Fetoscopic interventions in complicated monochorionic twin pregnancies

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General discussion and future perspectives

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In monochorionic twin pregnancies, the fetuses share a common placenta with vascular anastomoses between both circulations and have a significantly higher risk of adverse outcome than dichorionic twins and singletons. Complications in monochorionic twin gestation include twin-to-twin transfusion syndrome (TTTS), severe intrauterine growth retardation (IUGR), twin reversed arterial perfusion (TRAP), increased rate of fetal anomalies, and death of the co-twin. In the case of single intrauterine fetal demise in monochorionic twin pregnancies, the vascular anastomoses allow the transfer of blood from the surviving twin to the dead twin, the so-called acute perimortem intertwin transfusion, which can lead to periods of hypoperfusion, hypotension, acute fetal anaemia, eventually resulting in co-twin demise and neurologic abnormality in the surviving co-twin.

In the last decades, important advances have been made in fetoscopic treatment. However, few of these interventions are evidence-based, and many questions remain to be answered. These questions pertain to type and timing of treatment in TTTS and severe discordant IUGR, and to the prevention of PROM after fetoscopic interventions.

TTTS

Today, laser surgery is considered to be the first choice of treatment for severe TTTS between 16 and 26 weeks' gestation.[1] There is still debate, however, on whether and how to treat TTTS Quintero stage 1. In contrast to Quintero *et al,* who reported that stage is not an important prognostic factor when laser therapy is involved, we found that the earlier the Quintero stage at the time of treatment, the better the outcome (Chapter 3).[2] Our findings are in accordance with the results of a randomised study reporting significantly better perinatal outcome of fetoscopic laser surgery in Quintero stages 1 and 2 as compared to stages 3 and 4; our findings also agreed with the results published by Huber *et al*, who reported a significant trend toward reduced survival rates

after treatment with laser surgery for fetuses at later Quintero stages.[1;3] These findings support the hypothesis that laser surgery should be the first choice of treatment, even in early Quintero stages.

There is controversy about the best way to manage TTTS diagnosed early in the 3rd trimester. Apart from expectant management or amniodrainage, elective delivery is an option. In otherwise healthy fetuses, premature birth can lead to major handicaps, such as cerebral palsy, severe cognitive deficits, and severe visual or hearing impairments. Neonates that have suffered from chronic TTTS in utero are known to have an additional risk of neurological morbidity, and other characteristic morbidities in TTTS, such as cardiovascular and renal morbidity.[5-7] Laser surgery is usually not advocated as the treatment of choice in early third trimester TTTS, possibly because of the expected higher rate of complications compared with amniodrainage, including premature rupture of membranes. The preliminary data described in this thesis (Chapter 8), comparing amniodrainage and laser surgery for treatment of TTTS diagnosed after 26 weeks' gestation, shows that laser surgery should be considered as a valid alternative to amniodrainage in early third trimester TTTS. In order to determine the best way to manage early third trimester TTTS, further studies are urgently needed. Considering the low incidence of TTTS appearing after 26 weeks' gestation, the ideal setting of such a study would be a sufficiently large, multi-centre randomised study.

Incomplete laser surgery and residual anastomoses do not necessarily result in recurrence or reversal of TTTS (see Chapter 4). Recently, an atypical form of chronic TTTS has been described, the so-called twin anaemia-polycythaemia sequence.[7] This phenomenon occurs in the absence of a twin oligo-polyhydramnios sequence (TOPS) and therefore does not fulfill the criteria of TTTS. In the reported cases, placental injection studies revealed the presence of very small (<1 mm) uni-directional arterio-venous anastomoses. Robyr *et al* also reported that TAPS developed after incomplete laser surgery, in 13 of 101 TTTS cases, and Lewi *et al* reported it in 4 of 43 TTTS cases with double survivors at birth.[8;9] Usually, it was the former recipient who became anaemic,

whereas the former donor became polycythaemic. Treatment options include expectant management, re-intervention with laser coagulation of the residual vascular anastomoses, feticide by cord coagulation, intrauterine transfusion, and elective delivery when appropriate. Expectant management carries the risk of the anaemic fetus developing hydrops, followed by intra-uterine death. Re-intervention incurs both procedure-related risks and the risk of operative failure as a result of the inability to identify the residual anastomoses due to their small diameter. Because of ongoing fetofetal transfusion, intra-uterine transfusion only gives a temporary rise of the anaemic fetus' hemoglobine count, and it exposes the polycythaemic fetus to the risk that polycythaemia-hyperviscosity syndrome will be aggravated, which is known to be a risk factor for necrotic tissue injury and gangrene.[10;11] However, since it is not certain whether TAPS is associated with increased morbidity or mortality, the question whether and how to treat it still needs to be clarified.

Severe discordant IUGR

The distinction between TTTS and IUGR is based on the absence of polyhydramnios in the sac of the appropriately grown fetus in discordant IUGR. Birth weight discordance carries a greater risk of complications in monochorionic twin pregnancies than in dichorionic ones because of the vascular anastomoses on the placental surface.
Several studies have reported on perinatal outcome of monochorionic pregnancies complicated by discordant growth retardation. Gratacos *et al* reported that the presence of intermittently absent or reversed end diastolic flow in the umbilical artery in monochorionic twins with selective IUGR, identifies a subgroup with an elevated risk of intrauterine demise of the smaller twin and neurological damage in the larger twin, the latter even in the case where the smaller co-twin survives.[12] Another study showed that monochorionic infants had a seven-fold higher incidence of cerebral white matter lesions than dichorionic infants.[13] Discordant birth weight, TTTS, and being a survivor after co-twin demise were independent risk factors

for cerebral white matter lesions. Huber *et al* concluded that amniotic fluid discordance in monochorionic diamniotic twin pregnancies in combination with IUGR and absent or reversed end diastolic flow in the umbilical artery in one fetus represents an extremely high-risk constellation for adverse pregnancy outcome.[14] This raises the question whether an intervention could optimise outcome. Treatment options are expectant management, fetoscopic laser coagulation of vascular anastomoses, umbilical cord ligation of the growth-retarded fetus, or elective delivery when appropriate. The risks of expectant management have been described above. Fetoscopic laser surgery aims to "bichorionise" the monochorionic twin pair, after which nature can follow its course without risk of adverse effects on the normal co-twin in case the condition of the growth-retarded fetus deteriorates. However, in the absence of severe oligo-polyhydramnios sequence, fetoscopic laser surgery is a technical challenge, with the potential risk of impaired visualisation and inability to identify and coagulate all anastomoses, as well as possibly requiring excessive amnion infusion. When performing umbilical cord ligation of the growth-retarded fetus, fetoscopic entry is preferably via the sac of this fetus without perforating the intertwin membrane, but severe oligohydramnios may prevent optimal fetoscopic entry. Moreover, the decision to perform umbilical cord ligation puts the parents in the difficult emotional situation, where they have to choose to give up on one child in order to save the other. Quintero *et al* suggested that a trial of laser surgery versus expectant management is indicated in monochorionic twins with highly discordant intrauterine growth restriction, and such a randomised trial is currently being conducted in the United States.[15]

Rupture of the fetal membranes after fetoscopic interventions

One of the major problems associated with invasive procedures is the risk of "iatrogenic" preterm prelabour rupture of membranes (iPPROM). Subclinical amniotic fluid leakage in the immediate postoperative period probably occurs more often than previously thought, but when it persists and becomes clinically

relevant it is called iPPROM.[16;17] Within 1 week of intervention, 7% of fetoscopic laser procedures for TTTS are complicated by iPPROM.[18] For more complex fetoscopic procedures, the risk can be up to 30%.[19] Since most invasive procedures are performed in the second trimester of pregnancy, iPPROM usually occurs at an early gestational age, with important fetal consequences (perinatal mortality and morbidity) and maternal ones (chorioamnionitis). This, of course, limits the clinical use of the fetoscopic technique and is a major obstacle for further development. It is important to develop strategies to seal the membrane defect or stimulate the repair mechanisms of fetal membranes at the time of the procedure. In the last six years, several (case) reports have been published on fetal membrane sealing strategies after iPPROM. In a series of 22 cases, Quintero *et al* describe 8 cases with iPPROM and 14 cases with amnion-chorion dissociation after amniocentesis or fetoscopy between 16 and 24 weeks' gestation.[20] As an experimental treatment, the uterine cavity was punctured with a 22 Gauge needle, and various volumes of platelets and cryoprecipitate were injected intra-amniotically. Using this "amnion-patch" technique, the amniotic fluid leakage stopped in 9 cases, and 18 of 32 fetuses survived (56%). However, 2 cases were complicated by sudden intrauterine fetal death, possibly as a result of severe haemodynamic changes induced by platelet activation. These serious complications stress the need for further research to develop strategies and regimens to heal defects in the fetal membranes after iPPROM.[21] In the meantime, every indication for fetoscopic surgery should be carefully weighed by an experienced team. During fetoscopic procedures, the best means of preventing iPPROM is by reducing the size and number of uterine entry ports.

Important advances have been made in the field of fetoscopic fetal therapy during the past decade. However, untimely treatment and pregnancy and neonatal complications still occur frequently. More research and new developments are required to further improve fetoscopic techniques and to further reduce complications.

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