Chapter 14

Future perspectives
Fetal medicine is a new discipline, gradually evolving from a field with mainly diagnostic function to a broader field with also life-saving therapeutic possibilities. However, few interventions in fetal medicine are evidence-based. Most fetal medicine studies are observational and often limited by small numbers of included patients. To date, only few randomized controlled trials in fetal medicine have been performed. Interestingly, two of these trials involved the treatment of TTTS. Hopefully, TTTS can pave the way for more randomized controlled studies in fetal medicine.

There are still several aspects in TTTS requiring further investigation:

1. The exact pathogenesis of TTTS needs to be further unraveled. Due to the absence of animal models, computer modeling of TTTS may prove to be a valuable alternative. However, for computer models to be reliable, they require realistic input from in vivo cases. Intensive collaboration between perinatologists and computer modeling scientists may lead to new important discoveries. New research should also keep focusing on the role of various hormonal factors. These data may then in return be used to improve computer modeling of TTTS.

Routine placental injection study of all monochorionic placentas, with and without TTTS, has already yielded interesting discoveries (e.g. in our studies) and can still lead to new insights. Injection studies of TTTS placentas treated with laser may also help in understanding the underlying cause of the high incidence of residual anastomoses. This information may be crucial for the individual fetal surgeon to reduce the frequency of residual anastomoses. Furthermore, determination of the type and number of placental vascular anastomoses can be used to study the possible relation between angioarchitecture and timing of onset of TTTS. As suggested at the last Eurofoetus meeting (Paris, May 2006) late onset TTTS (i.e. after 26 weeks) may occur when a large amount of anastomoses is present. Finally, more placental casting studies are needed to determine the incidence and clinical implications of the recently reported deep anastomoses which are not visible on the placental surface. We recently finished a casting study of monochorionic placentas with TTTS (after laser treatment) and without TTTS and are currently in the process of analyzing the data.
2. The *diagnosis* of TTTS and its related complications may, in the near future, gain more accuracy with the use of improved imaging techniques. Several studies have investigated the value of (Doppler) ultrasound examination in predicting the development of TTTS or the outcome in TTTS, including a study performed at our institution by Sueters et al (TULIPS study)\(^68;109\). Other studies have reported that detection of an arterio-arterial anastomosis decreases the risk of developing TTTS by 9-fold\(^66;68\). Fetal magnetic resonance imaging (MRI) is a new promising technique which is nowadays increasingly being used\(^17;265-267\). Fetal brain MRI is particularly useful in TTTS as it appears to detect brain lesions earlier and with better definition than prenatal ultrasound\(^177\). However, more research is required to evaluate the optimal timing of fetal MRI in TTTS and determine the exact prognosis of each type of detected lesion. A study entitled “Cerebral Imaging in Monochorionic Twins: CIMT study” will soon start at the Leiden University Medical Center. The objective of this study is to evaluate the incidence, character and origin of cerebral lesions in monochorionic twins with TTTS treated with laser using sequential fetal and neonatal MRI and 4D ultrasound. A group of monochorionic twins without TTTS will serve as control group. The most important research question is whether cerebral injury occurs before or after laser surgery. If severe cerebral lesions occur before laser and can be detected accurately, then this could have major implications for future management strategies in TTTS.

3. The optimal *management* of TTTS, and especially the occurrence of early and late complications in TTTS treated with laser, requires further investigation. Future studies should focus on the optimization of various treatments to improve the outcome in TTTS. New techniques, such as combined laparoscopy and fetoscopy in complete anterior placenta developed at our center, may further improve outcome (Eurofoetus meeting, Paris 2006). Recently, we also proposed the use of laser surgery in TTTS up to 28 weeks of gestation, as neonatal morbidity was lower compared to TTTS cases treated with amnioreduction (Eurofoetus meeting, Paris 2006). Other major issues, such as reduction of preterm delivery and rupture of membranes after fetoscopy, may further increase survival rates in TTTS.
4. There is paucity of *long-term follow-up* studies in monochorionic twins. More data on long-term studies in monochorionic twinning are strongly required. We are currently investigating the long-term neurodevelopmental outcome at 2 years of age in all monochorionic twins with and without TTTS delivered at our center between June 2002 and September 2005. We also intend to examine this cohort of monochorionic twins at 5 years of age to assess the neurodevelopmental outcome at school age. Well documented cohorts of monozygotic twins with single intrauterine growth restriction form also an ideal group to test the ‘Barker hypothesis’\(^\text{256}\). According to this hypothesis, the risk of adult diseases such as coronary heart disease, diabetes, hypertension and stroke is increased in adults who were growth restricted during fetal life\(^\text{256}\). Monozygotic twins are genetically identical but may be subjected to a different intrauterine environment. Whether monozygotic twins with discordant fetal growth also have a discordant risk of adult diseases requires further investigation.

5. *In general*, there are several important aspects to be taken into consideration for future research in TTTS. One of the main limitations of most TTTS studies is the small size of included patients, which is inherent to the rarity of the disorder itself. To overcome this major problem, future study designs should preferentially be multicentered. A second general problem concerns the definition of adverse outcome. To date, most TTTS studies focus on “survival” instead of “disease-free survival”. Given the high percentage of cerebral injury in TTTS, future studies should aim at evaluating long-term neurodevelopmental outcome, or at least short-term neurological outcome.

To reach a consensus on the optimal treatment in monochorionic twin pregnancies and TTTS in particular, more randomized trials are required. Various trials have already been proposed. Moise *et al* suggested that a randomized trial of combination amnioreduction/septostomy versus laser surgery in early stage TTTS should be performed\(^\text{140}\). Quintero *et al* suggested that a trial of laser surgery versus expectant management is indicated in monochorionic twins with highly discordant intrauterine growth restriction\(^\text{135}\). Lastly, given the high rate of unexpected late fetal deaths in uncomplicated monochorionic
twins, Barigye et al suggested that a trial should be designed to test the potentially beneficial role of early delivery in monochorionic twins. Although these trials may certainly be indicated, studies in TTTS should not only focus on perinatal “survival” but especially on “intact-survival”. If the fetus is truly to become a unique patient, then primary outcome measures in fetal medicine, and TTTS in particular, should be “survival without severe morbidity”.