Fetoscopic interventions in complicated monochorionic twin pregnancies

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TTTS after 26 weeks gestation: is there a role for fetoscopic laser surgery?

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Abstract

Objective: To compare fetoscopic laser surgery with amniodrainage in the treatment of twin-to-twin transfusion syndrome (TTTS) diagnosed after 26 weeks' gestation.

Methods: Treatment of TTTS consisted of either amniodrainage or fetoscopic laser coagulation of vascular anastomoses. Primary outcome was adverse outcome (intrauterine or neonatal death, major neonatal morbidity and/or severe cerebral injury). Secondary outcome was gestational age at birth.

Results: 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).

Conclusions: In TTTS diagnosed after 26 weeks' gestation, amniodrainage and laser surgery both result in 100% survival. However, infants born after laser surgery have less major neonatal morbidity.

Introduction

Monochorionic twin pregnancies are at risk for developing chronic 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 polyhydramnios and associated risks for preterm birth. Hereafter, more severe signs may occur such as anhydramnios in the donor twin, hydrops fetalis in the recipient twin, and eventually fetal demise.

Serial amnioreduction has been the symptomatic treatment for TTTS for more than two decades. More recently, a cause-oriented approach for TTTS, fetoscopic laser coagulation of vascular anastomoses on the placental surface, was shown to result in significantly higher perinatal survival and improved neurological outcome.[2] However, this randomised controlled trial and most other published studies on the treatment of TTTS with laser surgery were limited to pregnancies treated before 26 weeks' gestation.[2-4]

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, 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 on neurological morbidity, and other characteristic morbidities in TTTS, such as cardiovascular and renal morbidity.[5-7]

The aim of this study was to evaluate the pregnancy and neonatal outcome in TTTS diagnosed after 26 weeks' gestation in relation to treatment with either laser surgery or amniodrainage.

Methods

All consecutive cases of monochorionic twins with chronic TTTS, diagnosed and treated after 26 weeks' gestation at our centre between January 1991 and February 2006 were included in the study. The Leiden University Medical Centre is the national referral centre for fetal therapy. During the study period, indications for treatment for TTTS were as follows: before August 2000, women with TTTS were routinely treated with amniodrainage. Amniodrainage was performed when chronic TTTS was diagnosed using standard prenatal ultrasound criteria: oligohydramnios (deepest vertical pocket ≤ 2cm) in the twin sac of one fetus and polyhydramnios (deepest vertical pocket ≥ 8cm before 20 weeks of gestation or ≥ 10cm after 20 weeks of gestation) in the twin sac of the other fetus.[8] In August 2000 a fetoscopic laser surgery program for TTTS was started at our centre. Since then, women presenting between 16 and 26 weeks' gestation with TTTS Quintero stage 1 and symptomatic polyhydramnios, or Quintero stages ≥ 2, were treated with laser surgery. After August 2000, amniodrainage and laser surgery, when technically feasible, were both discussed as options in case of TTTS Quintero ≥ 2. In Quintero stage 1, or Quintero stage ≥ 2 with a completely anterior placenta, amniodrainage was performed. All procedures were sonographically guided. The fetoscopic laser surgery technique used was described in detail previously and is similar to the method reported by Hecher *et al* and Senat *et al*.[2;4;9] To coagulate the anastomoses a Nd:YAG laser was used (Dornier Medizin Technik, Germering, Germany). The majority of fetoscopic procedures were performed under regional anaesthesia. A prophylactic dose of tocolytics (indomethacin) and antibiotics (amoxycillin/clavulanate) was given routinely. Amniodrainage was performed under continuous ultrasound guidance, using an 18 or 20 Gauge needle. Amniotic fluid was removed until deepest pocket was 6 cm. The procedure was repeated when clinical signs of maternal discomfort recurred. A prophylactic dose of tocolytics (indomethacin) was given routinely.
The following data were extracted from the medical records: gestational age at the time of diagnosis and treatment, Quintero stage prior to treatment, intrauterine fetal death, gestational age at delivery, and mode of delivery.

In the amnioreduction group we recorded the number of therapeutic amnioreductions and total volume of amniotic fluid removed. In the laser surgery group we recorded the total volume of amniotic fluid drained at the end of the laser procedure. In TTTS pregnancies treated after 1999, Quintero stage was assessed routinely prior to treatment.[10] In pregnancies treated before 1999, Quintero stage was determined retrospectively for the purpose of this study. The following neonatal data were recorded: neonatal cranial ultrasound findings, chronic lung disease, symptomatic patent ductus arteriosus, necrotising enterocolitis, renal failure, hydrops fetalis, retinopathy of prematurity, anaemia at birth, polycythaemia-hyperviscosity syndrome requiring partial exchange transfusion and major congenital malformations. Haemoglobin levels were measured from umbilical cord blood. Anaemia at birth was defined as haemoglobin level below the 3rd percentile for gestational age requiring a blood transfusion during the first day of life. Cerebral ultrasound scans were performed in all neonates on the first day of life and thereafter according to our unit protocol. The cranial ultrasound protocol at our neonatal intensive care unit requires a minimum of 3 scans during the first week of life (day 1, 3 and 7), followed by at least 1 scan weekly until discharge. In term infants, repeat cranial ultrasound scans are not performed if scans are normal at birth. Severe cerebral injury on cranial ultrasound scans was defined as the presence of at least one of the following findings: intraventricular haemorrhage grade III, intraventricular haemorrhage with parenchymal involvement, cystic periventricular leucomalacia ≥ grade II, ventriculomegaly, porencephalic or parenchymal cysts or other major cerebral abnormalities associated with adverse neurological outcome, as previously described.[11] Major neonatal morbidity was defined as any of the following: chronic lung disease, necrotising enterocolitis ≥ grade II, retinopathy of prematurity ≥ stage III, major cardiac morbidity requiring surgery or major ischemic limb injury, as previously described.[12]

The primary outcome was a composite outcome, adverse outcome, defined as intrauterine fetal demise, neonatal death, major neonatal morbidity or severe cerebral injury. Gestational age at birth was considered a secondary outcome. Outcome was compared between the amniodrainage and the laser surgery

group. Statistics: Results of categorical variables were compared using Fisher's exact test. Unpaired Student's *t* test was used to compare normally distributed values between two groups. Differences in Quintero stage, in gestational age at treatment and at birth, and in haemoglobin difference at birth were tested by Wilcoxon. A P-value of < 0 .05 was considered statistically significant. Statistical analysis was performed with SPSS version 11.0 (SPSS, Inc., Chicago, Illinois, USA).

Results

During the study period, 21 TTTS cases were diagnosed and treated after 26 weeks' gestation. Before August 2000, 4 TTTS cases were treated with amniodrainage after 26 weeks' gestation. Between August 2000, when the laser program was started, and February 2006, 153 fetoscopic procedures for laser coagulation of vascular anastomoses for TTTS were performed. During this period, another 7 TTTS cases were treated with amniodrainage and 10 TTTS cases underwent laser surgery after 26 weeks' gestation.
In the amniodrainage group, Quintero stage 1, 2, 3 and 4 occurred in 4, 2, 4 and 1 case, respectively. The median gestational age treatment was 27 (range 26-29) weeks' gestation. A mean of 1.6 (range 1-3) amniodrainage procedures was performed, 45% (5/11) of the women underwent more than 1 amniodrainage procedure. Per amniodrainage procedure, a median amniotic fluid volume of 2000 ml (range 500-3500 ml) was removed.
In the laser group, 2 cases had TTTS Quintero stage 2 and 8 cases had TTTS Quintero stage 3. The median gestational age treatment was 27 (range 26-28) weeks' gestation. A median of 5 (range 2-10) anastomoses was coagulated. The maximum power used for coagulation was 70 Watts. At the end of the procedure, a median amniotic fluid volume of 1800 ml (range 0-4200 ml) was removed. The quality of chorionic plate exposure was good in all but one case, there were no difficulties with turbidity of amniotic fluid, and there was no need for amniotic fluid exchange to improve visualisation. Neither placental bleeding nor uterine bleeding occurred. In one case in the laser surgery group,

one amniodrainage procedure was performed three days before laser surgery. In another case in the laser surgery group, the procedure had to be abandoned because of poor visualisation, due to rapid leakage of amniotic fluid into the intraperitoneal cavity after severe vomiting of the patient. In a third case in the laser surgery group, after normalisation of the amniotic fluid in both sacs, the ex-recipient became severely anaemic and was treated with an intrauterine blood transfusion two weeks after laser surgery. Within 48 hours after the intrauterine transfusion, MCA-PSV Doppler studies showed again signs of severe fetal anaemia, cardiotocography demonstrated a sinusoidal pattern and a caesarean section was performed. This case has been described in detail, previously.[13]

Median gestational age at birth in the amniodrainage and laser surgery group was 29 and 31 weeks, respectively (p = 0.17). Median treatment-to-delivery interval in the amniodrainage and laser group was 9 and 31 days, respectively (p = 0.07). In the amniodrainage group, 9/11(82%) patients needed additional tocolysis for which a variety of drugs were used due to changing protocols including ritodrin, atosiban, indomethacin or nifedipin, versus 2/10(20%) in the laser surgery group (nifedipin) (p = 0.009). Steroids for fetal lung maturation were administered in 8/9(89%) and in 6/7(86%) of cases with premature birth < 34 weeks, in the amniodrainage and in the laser surgery group, respectively (p = 1.0) Premature prelabour rupture of membranes (PPROM) < 2 weeks after the intervention occurred in 1/11 (9%) of the cases in the amniodrainage group and in none of the cases in the laser surgery group (p = 1.0). There were no intra-uterine deaths, neither in the amniodrainage group, nor in the laser surgery group.

More then 25% birth weight discordance occurred in 2/11 (18%) of the amniodrainage group and in 2/10 (20%) of the laser surgery group. Major neonatal morbidity occurred only in the amniodrainage group (necrotising enterocolitis grade III, n =3, chronic lung disease, n = 2, terminal renal failure, n=1). Severe cerebral injury was diagnosed in 5 infants in the amniodrainage group (cystic periventricular leucomalacia ≥ grade II, n = 2, bilateral intraventricular haemorrhage grade III, n = 1, bilateral intraventricular haemorrhage with parenchymal involvement and post-haemorrhagic

ventricular dilatation, n =1, ventriculomegaly, n = 1) and in 3 infants in the laser group (ventriculomegaly, n = 1, porencephalic cyst, n = 1, middle cerebral artery infarction, n = 1). Neonatal death occurred in three infants in the amniodrainage group and was caused by terminal renal failure (n =1), bilateral intraventricular haemorrhage with parenchymal involvement and post-hemorrhagic ventricular dilatation (n = 1), and necrotising enterocolitis grade III (n = 1). Overall, adverse outcome in amniodrainage group and laser surgery group was 36% (8/22) and 15% (3/20), respectively (p = 0.17). Details on pregnancy outcome and neonatal outcome in the amniodrainage group and laser surgery group are reported in table 1.

Table 1 *Pregnancy outcome and neonatal outcome in the serial amniodrainage group and laser surgery group*

	Amniodrainage group n = 11/22	**Laser surgery group n = 10/20**	**P-value**
Treatment to delivery interval – days[a]	9 (0-65)	31 (5-75)	0.07
PPROM < 2 weeks after intervention – n (%)	1 (9)	0 (0)	1.0
Gestational age at birth – weeks[a]	29 (27-36)	31 (28-37)	0.17
Birth weight – gr[b]	1472 ± 634	1615± 516	0.43
Haemoglobin difference at birth - g/d[a]	4.0 (0.8-12.2)	1.2 (.0-16.6)	0.37
Anaemia at birth - n (%)	2 (9)	4 (20)	0.40
Polycythaemia at birth - n (%)	3 (14)	1 (5)	0.61
Major neonatal morbidity - n (%)	6 (27)	0 (0)	0.02
Severe cerebral injury - n (%)	5 (23)	3 (15)	0.70
Neonatal death - n (%)	3 (14)	0 (0)	0.23
Adverse outcome[c] - n (%) (%)	8 (36)	3 (15)	0.17

[a] *values given as median (range)*
[b] *values given as mean ±SD*
[c] *intrauterine fetal demise, neonatal death, major neonatal morbidity or severe cerebral injury*

Discussion

In this study we found that in TTTS diagnosed after 26 weeks' gestation, treatment with laser surgery was associated with a trend towards higher gestational age at birth and a longer treatment-to-delivery interval, and with significantly less major neonatal morbidity than in TTTS treated with amnioreduction. Neonatal morbidity such as necrotising enterocolitis and chronic lung disease are known to be directly related to prematurity, suggesting a direct relationship between the lower gestational age at birth in the amnioreduction group and the higher rate of major neonatal morbidity. Severe cerebral injury was similar in the laser group and amnioreduction group. As previously reported, the majority of cerebral injury in TTTS is of antenatal origin.[11;14-16] This may explain why TTTS survivors treated with laser surgery in this study do not have a lower incidence of severe cerebral injury despite the more advanced gestational age at birth. Overall, we found a trend towards less adverse outcome in TTTS treated with laser as compared with amnioreduction, but numbers were probably too small to reach significance. For a randomised controlled trial comparing amnioreduction with laser after 26 weeks' gestation with a power of 0.80, a total of 126 patients, 63 in each arm would be needed to show that the expected reduction in adverse outcome from 36% to 15% is statistically significant.

In severe second trimester TTTS, because of the poor survival rates with conservative management, there is general consensus that therapy should be offered. Fetoscopic laser coagulation of vascular anastomoses on the placental surface is associated with significantly higher perinatal survival and improved neurological outcome as compared with serial amioreduction[2]. However, most published series of TTTS cases treated with laser surgery are limited to gestational ages under 26 weeks.[2;4;17;18] Only one case series included patients until 28 weeks' gestation.[19] To our knowledge, no specific details on neonatal outcome after laser surgery or amniodrainage for TTTS performed after 26 weeks' gestation have yet been reported.

When TTTS occurs after 26 weeks' gestation, common advice for management is either to perform one or more amniodrainages or, in selected cases of severe

TTTS, preterm delivery. Both options are associated with a significant risk of neonatal death or major neurological sequelae, either due to problems related to the invasive nature of the procedure with inherent risks of premature birth, or to TTTS itself.[20-22] 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 such as premature rupture of membranes as compared with amniodrainage. Our preliminary data show that new consideration should be given to laser surgery as a valid alternative to amniodrainage in early third trimester TTTS.

Performing a successful uncomplicated laser procedure allows the fetuses to recover from TTTS in utero and results in more advanced gestational age at birth. Selection of the cases at minimal risk of complications is an important, but difficult issue. Placental localisation, and in particular anterior placental localisation, is an important issue in fetoscopic laser surgery. In this non-randomised descriptive study, placental localisation was mainly posterior (7 cases), or anterior with a placenta free window for lateral percutaneous access (3 cases). In this selected group of cases laser surgery was feasible. Obviously, due to the retrospective character of this study, our results are subjected to a selection bias. Another important, but inevitable limitation of this study is the small number of cases. In order to determine the best management of early third trimester TTTS, further studies are urgently needed. Considering the low incidence of TTTS presenting after 26 weeks' gestation, the ideal setting of such a study would be a sufficiently large multi-centre randomised study.

Conclusion

In this study, less major neonatal morbidity occurred in TTTS cases, diagnosed and treated after 26 weeks' gestation as compared with amniodrainage.

This finding suggests that fetoscopic laser surgery is a valid alternative to amniodrainage in the treatment of TTTS after 26 weeks.

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