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Fetoscopic interventions in complicated monochorionic twin pregnancies

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Summary

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Leiden University Medical Centre (LUMC) is a tertiary medical centre in the Netherlands and serves as the national referral centre for fetal therapy. Since august 2000, when the fetoscopic surgery program was started, several study projects on endoscopic fetal surgery were initiated in close collaboration with the neonatology division of the paediatrics department at LUMC. In this thesis, studies on fetoscopic interventions in complicated monochorionic twin pregnancies are presented.

Chapter 1 is a brief introduction concerning the characteristics of monochorionic twin pregnancies. The major complications of monochorionic twin gestation, twin-to-twin transfusion syndrome (TTTS), severe intrauterine growth retardation (IUGR), increased rate of fetal anomalies, death of the co-twin, and the various therapeutic options are discussed.

In **Chapter 2** we assessed the value of serial ultrasound examinations in combination with patient instructions, to report the onset of symptoms, for timely detection of TTTS in a cohort of monochorionic diamniotic twin pregnancies. Timely detection of TTTS was defined as diagnosis before severe complications of TTTS, such as preterm prelabour rupture of membranes, very preterm delivery (24-32 weeks of pregnancy), fetal hydrops, or intrauterine fetal death occurred. Ultrasound and Doppler measurements (nuchal translucency thickness, presence of membrane folding, estimated fetal weight, deepest vertical pocket, bladder filling, and Doppler waveforms of the umbilical artery, ductus venosus, and umbilical vein) were performed at least every 2 weeks. A prospective series of 23 monochorionic twin pregnancies was monitored from the first trimester until delivery. Measurements of TTTS cases were compared with those of non-TTTS cases matched for gestational age. Furthermore, patients were informed about the symptoms caused by TTTS, and instructed to consult us immediately in case of rapidly increasing abdominal size or premature contractions. During the study period, 4 cases of TTTS were diagnosed. In all these cases, the diagnosis was timely (one case was at Quintero Stage 1, two at Quintero Stage 2, and one at Quintero Stage 3). Two of the TTTS cases became apparent after the patients' feeling of rapidly increasing

girth. The identification of TTTS predictors was successful with respect to one parameter: isolated polyhydramnios in one sac, without oligohydramnios in the other, preceded the ultimate diagnosis of TTTS in two of the four TTTS cases. All other ultrasound measurements of TTTS cases, prior to the diagnosis of TTTS, were within the range of measurements of non-TTTS cases. We concluded that biweekly ultrasound examinations, with special attention to amniotic fluid compartments of both fetuses, combined with detailed patient instructions to report the onset of symptoms resulted in timely diagnosis of all TTTS cases and appears to be a safe program for monitoring monochorionic twin pregnancies.

Since August 2000, in the LUMC, fetoscopic laser surgery has been the preferred treatment modality for TTTS. In **Chapter 3** we evaluated the results of the first 100 consecutive pregnancies with severe second trimester TTTS treated with selective fetoscopic laser coagulation of vascular anastomoses on the placental surface at our centre. Perinatal survival was analysed in relation to Quintero stage at the time of treatment.

The median gestational age at fetoscopy was 20 weeks (range 16-26), and the median gestation age at delivery was 33 weeks (range 18-40). Perinatal survival rate was 70% (139/200). The treatment resulted in at least one survivor at the age of 4 weeks in 81% of pregnancies. Perinatal survival was significantly higher when treatment was performed in the early Quintero stages (95% in stage 1, 76% in stage 2, 70% in stage 3, 50% in stage 4) ($p=0.02$). We concluded that the initial results of fetoscopic laser surgery for TTTS in our centre were similar to those in specialised centres in other countries. Diagnosis and treatment in the early Quintero stages resulted in significantly higher perinatal survival.

In **Chapter 4** the frequency of residual placental vascular anastomoses after fetoscopic laser surgery for TTTS was studied. Presence of residual anastomoses was studied in association with adverse outcome and inter-twin hemoglobin difference at birth. Adverse outcome (fetal demise, neonatal death

or severe cerebral injury) was similar in the groups with and without residual anastomoses, 18% (6/34) and 29% (20/70) respectively ($p = 0.23$). Large inter-twin hemoglobin differences (> 5 g/dL) were found in 65% (11/17) of cases with residual anastomoses and 20% (7/35) of cases without residual anastomoses ($p < 0.01$). Anterior placental localization was not associated with a more frequent presence of residual anastomoses. The first conclusion of this study is that laser treatment needs to be improved, as only 2/3 of monochorionic placentas are functionally "bichorionised". The second conclusion is that residual anastomoses in this study are not associated with adverse outcome. Lack of association between residual anastomoses and adverse outcome may be partly due to the small size of most residual anastomoses (<1 mm diameter in 64% of the cases) and the presence of "protective" residual superficial anastomoses in 35% of the cases. Finally, we conclude that residual anastomoses are often associated with haematological complications in the neonatal period.

In patients with placental localisation on the posterior wall of the uterus, percutaneous insertion of the fetoscope for laser coagulation gives perpendicular access to the chorionic plate and the vascular anastomoses on its surface, and is, in experienced hands, a straightforward procedure. An angle of approximately 90 degrees between chorionic plate and fetoscope and laser fibre provides maximal visualisation of the vascular equator and optimal laser effectiveness. An anterior placenta, however, presents a technical challenge, because perpendicular access is not possible. In **Chapter 5** we describe a novel technique for fetoscopy in TTTS with completely anterior placenta where laparoscopy is used to guide safe percutaneous insertion of the fetoscope through the lateral abdominal wall and the dorsal side of the uterus. We compared 16 TTTS pregnancies with completely anterior placenta (study group) treated with this novel technique with 49 TTTS pregnancies treated with conventional percutaneous fetoscopic laser without laparoscopy: 9 of these with partially anterior placenta (control group A) and 40 with lateral or posterior placenta (control group B). In the study group, the procedure-related complication rate was 25% (4/16). In one case uterine entry of the fetoscope from the lateral abdominal wall was not possible due to complex bowel

adhesions. In 3 patients, intraamniotic haemorrhage occurred after fetoscopic entry, preventing complete laser coagulation of anastomoses. One of these patients required two units of blood transfusion. The procedure-related complication rate in control group A and B was 22% (2/9) and 5% (2/40), respectively (intraamniotic haemorrhage n = 3, severe leakage of amniotic fluid into the peritoneal cavity, n=1). Perinatal survival in the study group, control group A and control group B was 63% (20/32), 78% (14/18) and 70% (56/80), respectively. We concluded that combined laparoscopy and fetoscopy is a novel technique that enables safe uterine entry and creates optimal visualisation for laser coagulation of inter-twin anastomoses in TTTS pregnancies with completely anterior placenta. Procedure-related complication rate and perinatal survival rate were similar compared to the conventional percutaneous technique. Procedure-related complications occur more often with partially or completely anterior placenta.

Chapter 6 describes the long-term neurodevelopmental outcome in TTTS treated with fetoscopic laser surgery. All TTTS cases treated consecutively at our centre between August 2000 and December 2003 were included in the study. Perinatal mortality was 30% (49/164). Neurological, mental and psychomotor development at 2 years for age was assessed in all TTTS survivors (n = 115). Overall, the incidence of neurodevelopmental impairment was 17% (19/115) and was due to cerebral palsy (n = 8), severe mental developmental delay (n = 9), severe psychomotor developmental delay (n = 12) and deafness (n = 1). From this long-term follow-up study, we concluded that the incidence of neurodevelopmental impairment in TTTS survivors, treated with fetoscopic laser surgery, is high and warrants long-term follow-up.

In monoamniotic twin pregnancies discordant for fetal anomaly, parents may opt for selective feticide by umbilical cord coagulation. However, the normal co-twin remains at risk of sudden demise from cord entanglement. In **Chapter 7** we report on three cases of successful selective feticide by cord occlusion combined with cord transection to prevent complications caused by entanglement. We describe technical details and outcome of three

monoamniotic twin pregnancies, discordant for fetal anomaly (two cases of anencephaly and one case of congenital heart block), in which cord occlusion was followed by transection of the cord, using contact laser. The fetoscopic cord occlusion and transection, using laser, was successfully performed at 15, 16 and 19 weeks' gestation, respectively. In one case, amniotic fluid leakage occurred after fetoscopy. The surviving co-twins were born healthy, two out three vaginally, at 36, 38 and 36 weeks' gestation, respectively. We concluded that in monoamniotic twins, selective feticide using laser occlusion and transection of the umbilical cord is technically feasible and can lead to near-term vaginal birth of healthy co-twins.

In monochorionic twin pregnancies, complicated by TTTS diagnosed after 26 weeks' gestation, apart from expectant management or amniodrainage, therapeutic delivery is a management option. In otherwise healthy fetuses, however, 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. In **Chapter 8** we retrospectively studied 21 TTTS cases, diagnosed after 26 weeks' gestation, and treated in the Leiden University Medical Centre between January 1991 and February 2006 with either amniodrainage or fetoscopic laser surgery. Main outcome measures were adverse outcome (intrauterine or neonatal death, major neonatal morbidity and/or severe cerebral injury) and gestational age at birth. Eleven TTTS cases were treated with amniodrainage and ten with laser surgery. Median gestational age at birth in the amniodrainage group and laser surgery group was 29 and 31 weeks respectively ($p = 0.17$). All infants were born alive. Major neonatal morbidity occurred more often in the amniodrainage group than in the laser surgery group, 27% (6/22) and 0% (0/20) respectively ($p = 0.02$). Severe cerebral injury in the amniodrainage group and laser surgery group occurred in 23% (5/22) and 15% (3/20) respectively ($p = 0.70$). Neonatal mortality in the amniodrainage group and laser surgery group was 14% (3/22) and 0% (0/20) respectively ($p = 0.23$). Overall adverse outcome was 36% (8/22) in the

amniodrainage group and 15% (3/20) in the laser surgery group ($p = 0.17$). We concluded, that in TTTS diagnosed after 26 weeks' gestation, amniodrainage and laser surgery both result in 100% survival. However, the incidence of major neonatal morbidity in infants born after laser surgery was lower. Our findings suggest that even in TTTS diagnosed after 26 weeks' gestation laser surgery should be considered.

In conclusion, although important advances have been made in the field of fetoscopic fetal therapy during the past decade, untimely treatment and severe perinatal complications still do occur very frequently. More research and new developments are required to further improve fetoscopic techniques and to further reduce complications.