Twin-to-twin transfusion syndrome: from placental anastomoses to long term outcome
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Chapter 13

General discussion
Twin-to-twin transfusion syndrome (TTTS) is a severe complication of monochorionic twin pregnancies resulting from unbalanced inter-twin blood flow between the donor twin and the recipient twin through placental vascular anastomoses. TTTS leads to hypovolemia and oligohydramnios in the donor and hypervolemia and polyhydramnios in the recipient. During the last decades, new insights have been gained in the pathogenesis, diagnosis and management of TTTS. An important milestone in the history of TTTS was the definition of clear and uniform diagnostic criteria\textsuperscript{105} and a staging system\textsuperscript{9}. Most importantly, new therapeutic modalities have led to improved outcome\textsuperscript{10}. Finally, increased attention on TTTS from (medical) journals has resulted in improved “TTTS-awareness” in perinatologists, mid-wives and parents. A PubMed search with the term “twin-twin transfusion syndrome” between 1965 and 2005 yielded a total of 952 hits. The vast majority of these studies are of recent date. As shown in figure 1, the number of publications on TTTS is increasing every year with a current average of 3 new publications per week.

![Figure 1: Number of TTTS publications per year.](image)

However, despite the multitude of data currently available, various aspects of TTTS are still enigmatic and remain to be elucidated.
The pathogenesis of TTTS is nowadays regarded as a multifactorial process. Various studies have shown that unbalanced inter-twin blood flow occurs principally in the absence of equilibrating superficial arterio-arterial anastomoses. However, the view that TTTS may develop only from simple blood transfer from donor to recipient has been discarded. Inter-twin transplacental transfer of various hormones, in particular hormones related to the renin angiotensin system, play an important role in the development of TTTS. Understanding of the pathophysiology of TTTS is hampered by the absence of a suitable animal model. Computer models for TTTS have proved to be a valid alternative for animal models. However, computer models require input from clinical data. Determination of anastomotic blood flow is an example of the type of data which can be used to validate these computer models. In the TTTS case presented in Chapter 3, we calculated that the blood flow across the anastomoses was approximately 28 ml/24h at 29 weeks’ gestation. Meanwhile, an almost identical TTTS case was treated at our institution, in which we also measured the percentage of transfused adult red blood cells (or adult hemoglobin) in the “new” recipient after birth. Blood flow through the only patent residual arterio-venous anastomosis in this second TTTS case was determined to be 18ml/24h at 29 weeks’ gestation, which is in excellent agreement with the arterio-venous flow measured in the previous case. These results confirm the accuracy of the two different calculation methods. These mathematical experiments which enabled us to calculate arterio-venous anastomotic flow, can also be repeated in similar TTTS cases found by other research groups. The main pre-requisites required for these tests are: (1) hemoglobin levels (fetal and adult hemoglobin values) measured before and after the various intrauterine transfusions and at birth and (2) a placental injection study showing patent arterio-venous anastomoses in only one direction. These measurements and their correlations with different anastomotic patterns may further enhance computer modeling for TTTS and improve our understanding of the pathogenesis of TTTS.

It is now generally accepted that TTTS is not a homogeneous disease, and should be subdivided into two major forms: chronic TTTS and acute TTTS. Diagnosis of chronic TTTS is based on strict antenatal ultrasound criteria.
The main criterion required to reach the diagnosis of chronic TTTS is the twin oligo-polyhydramnios sequence (TOPS). However, as shown in the two reported cases in Chapter 6, significant chronic inter-twin blood transfusion can also occur in the absence of TOPS. We named this atypical form of chronic TTTS, twin anemia-polycythemia sequence (TAPS) and established new diagnostic criteria required to reach the diagnosis of TAPS. We have recently detected another case of TAPS at our center with similar hematological and placental findings as in the two previously reported cases. In a consecutive series of 81 monochorionic twins/triplets without chronic TTTS delivered at our center since 2002, TAPS was found in only 3 cases, which yields an incidence of TAPS of 4% (3/81). This would suggest that TAPS is not a very frequent phenomenon in monochorionic twinning. However, recent studies report an unexpected and unexplained high risk (5%) of late fetal death in monochorionic twins without TTTS\(^{260}\), which may, hypothetically, be caused by TAPS. In addition to the “natural” form of TAPS, recent studies also report the existence of an iatrogenic form of TAPS\(^{214}\). In a large study of 151 TTTS cases treated with laser, Robyr et al found that 13% of the cases developed isolated anemia-polycythemia sequence without oligo-polyhydramnios sequence\(^{214}\), so-called iatrogenic TAPS. Interestingly, it was usually the former recipient who became anemic, whereas the former donor became polycythemic\(^{213,214}\). In a recent study with mathematical modeling, we were able to explain this clinical presentation of feto-fetal transfusion reversal after incomplete laser therapy and predict significant discordant hematocrit values in both twins in the absence of amniotic fluid abnormalities due to residual anastomoses\(^{261}\). This phenomenon results from, first, the increased colloid oncotic pressure present in the former recipient prior to and shortly after laser, and second, continued feto-fetal transfusion\(^{261}\). The acute form of TTTS can be divided in acute perimortem TTTS and acute perinatal TTTS. The occurrence of acute perimortem TTTS has been undoubtedly proven and is known to be associated with a high risk of perinatal mortality and morbidity in the surviving twin\(^{15-16,30-33}\). In contrast, acute perinatal TTTS is only based on a few, often incomplete case reports\(^{34-39}\). Most case reports of acute perinatal TTTS failed to determine the inter-twin difference in reticulocyte count (or erythropoietin levels) and lacked accurate placental injection study. Therefore some of the cases
may well have been TAPS cases instead of acute perinatal TTTS. In our series of 81 consecutive uncomplicated monochorionic twins, no cases of acute perinatal TTTS have been observed. However, we noticed another important perinatal hematological phenomenon which may often occur in monochorionic twinning and is related to birth order and placentofetal transfusion. As shown in Chapter 7, second-born twins have higher hemoglobin levels than first-born twins. Hypothetically, after clamping of the first-born’s umbilical cord, uterine contractions may allow placental blood from the first twin’s low-pressure placental bed to be transfused through the low-resistance superficial vascular anastomoses into the higher pressure circulation of the second twin. Large inter-twin hemoglobin differences in monochorionic twins without chronic TTTS may thus be due to acute placento-fetal transfusion rather than feto-fetal transfusion.

The optimal management of TTTS is limited by a paucity of well-designed studies. Most studies are observational and few studies have focused on the long-term outcome. Only two randomized controlled trials on the management of TTTS have been published. Moise et al compared serial amnioreduction and septostomy and reported similar short-term outcomes between both treatments. Senat et al compared serial amnioreduction and fetoscopic laser surgery and found that perinatal mortality and short-term neurologic morbidity were significantly lower in the group treated with laser surgery. Despite the significant improvement due to treatment with fetoscopic laser surgery, perinatal mortality and morbidity in TTTS remain strikingly high, especially when considering that both fetuses were probably initially structurally normal. Several studies presented in this thesis, report in detail the significant short and long-term perinatal morbidity in TTTS survivors treated with laser. The most deleterious type of morbidity encountered in TTTS survivors is severe cerebral injury. We found that 14% of TTTS survivors after laser surgery have severe cerebral injury on cranial ultrasound. Nevertheless, the incidence of severe cerebral injury in TTTS treated with laser is still significantly lower than in TTTS treated with amnioreduction. In the randomized trial from Senat et al, extensive cystic periventricular leukomalacia grade III or IV occurred less often in the laser group than in the amnioreduction group, 6% versus 14%, respectively (RR 0.39, 95% CI 0.18 - 0.86, p = 0.02). The timing of
cerebral injury in TTTS treated with laser is not known, and could occur before, during or after laser surgery. To answer this question, a sequential fetal MRI study performed before and after laser surgery is required. The origin of cerebral damage in TTTS is not clear and may be related to hemodynamic imbalance in cerebral flow causing hypoxic-ischemic or hemorrhagic injury. Recently, Rodeck et al presented a new hypothesis (the placental ‘steal’ phenomenon) which can explain the severe neurological outcome seen in TTTS cases treated with amnioreduction. They suggest that amnioreduction may lead to a radical shift of blood from the fetus into the placenta causing hypoxic-ischemic brain damage. Since single amnioreduction is also performed routinely in patients during fetoscopic laser surgery procedures, the placental ‘steal’ phenomenon may also occur in TTTS treated with laser.

The 14% incidence of severe cerebral injury in TTTS survivors after laser treatment found in our study is in accordance with the 17% incidence of neurodevelopmental impairment detected in long-term survivors (see Chapter 12). Nevertheless, the reported incidence of neurodevelopmental impairment in TTTS treated with laser appears to be lower than in TTTS treated with serial amniocentesis (see also Chapter 11). Obviously, caution is advised when comparing the various results in view of the observational nature of these follow-up studies and the methodological differences between the studies. To assess the true difference in neurodevelopmental impairment in TTTS survivors treated with either laser surgery or serial amnioreduction, results of the long-term follow-up in the ongoing randomized trial must be awaited.

In conclusion, despite significant progression during the last decades, the management of TTTS remains one of the most challenging medical problems in fetal medicine. More research is necessary to further improve the prognosis of TTTS.