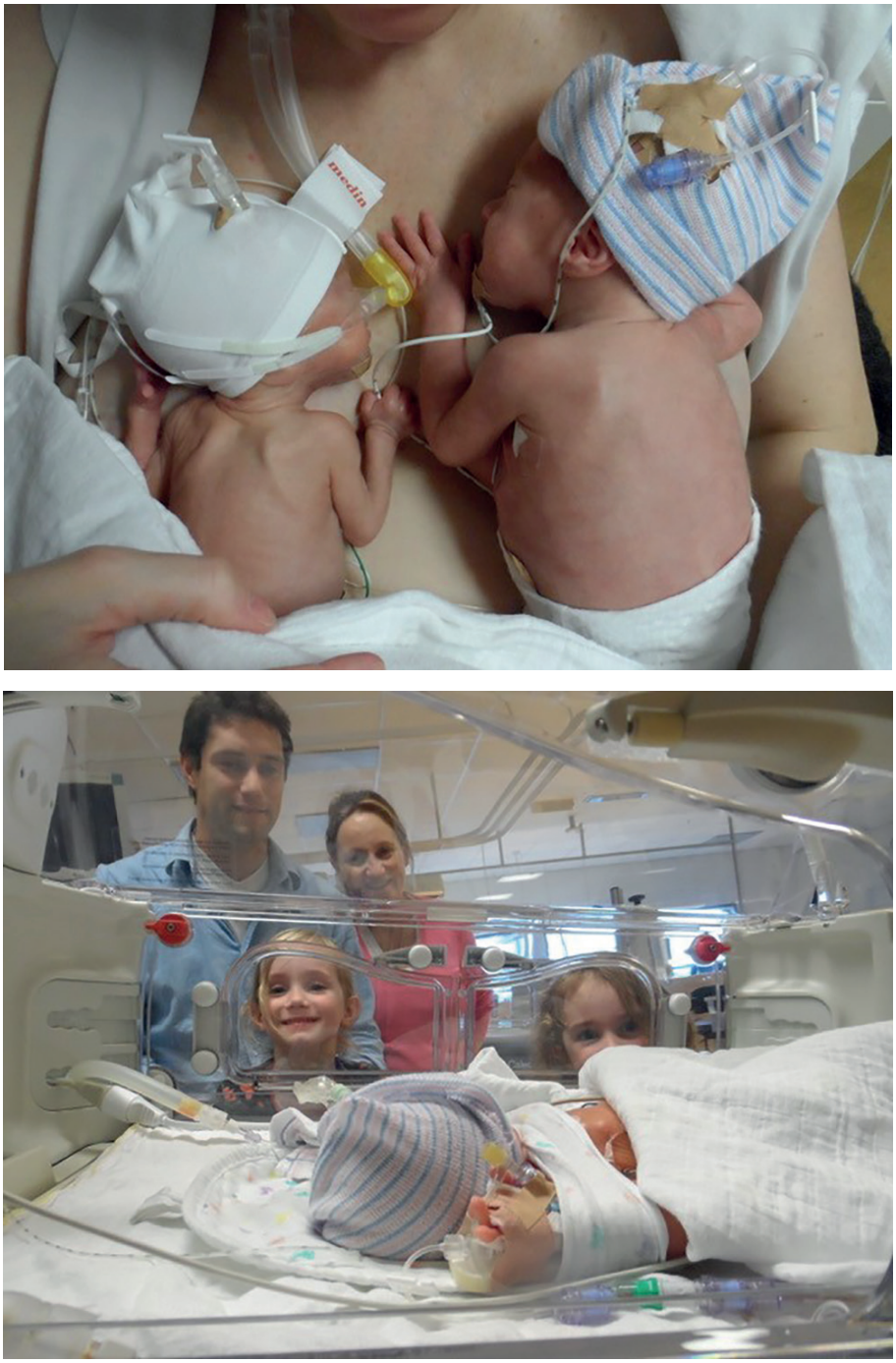

Figure 5. Pictures of Max and Daan at the NICU. Upper picture: Max (left) and Daan (right) kangarooing with Alexandra. Lower picture: The family looking at Daan through the incubator walls.

Due to his chronic lung disease, Max is unfortunately not there yet. Having one baby home is wonderful for the parents, but it is also a logistical and practical challenge to divide their care between an ex-premature baby and two girls at home and their brother in a hospital half an hour away. Luckily, just before Christmas, Max is transferred to yet another hospital, closer by. Finally, after 95 days in the hospital, Max is ready to follow his brother home, and the family is reunited at last.

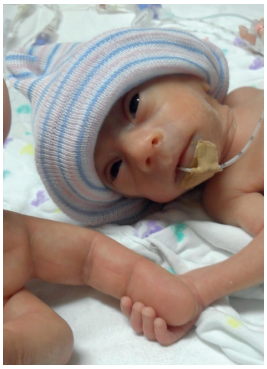

Figure 6. Max at the NICU

First years of life

During the first years of their lives, the twins are doing relatively well. However, both boys appear to be very prone to pulmonary infections resulting in multiple prolonged hospital admissions during their first year. At 1.5 years Max's motor development seems to be lagging behind his brother. Max is still not able to sit up straight, and Daan has already takes his first steps. Max gets physical therapy, helping him sit and eventually walk. Although he needs some help to achieve his developmental milestones, Max appears to be quite a strong boy and has no fear in exploring the world around him. When the boys are 2 years of age, the family moves from the Netherlands to Switzerland due to work-related motives. This is a big change: they need to adapt to a different environment, a new system and a new language.

Around this period, Alexandra and Jan Marten also start noticing that Max is significantly behind his brother Daan in regard to speech and language development. While Daan is already verbally strong and speaks in short sentences, Max is unable to speak at all. A Dutch pediatrician tells them the speech delay is not be anything to be worried about now, and could also be related to the new language Max has to adapt to. Therefore, no additional diagnostics or intervention are required at this moment. The parents try to understand the cause of the remarkable difference between the boys' language development and suggest that a hearing problem might be the cause of his speech delay, but this explanation is disregarded. They should reevaluate the situation when Max is 3 years old.

A year later, Max is still not able to speak and an extensive list of doctors appointments follow. The first ear-nose-throat (ENT) doctor that evaluates his hearing says that his left ear is totally fine, and that there is some slight hearing loss in his right ear, but that it's more a problem of "not wanting to talk" than "not being able to". As this observation does not coincide with Jan Marten and Alexandra's experience with Max, they visit another ENT doctor in the academic hospital in Zurich. Remarkably, this doctor concludes the exact opposite: his right ear is totally fine, but there is a slight hearing loss in his left ear. A very confusing and frustrating message for the family.

Max is now almost four years old, still not able to speak, the cause is unknown and therefore Max is not receiving the care that he should receive. To clear up the uncertainty about the hearing issues Max has, another examination is planned. An 'Auditory Brainstem Response' test is performed under general anesthesia, finally revealing the cause of his problem: Max has profound hearing loss in both ears, caused by auditory neuropathy spectrum disorder. At 4 years of age, Max finally receives two hearing aids and learns to speak within 3 months.

Figure 7. Max, just after he received his hearing aids. As a surprise, the ENT doctors also gave him a stuffed dog with hearing aids.

Before school

Between 4 and 5 years of age Max's vocabulary expands greatly. While forming words was first a big issue, he's now talking his parents' ears off. Some sounds still remain a challenge, but Alexandra and Jan Marten are helping him out. Although Max may be lagging behind his brother in development, he completes his milestones at his own pace, including riding a bicycle, swimming and even skiing in the Swiss mountains. The chronic lung disease that he developed when he was a premature baby still hampers him sometimes, and he is easily exhausted when doing activities. But when the family includes more breaks in their schedule, Max is able to enjoy it just as much as everyone else. In Daan's first years, he quickly shows to be an eager learner and already demonstrated a great vocabulary at age four. He craves for more educational challenges, but

has to wait until he is 5 years old to be allowed to go to school in Switzerland. Therefore, his parents start teaching him to read and write at home.

Going to school

At age 5, Daan and Max are finally allowed to go to school. Already very early on, one of the teachers tells the parents that this school is not the right place for Max and that he would be better off with special education. This is sad news for the parents. Not only do they have to separate their twin boys, this would also mean that they have to drop their 5-year old boy off to a taxi for impaired children that will take him to a school half an hour away, in a foreign country.

Figure 8. Daan (right) and Max (left) on ski holiday

Figure 9. Max (right) and Daan (left) going to school

Fortunately, already after a few weeks at his new school, the transfer appears to be the right choice. Max is thriving at the school for children with impaired hearing, and the attention and care that he receives feels like a warm embrace to the family. At school, the teachers highly stimulate Max's self-confidence. This, and the fact that he now is the best in his class, greatly boosts his self-image. It fills Alexandra and Jan Marten with joy and pride to hear from the school that Max, although he might not always able to express it, has great potential.

Back in the Netherlands

When the boys are 6 years old, the family moves back to the Netherlands. As Daan is already able to write and read, he is allowed to skip first grade. Due to the pleasant experience with special education in Switzerland, Alexandra and Jan Marten again choose for special education in The Netherlands and find a nice school in their neighborhood. There, Max follows the regular curriculum, but with more attention to his impairment and in smaller classes.

Now

Alexandra and Jan Marten are looking back on an emotional time with Daan and Max, but feel happy and grateful to get to see both boys coming from vulnerable premature babies to strong and happy individuals. Together with the ENT doctors, parents are still looking for ways to further improve Max's hearing. However, seeing the progress Max has made in the last few years, Alexandra and Jan Marten feel more confident every day that both boys will be fine.

Figure 10. The family, back in the Netherlands. Left to right: Rosalie, Alexandra, Max (holding his hamster Fransje), Sarah, Jan Marten and Daan.

Researcher's perspective

Daan and Max represent a case of severe TAPS, which was not identified antenatally and was first diagnosed at birth. In order improve our care for TAPS twins, some critical remarks and questions need to be made with regard to the following aspects:

Antenatal diagnosis

Despite the severity of TAPS postnatally, Daan and Max did not meet our proposed antenatal criteria for TAPS. They did however show a large difference in MCA-PSV measurements and presented with additional ultrasound markers including cardiomegaly and placental echogenicity. This raises the following questions: are the currently cut-off levels of < 1.0 MoM (for the recipient) and > 1.5 MoM (for the donor) accurate enough to diagnose TAPS during pregnancy, or should we use an inter-twin MCA-PSV difference? What is known about the prevalence of cardiomegaly and a difference in placental echogenicity in TAPS? Are these findings unique for this case, or are they more ubiquitous in the TAPS population?

Antenatal therapy

Being born at 30^{+1} weeks of gestation has placed Daan and Max at risk for severe prematurity-related complications, including pulmonary problems and brain damage. Early identification of TAPS could have allowed considering antenatal fetal intervention to treat the condition and to prolong pregnancy. If TAPS would have been detected early on, what management strategy would have been best for Daan and Max?

Growth restriction

Growth restriction in Max was not based on unequal placental sharing as seen in selective fetal growth restriction, on the contrary; Max' placental share was paradoxically larger than the placental share of his brother. Therefore, the restricted growth in Max was likely a result of chronic severe anemia. What is the prevalence of severe growth restriction in TAPS? Is Max an exceptional case, or is severe growth restriction more frequent in TAPS?

Postnatal diagnosis

In line with the sonographic observation antenatally, the maternal side of the TAPS placenta showed a striking color difference. Is this feature related to the hemoglobin difference in TAPS twins? Could looking at the maternal side of the placenta be helpful in reaching the diagnosis of TAPS shortly after birth (even before reticulocytes are available and placental injection is performed)? Could it help to differentiate between other causes of large inter-twin hemoglobin discordances such as acute peripartum twin-twin transfusion syndrome?

Long-term outcome

Whereas both boys suffered from severe neonatal problems, they demonstrate a remarkable difference in long-term outcome. Especially Max' development is extensively hampered by bilateral hearing loss. Currently, no information is available on long-term outcome in TAPS survivors. In order to optimize our care and counseling for parents expecting TAPS twins, we need to know: what is the long-term neurodevelopmental and behavioral outcome in TAPS survivors? Are there differences in long-term outcome between TAPS donors and recipients? Does Max represent a unique case of deafness in TAPS, or are hearing problems more prevalent in this population?

At the end of this thesis, we will try to answer these questions based on the studies we performed in the last three years, and will discuss if and how our new insights could have improved the care for future TAPS twins like Daan and Max.