Fetoscopic interventions in complicated monochorionic twin pregnancies

Middeldorp, J.H.

Fetoscopic laser surgery in 100 pregnancies with severe twin-to-twin transfusion syndrome in the Netherlands

Johanna M Middeldorp
Marieke Sueters
Enrico Lopriore
Frans JCM Klumper
Dick Oepkes
Roland Devlieger
Humphrey HH Kanhai
Frank PHA Vandenbussche

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3

Abstract

Objective: In this prospective cohort study we evaluated the initial results of fetoscopic laser surgery for severe second trimester twin-to-twin transfusion syndrome (TTTS) treated at our centre.

Methods: A total of 100 consecutive pregnancies with severe second trimester TTTS treated at our centre with selective fetoscopic laser coagulation of vascular anastomoses on the placental surface between August 2000 and November 2004 were included in the study. Perinatal survival was analysed in relation to Quintero stage.

Results: Median gestational age was 20 weeks at fetoscopy (range 16-26) and 33 weeks at delivery (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).

Conclusions: Results of fetoscopic laser surgery for TTTS in our centre are similar to those in specialised centres in other countries. Diagnosis and treatment in the early Quintero stages resulted in significantly higher perinatal survival.

Introduction

Monochorionic twin pregnancies are at risk for developing twin-to-twin transfusion syndrome (TTTS) due to unbalanced inter-twin blood-flow through placental vascular anastomoses. TTTS may occur in 10-15% of monochorionic twin pregnancies, mostly in the second trimester of pregnancy.[1] The first sonographic signs of TTTS are oliguria in the donor, resulting in oligohydramnios in the donor sac, and polyuria in the recipient, resulting in a polyhydramnios in the recipient sac. Hereafter, more severe signs may occur such as anuria, heart failure, hydrops and single or double fetal demise. Premature contractions or preterm rupture of membranes, leading to preterm birth, may result from the polyhydramnios. Quintero proposed a staging system to classify the severity of the syndrome.[2]

Until recently, it was unclear which treatment modality provided the best result in TTTS. Serial amnioreduction is a symptomatic treatment for TTTS that has been used for more than two decades. The transient reduction of amniotic fluid reduces pressure on the placenta with improvement of transplacental fluid flow between mother and fetus, and reduces the risk of preterm delivery.[3] More recently, a cause-oriented approach for TTTS was developed in the United States and the United Kingdom: fetoscopic laser coagulation of vascular anastomoses on the placental surface.[4-6] A recent randomised trial reported significantly higher perinatal survival and improved neurological outcome in TTTS survivors after fetoscopic laser surgery compared to serial amnioreduction.[7]

The number of TTTS pregnancies in the Netherlands, with 200,000 births annually, is estimated to be 60-90 per year. At Leiden University Medical Centre, the national referral centre for invasive fetal therapy, fetoscopic laser surgery has been the preferred treatment modality since August 2000. We report the perinatal outcome after fetoscopic laser surgery of a consecutive series of 100 pregnancies complicated by severe second trimester TTTS.

Methods

Inclusion criteria for fetoscopic laser surgery were: monochorionic twin pregnancy, gestational age between 16 and 26 weeks, not in labour, no congenital malformations, TTTS Quintero stage 1 with severe clinical symptoms of polyhydramnios, or TTTS Quintero stage ≥ 2. Before fetoscopy, detailed sonographic evaluation was performed to exclude congenital anomalies, to confirm the diagnosis of TTTS, and to determine the Quintero stage. The sonographic investigation included: fetal anatomy and biometry, deepest vertical pocket of amniotic fluid of each fetus, bladder filling, arterial and venous Doppler studies, placental location, location of umbilical cord insertions, and cervical length. On the basis of these findings, an estimation of the location of the vascular equator and the optimal insertion site of the fetoscope in the uterine wall was made. In the majority of cases, fetoscopic laser surgery was performed under regional anaesthesia, but in some cases with anterior placenta general anaesthesia was used. A prophylactic dose of tocolytics (indomethacin) and antibiotics (amoxycillin/clavulanate) was given routinely. In 85 women, the 2 mm semi rigid fetoscope (Storz, Vianen, the Netherlands) was introduced percutaneously in the sac of the recipient through a straight or curved (up to 40 degrees) shaft with an outer diameter of 3.3 mm. In 8 cases with an anterior placenta a small (3-5 cm) laparotomy was performed in the lateral abdominal wall near the mid-axillary line, between the lower ribs and the iliac crest. After opening the peritoneum, bowels were moved aside with gauze and the lateral uterine vessels were identified. The shaft was then inserted through the posterior uterine wall in order to obtain a perpendicular angle between the fetoscope and the vascular equator. In 7 women, introduction of the shaft in the posterior uterine wall was assisted by open entry laparoscopy instead of mini laparotomy. After introduction of the fetoscope, vessels crossing the inter-twin membrane were followed to identify the anastomotic vessels in the recipient's sac. When it could be confirmed that these crossing vessels belonged to just one twin, they were left intact. All vessels that connected to vessels of the other twin were coagulated by laser light (diode laser (Diomed Limited, Cambridge, UK) or ND:YAG laser

(Dornier Medizin Technik, Germering, Germany)). Isolated arteries and veins, coming from the recipient and crossing the inter-win membrane, that could not be followed any further, were also coagulated.[7;8] Finally, amniotic fluid was drained until the deepest vertical pool was less than 6 cm. During the procedure, fetal condition was evaluated continuously by ultrasound.

Percentage of fetal survival was defined as 100 x number of live born children/2 x number of pregnancies. Percentage of perinatal survival was defined as 100 x number of children alive at 4 weeks/2 x number of pregnancies. Differences in outcome between Quintero stages were analysed with Chi square test (linear by linear association). A p-value < 0.05 was considered to indicate a statistical significance. Statistical analysis was performed with SPSS version 11.0 (SPSS, Inc., Chicago, Illinois, USA).

Results

From August 2000 until November 2004, a consecutive series of 100 pregnancies complicated by severe second trimester TTTS were included in the study: 10 with Quintero stage 1 (10%), 42 with stage 2 (42%), 41 with stage 3 (41%) and 7 with stage 4 (7%). The median gestational age at intervention was 20 weeks (range 16-26). There were no cases of intra-amniotic bleeding that prevented completion of surgery. Rupture of membranes within 2 weeks of the procedure occurred in 13/100 (13%) cases. In 2 of these 13 cases there were clinical signs of chorioamnionitis. Of the 13 cases, 8 pregnancies ended within two weeks after the fetoscopic procedure and resulted in death of both fetus. The remaining 5 pregnancies resulted in at least one survivor at 4 weeks of age.

One woman suffered from a short episode of pulmonary oedema directly after laser procedure and was treated with oxygen and diuretics. Another woman presented a few months after delivery with complaints of bowel herniation in the mini-laparotomy scar. There were no other maternal complications.

In five pregnancies (5%), polyhydramnios recurred, either in the sac of the former recipient (recurrence n=2) or in the sac of the former donor (reversal n=3). In two of these cases re-intervention with laser coagulation of the residual anastomoses was performed, both at 20 weeks. In the other three cases, caesarean section was performed at 29, 31 and 31 weeks, respectively. Table 1 shows a comparison of the results of our series with those of other published series.[7-10] Follow-up was complete until 4 weeks after birth. In our series, the incidence of single intrauterine fetal demise was 17% (17/100) (12 former recipients and 5 former donors). The incidence of miscarriage was 14% and the incidence of double intrauterine demise was 4%. The overall incidence of fetal

Table 1 *Comparison of perinatal outcome after fetoscopic laser surgery in the Leiden University Medical Centre with other published series*[7-10]

	present study† ***N=100***	***De Lia†*** **1999[9]** ***N=67***	***Hecher†*** **2000[8]** ***N=200***	***Quintero†*** **2003[10]** ***N=95***	***Senat**** **2004[7]** ***N=72***
median gestational age at delivery	33	31	34	32	33
2 survivors (%)	58/100 (58%)°	38/67 (57%)°	100/200 (50%)°°	43/95 (45%)°	26/72 (36%)°°
1 survivor (%)	23/100 (23%)°	17/67 (25%)°	61/200 (30%)°°	36/95 (38%)°	29/72 (40%)°°
0 survivors (%)	19/100 (19%)°	12/67 (18%)°	39/200 (20%)°°	16/95 (17%)°	17/72 (24%)°°
neonatal death (%)	8/200 (4.0%)	5/134 (3.7%)	15/400 (3.8%)	14/190 (7.4%)	11/144 (7.6%)

† *cohort studies*
* *randomised controlled trial*
° *survival at 4 weeks*
°° *survival at 6 months*

demise was thus 53% (53/200). Most fetal losses (81%, 43/53) occurred within 4 weeks after the initial treatment.
Neonatal death occurred in 8 children. Overall perinatal mortality was 61/200 (30%). Perinatal survival of at least one child occurred in 81% (81/100) of TTTS pregnancies. There were no significant differences in perinatal survival according to placental localisation. Survival of at least one child was 30/38 (79%, 95% CI 63-89) in anterior (complete or partial), and 51/62 (82%, 95% CI 71-90) in posterior placental localisation. Table 2 shows the pregnancy outcome by Quintero-stage. Perinatal outcome was significantly better in the early Quintero stages (p=0.02).

Table 2 *Pregnancy outcome after fetoscopic laser surgery for severe TTTS in the Leiden University Medical Centre by Quintero stage.*

Stage by Quintero[2]	**1** **N=10**	**2** **N=42**	**3** **N=41**	**4** **N=7**
median gestational age at delivery	35	33	33	33
2 survivors at birth (%)	9/10 (90%)	29/42 (69%)	24/41 (59%)	3/7 (43%)
1 survivor at birth (%)	1/10 (10%)	6/42 (14%)	9/41 (22%)	1/7 (14%)
0 survivors at birth (%)	0/10 (0%)	7/42 (17%)	8/41(19%)	3/7 (43%)

(chi-square test, linear-by-linear association p=0.02)

Discussion

We report the initial results of fetoscopic laser coagulation of vascular anastomoses for severe TTTS at our centre. In 81% of pregnancies, laser treatment resulted in the birth of at least one surviving child. These results are similar to those of other published large series.[7-10] 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 stage at the time of treatment, the better the outcome.[10] Double perinatal survival decreased

from 90% in Quintero stage 1 to 43% in Quintero stage 4. Our findings are in accordance with the results of a recent study reporting significantly better perinatal outcome of fetoscopic laser surgery in Quintero stage 1 and 2 as compared to stage 3 and 4.[7]

In untreated severe TTTS, perinatal survival rate is reported to range between 20% and 37%.[11-13] In treated severe TTTS, with serial amnioreduction or fetoscopic laser coagulation of vascular anastomoses, perinatal survival rates increase up to 57% and 66%, respectively.[13] The incidence of neurological sequelae in TTTS is also related to the prenatal treatment modality. Severe neurological damage is found in 25% of survivors without prenatal treatment, in 16-22% in survivors after serial amniodrainage, and 5-11% after fetoscopic laser surgery.[11;13-17] In a recent randomised multi-centre study, Senat *et al* found significantly better outcomes after fetoscopic laser surgery compared to serial amnioreduction. Survival of at least one twin at the age of six months was 51% in the amnioreduction group and 76% in the laser group (p=0.002). At the age of six months, major neurological sequelae were found in 19% of the surviving children after amnioreduction and in 7% after laser surgery (p=0.05). The overall higher mortality rate in this randomised trial in comparison with cited retrospective studies is probably due to a higher proportion of severe TTTS cases included, and to the fact that the authors followed the intention-to-treat principle with inclusion of cases where intra-uterine death occurred between the moment of randomisation and treatment.[7;12;13]

In our centre, fetoscopic laser surgery was started in August 2000. To optimise the learning curve, each procedure was attended by two of the four operators. To evaluate the results of laser surgery we routinely perform placental injection study with coloured dye. The presence of four operators (presently FK, DO, FV, JM) guarantees the availability of at least one operator at all times, an obvious necessity for a national referral centre. In a recent editorial, Fisk *et al* debated the feasibility of fetoscopic laser surgery. They concluded that widespread adoption of this challenging and difficult procedure by fetal specialists without adequate training in endoscopy and placental

vascular anatomy has the potential to do more harm than good[18]. The results of fetoscopic laser treatment in our centre were from the beginning of the fetoscopy program comparable to those reported in the literature.[19] We think, our results positively underline the statement of Fisk *et al*.[18] Setting up a fetoscopic laser surgery program in a centre for fetal therapy is feasible, provided that adequate training is given, that operators receive feed-back by studying placental vascular anatomy after birth, that enough operators are available to run a 24 hours service, and that a minimum of 30 procedures per year are performed to ensure the maintenance of skills. The aim of each fetoscopic laser surgery program should also include accurate evaluation of short-term and long-term paediatric outcome. We have recently reported on the neonatal and short-term neurological outcome in TTTS treated with laser surgery at our centre.[20;21] Long-term neurodevelopmental outcome at 2 years of age is currently being evaluated.

In our study, treatment in earlier Quintero stages resulted in significantly better outcome. Care should be taken when interpreting these results. A potential bias could be that not all early Quintero stages necessarily progress to higher stages. Luks *et al* studied natural evolution of 18 TTTS women in week-to-week evaluations and found no change in 72%, down-staging in 12% and up-staging in 15%.[22] To prevent over-treatment in the 10-15% of cases that show spontaneous improvement, early TTTS stages can be followed closely, with laser treatment only in case of progression. On the other hand, waiting for TTTS to progress to higher stages may involve an increased risk of mortality and morbidity. It is still unknown, however, whether neurological damage in monochorionic twins treated with fetoscopic laser surgery occurs before, during or after laser surgery. As shown in a recent study, monochorionic twins without TTTS already are at considerable risk of developing neurological morbidity[23]. Thus, whether treatment in the early Quintero stages results in better outcome and prevents neurological morbidity can only be clarified in a randomised controlled trial between early laser and waiting for progression. Such a trial is urgently needed.

Conclusion

Perinatal outcome in TTTS after fetoscopic laser coagulation of vascular anastomoses treated at our centre was similar to that in specialised foreign centres. Perinatal survival was significantly higher after laser surgery in the early Quintero stages.

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