Endoscopic Placental Laser Coagulation in Dichorionic and Monochorionic Triplet Pregnancies

Running title: Laser Coagulation in Triplet Pregnancies

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Acknowledgement: The study was supported by a grant from the Fetal Medicine Foundation (Charity No: 1037116). This paper is part of the PhD thesis of Gergana Peeva for Universidad Autonoma De Madrid.

Key Words: Monochorionic triplets; Dichorionic triplets; Twin-to-twin transfusion syndrome; Selective fetal growth restriction; Endoscopic laser coagulation

Abstract

Objective: To report outcome of monochorionic (MC) and dichorionic (DC) triamniotic (TA) triplet pregnancies treated with endoscopic laser coagulation of communicating placental vessels for severe fetofetal transfusion syndrome (FFTS) and selective fetal growth restriction (sFGR).

Methods: Laser surgery was performed at 18 (15-24) weeks´ gestation in 11 MCTA and 33 DCTA pregnancies complicated by FFTS and 14 DCTA pregnancies complicated by sFGR. Data from our study and previous reports were pooled using meta-analytic techniques.

Results: Survival of at least one baby and survival among all fetuses was 97.0% and 72.7% in DCTA pregnancies with FFTS, 78.6% and 52.4% in DCTA pregnancies with sFGR and 81.8% and 39.4% in MCTA pregnancies with FFTS. In the combined data from our study and previous reports, the pooled survival rates in 132 DCTA pregnancies with FFTS were 94.4% and 76.1% and in 29 MCTA pregnancies with FFTS were 80.6% and 57.5%.

Conclusions: Survival after laser surgery is higher in DC triplets with FFTS than those with sFGR and in DC than MC triplets with FFTS.

Introduction

Monochorionic (MC) pregnancies are often complicated by severe fetofetal transfusion syndrome (FFTS) and / or selective fetal growth restriction (sFGR). The established treatment of choice in the management of severe FFTS in MC twin pregnancies is endoscopic laser coagulation of the inter-twin communicating placental vessels [1-3]. In sFGR with abnormal Doppler findings in the umbilical artery of the affected fetus, there is a high risk of perinatal death and handicap for both twins; the management for affected pregnancies presenting at mid-gestation includes endoscopic laser coagulation of the inter-twin communicating placental vessels or cord occlusion of the FGR twin [4-8]. Few studies in a small number of patients have reported on endoscopic laser coagulation of communicating placental vessels for the management of FFTS in MC or dichorionic (DC) triamniotic (TA) triplet pregnancies complicated by FFTS [9-16].

The objectives of this study are to report our experience with endoscopic laser surgery in the management of severe FFTS or sFGR in MC and DC triplet pregnancies and compare the results with those of previous studies.

Methods

Study design and participants

This was a retrospective study of all cases of MCTA and DCTA triplet pregnancies treated by endoscopic laser coagulation of communicating placental vessels at 15-24 weeks' gestation in our fetal medicine centre between 1996, four years after we first introduced endoscopic laser surgery in twins [1], and June 2015. Umbilical cord occlusion was not a treatment option for sFGR or FFTS in our centre. The cases included 11 MCTA and 33 DCTA pregnancies complicated by FFTS and 14 DCTA pregnancies complicated by sFGR without coexisting FFTS.

Chorionicity and amnionicity were established in the first trimester as previously reported [17]. Gestational age was calculated from the crown-rump length of the biggest fetus [18]. The diagnosis of FFTS was made if there was a marked discordance in amniotic fluid volume between the MC fetuses with deepest vertical pool of $\leq$2 cm in at least one sac and $\geq$8 cm in the other; the severity of the disease was classified as stage I if the Doppler findings in the umbilical artery and ductus venosus of both fetuses were normal and the bladder of the donor was visible, stage II with normal Doppler findings but not visible bladder, stage III with abnormal Doppler findings in either of the MC fetuses and stage IV with presence of ascites or hydrops in either MC fetus [19].

In the DCTA pregnancies, diagnosis of sFGR was based on the demonstration that firstly, the abdominal circumference at <22 weeks or estimated fetal weight at $\geq$22 weeks was below the 5^{th} percentile of the appropriate reference range [20-22] and secondly, the inter-twin discordance in estimated fetal weight (weight difference divided by the weight of the large twin) was $\geq$25%; the estimated fetal weight at <20 weeks was derived by the formula by Warsof *et al,* [23] and at $\geq$20 weeks it was derived by the formula of Hadlock *et al*, [21]. In all of our cases of sFGR there was Doppler evidence of absent or reversed end diastolic flow (AREDF) in the umbilical artery of the small fetus and they were therefore classified as type II [24].

Endoscopic laser surgery was carried out transabdominally using a semi-rigid 2.0 mm diameter fetoscope (Karl Storz Gmbh, Tuttlingen, Germany), through a 3.3 mm diameter cannula (Cook Medical, Bloomington, Indiana, USA), after the administration of prophylactic antibiotics and local anesthesia. In DC triplet pregnancies with TTTS or sFGR the fetoscope was introduced into the sac of the larger fetus of the MC pair; a 400 µm diameter Nd:YAG laser fibre (Dornier Med Tech, Wessling, Germany) and power output of 40 W was used to coagulate the inter-twin communicating placental vessels as previously described for MC twin pregnancies [7]. In MC triplet pregnancies with TTTS the fetoscope was introduced into the sac of the recipient fetus and laser was used to coagulate the vessels between this fetus and each of the other two fetuses; subsequently, the fetoscope was advanced through the inter-twin membrane into the sac of one of the other fetuses to coagulate the vascular connections between them. In cases of polyhydramnios, amnioreduction was undertaken through the cannula over a period of 10-15 minutes to obtain subjective normalization of the amniotic fluid volume. After a period of rest for one to three hours, the patients were discharged home. Follow up and management of the pregnancies was usually undertaken in the referral hospitals.

Maternal demographic characteristics, ultrasound findings and details of intrauterine intervention were recorded in a database. Pregnancy outcomes were collected into the same database when they became available from the referring hospitals, general practitioners or from the patients themselves.

Comparison and synthesis with results from previous studies

Searches of PubMed and Medline (August 2015) were performed to identify all studies in the English language that reported on the use of endoscopic laser surgery for at least two triplet pregnancies. The inclusion criteria were DCTA or MCTA pregnancies complicated by FFTS and / or sFGR, treated by endoscopic laser and providing outcome data. In case of data duplication or overlap, only the largest or most recent study with available data was included.

Statistical analysis

Data from our study and previous reports were pooled using meta-analytic techniques. Random effects models were used to estimate weighted neonatal survival rates, with 95% confidence interval (CI). Heterogeneity between studies was analyzed using both Higgins' I^2 and Cochrane's Q-test [25,26].

The statistical software package SPSS 20.0 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp) and StatsDirect Version 2.0 (Statsdirect Statistical Software. England. 2013) were used for data analysis.

Results

Study population

During the study period of 1996 to 2015, we performed endoscopic laser coagulation of communicating placental vessels in 47 DCTA and 11 MCTA triplet pregnancies. The DCTA pregnancies included 14 with sFGR type II and 33 with FFTS; in the latter group, the Quintero stage was I in one, II in two, III in 29 and IV in one. In all MCTA pregnancies the FFTS was stage III or IV; in 6 cases there was one donor and one recipient, in 4 cases there were two donors and one recipient and in 1 case there was one donor and two recipients.

DCTA triplet pregnancies with FFTS

In the group of 33 DCTA triplet pregnancies with FFTS, endoscopic laser surgery was performed successfully in all cases at a median gestational age of 18 (range 15-23) weeks (Table 1). There was survival to discharge from hospital in 72.7% babies and there was at least one survivor in 97.0% of the pregnancies. The median gestational age at delivery of live births was 29 weeks and 68.8% were born at <32 weeks.

In 15 pregnancies all three babies survived after delivery at 8-16 weeks following laser surgery. In 10 pregnancies two babies survived. In 8 cases the donor triplet died either in utero or in the neonatal period at 1-14 weeks after laser surgery; the recipient triplet and the separate one were live born and survived. In 1 case, selective fetocide of the donor twin was carried out by intracardiac injection of potassium chloride immediately after the laser ablation at 17 weeks' gestation because, at presentation, this fetus was found to have ventriculomegaly and hyperechogenicity of the cerebral cortex; the other two babies were born 13 weeks later and survived. In another case, treated at 20 weeks' gestation, selective fetocide of the separate fetus was carried out because of the diagnosis of cerebellar atrophy after presentation with ruptured membranes at 29 weeks' gestation; the other two babies were live born and survived. In 7 pregnancies both MC twins died, 6 within two weeks and 1 four weeks after laser surgery; in these cases the separate triplet was live born and survived. In 1 pregnancy all three babies died; the MC pair died two weeks after laser and this was followed by spontaneous birth at 25 weeks' gestation of the separate triplet that died in the neonatal period.

Long term follow up was obtained from 70 of the 72 survivors at a median of 4 (range 1-10) years. In 69 there was normal neurodevelopment; in one ex recipient born at 36 weeks' gestation there is speech delay at the age of 5 years.

DCTA triplet pregnancies with sFGR

In the group of 14 DCTA triplet pregnancies with sFGR, endoscopic laser surgery was performed successfully in all cases at a median gestational age of 18 (range 16-24) weeks (Table 1). There was survival to discharge from hospital in 52.4% babies and there was at least one survivor in 78.6% of the pregnancies. The median gestational age at delivery of live births was 32 weeks and 45.5% were born at <32 weeks.

In 1 pregnancy all three babies survived after delivery at 32 weeks' gestation following laser surgery at 18 weeks. In 9 pregnancies the FGR triplet died within two weeks of laser surgery, but the other two babies were live born 6-20 weeks later and survived. In 1 pregnancy the MC twins died one week after laser surgery at 17 weeks; the separate triplet was live born at 37 weeks and survived. In 3 pregnancies all three babies died; in the first case there was miscarriage within one week of laser surgery, in the second case the MC pair died within two weeks after laser and this was followed by miscarriage of the separate triplet three weeks later and in the third case the pregnancy progressed uneventfully after laser surgery at 17 weeks' gestation but all three fetuses died after prelabor amniorrhexis and chorioamnionitis at 28 weeks.

Long term follow up was obtained from 20 of the 22 survivors and they all had normal neurodevelopment at a median of 4.5 years (range 1 month to 9 years).

MCTA triplet pregnancies

In the group of 11 MCTA triplet pregnancies, there were 6 cases with one donor and one recipient, 6 cases with two donors and one recipient and 1 case with one donor and two recipients. In the first 4 cases of the series, there was laser coagulation of the communicating vessels between the recipient triplet and the other two fetuses. In the subsequent 8 cases, after completion of the first step as above, the fetoscope was advanced through the inter-twin membrane into the sac of one of the other fetuses to coagulate the vascular connections between them.

Endoscopic laser surgery was performed at a median gestational age of 18 (range 16-23) weeks (Table 1). There was survival to discharge from hospital in 33.3% babies and there was at least one survivor in 81.8% of the pregnancies. The median gestational age at delivery of live births was 32 weeks and 66.7% were born at <32 weeks.

In 1 pregnancy all three babies survived after delivery at 30 weeks' gestation following laser surgery at 19 weeks. In 2 pregnancies the donor triplet died within two weeks of laser surgery at 16 and 20 weeks' gestation, respectively, but the other two babies were live born 14 and 8 weeks later and survived. In 6 pregnancies there was only one survivor; donor and recipient triplets died within four weeks after laser surgery. In 2 pregnancies all three babies died; there was miscarriage within one week of laser surgery.

Long term follow up was obtained from 11 of the 13 survivors at a median of 4.3 (range 2.5-9) years. In 10 there was normal neurodevelopment; in 1 ex donor born at 28 weeks' gestation there was moderate neurodevelopmental delay at the age of 2.5 years.

<u>Comparison of survival between the triplet pregnancies</u>

Survival of at least one baby in the DCTA pregnancies with FFTS (97.0%) was not significantly different from that in DCTA pregnancies with sFGR (78.6%, p=0.790) or MCTA pregnancies with FFTS (81.8%, p=0.276). Overall survival for all fetuses in the DCTA pregnancies with FFTS (72.7%) was significantly higher than in DCTA pregnancies with sFGR (52.4%, p=0.003) or MCTA pregnancies with FFTS (33.3%, p<0.0001).

<u>Synthesis with results from previous studies</u>

The literature search identified eight previous studies reporting data on DCTA pregnancies with FFTS treated by endoscopic laser surgery and the combined data from these studies with ours are shown in Table 2 and Figure 1 [9-16]. In a total of 132 such pregnancies, the pooled survival rate of at least one baby was 94.4% (95% CI 90.1-97.6%) and the overall survival for all babies was 76.1 (95% CI 71.9-80.2%); there was no significant heterogeneity between the studies. Delivery in live births at <32 weeks' gestation occurred in 56.7% (43.1-69.8%) of cases.

The literature search identified five previous studies reporting data on MCTA pregnancies with FFTS treated by endoscopic laser surgery and the combined data from these studies with ours are shown in Table 3 and Figure 2 [10-13,15]. In a total of 29 such pregnancies, the pooled survival rate of at least one baby was 80.6% (95% CI 64.9-92.4%) and the overall survival for all babies was 57.5% (95% CI 36.2-77.4%); there was significant heterogeneity between the studies. Delivery in live births at <32 weeks' gestation occurred in 65.4% (47.7-81.1%) of cases.

Discussion

The findings of this study demonstrate the feasibility of endoscopic laser coagulation of communicating placental vessels in the treatment of MC and DC triplet pregnancies complicated by severe FFTS or sFGR. In DC triplets the separate fetus can pose some technical problems in selecting the appropriate site of entry of the fetoscope but in general these problems can easily be overcome; consequently, the outcome of affected pregnancies either by FFTS or sFGR is similar to that in MC twins but with an inevitable higher incidence of early preterm birth. In contrast, in MC triplets endoscopic laser surgery can be technically difficult because of the necessity to coagulate the communicating placental vessels between all three fetuses; as a result of such technical problems or the inability to achieve the objective of complete separation between all fetuses the outcome is poorer than in DC triplets.

We obtained long term outcome for most survivors and recorded normal neurodevelopment from 89 of the 90 survivors from DC triplet pregnancies complicated by FFTS or sFGR and 10 of 11 from the MC triplet pregnancies. However, our follow up was not based on a formal assessment utilizing validated tools at a specific age.

In the combined data from this and previous studies, in DC triplets with FFTS, there was survival of at least one baby in about 95% of pregnancies and survival of 75% of all babies. These results are compatible with those of endoscopic laser surgery in MC twins with severe FFTS. However, in the triplet pregnancies, a very high proportion of survivors, about 60%, were born at <32 weeks' gestation. We have previously reported that in trichorionic triplet pregnancies with three live fetuses at 10-14 weeks' gestation that were managed expectantly, 35% delivered at <33 weeks; the rate in DC triplet pregnancies managed expectantly was 46% [27]. The higher rate of preterm birth in DC triplets complicated by severe FFTS and treated by endoscopic laser surgery is not surprising.

In our DC triplets with sFGR type II there was survival of at least one baby in 79% of pregnancies and survival of 52% of all babies. These results are compatible with findings in our series of 547 MC twin pregnancies with sFGR type II treated with endoscopic laser surgery; there was survival of at least one baby in 72% of pregnancies and 54% of all babies survived [7]. In the DC triplets with sFGR type II, 46% of survivors were born at <32 weeks' gestation. A likely explanation for this lower rate of early preterm birth than in our DC triplets with FFTS treated with endoscopic laser (46% vs. 69%) is that following laser surgery 93% of pregnancies with sFGR continued to delivery with only one or two live fetuses, whereas in those with FFTS the equivalent rate was 54%; consequently, in relation to preterm birth, only 7% in the sFGR group vs 46% in the FFTS group behaved as triplet pregnancies.

In MC triplets with severe FFTS, in comparison to DC triplets with FFTS, survival was poorer. In our MC triplets, at least one baby survived in 82% of pregnancies and 33% of all babies survived, compared to the respective rates of 97% and 73% in our series of DC triplets. The number of MC triplets is too small for definite conclusions to be drawn, but it is certain that endoscopic laser surgery in these pregnancies is considerably more difficult than in DC triplets.

The results from endoscopic laser surgery in triplet pregnancies in our series and those from previous smaller studies allow some general conclusions to be drawn on the effectiveness of such therapy and overall survival rates. However, the total number of cases is still too small to allow accurate assessment of outcome according to subgroups of triplets, including MC and DC complicated by FFTS and / or sFGR, different stages of FFTS, gestational age at therapy or techniques of endoscopic laser surgery.

Figure Legends

Figure 1. Pooled estimates of rates of at least one survivor and survival among all babies in dichorionic triplet pregnancies treated with laser coagulation of placental vessels for feto- fetal transfusion syndrome.

Figure 2. Pooled estimates of rates of at least one survivor and survival among all babies in monochorionic triplet pregnancies treated with laser coagulation of placental vessels for feto- fetal transfusion syndrome.

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Table 1. Outcome of our triplet pregnancies treated by endoscopic laser surgery.

Outcome measure	**DCTA, TTTS (n=33)**	**DCTA, sFGR (n=14)**	**MCTA, TTTS (n=11)**
GA at laser in w, median (range)	18 (15-23)	18 (16-24)	18 (16-23)
Survival, n (%)			
Three	15 (45.5)	1 (7.1)	1 (9.1)
Two	10 (30.3)	9 (64.3)	2 (18.2)
One	7 (21.2)	1 (7.1)	6 (54.5)
≥ one	32 (97.0)	11 (78.6)	9 (81.8)
Overall	72 (72.7)	22 (52.4)	13 (39.4)
GA at delivery of live births in w			
Median (range)	29 (24-36)	32 (28-36)	32 (28-42)
<32 w, n/N (%)	22/32 (68.8)	5/11 (45.5)	6/9 (66.7)

DCTA = dichorionic triamniotic; MCTA = monochorionic triamniotic; TTTS = twin-to-twin transfusion syndrome; sFGR = selective fetal growth restriction; GA = gestational age.

Table 2. Studies reporting on endoscopic laser surgery for fetofetal transfusion syndrome in dichorionic triamniotic triplet pregnancy

Author	Period	Gestation at laser, median (range)	Total (n)	Stage 3/4, n (%)	Survival of ≥1 baby, n/N (%, 95% CI)	Overall survival n/N (%, 95% CI)	Live birth at <32w n/N (%, 95% CI)
Van Schoubroeck *et al.,* 2004 [9]	1996-2002	20 (18-23)	5	5 (100)	5/5 (100, 47.8-100)	12/15 (80.0, 51.9-95.7)	4/5 (80.0, 28.4-99.5)
De Lia *et al.,* 2009 [11]	1992-2008	21 (18-25)	8	7 (87.5)	8/8 (100, 63.1-100)	20/24 (83.3, 62.6-95.3)	2/8 (25.0, 3.2-65.1)
Chmait *et al.,* 2010 [12]	1998-2008	20 (16-24)	40	26 (65.0)	37/40 (92.5, 79.6-98.4)	92/120 (76.7, 68.1-83.9)	Not known
Diemert *et al.,* 2010 [13]	2004-2008	20 (17-23)	13	9 (69.2)	11/13 (84.6, 54.5-98.1)	27/36 (75.0, 57.8-87.9)	7/11 (63.6, 30.8-89.1)
Peeters *et al.,* 2012 [14]	2000-2012	18 (15-25)	8	4 (50.0)	8/8 (100, 63.1-100)	19/24 (79.2, 57.8-92.9)	4/8 (50.0, 15.7-84.3)
Argoti *et al.,* 2014 [15]	2005-2011	20 (15-25)	16	13 (81.2)	16/16 (100, 79.4-100)	39/48 (81.3, 67.4-91.1)	Not known
Ishi *et al.,* 2014 [16]	2007-2013	21 (16-25)	9	6 (66.7)	9/9 (100, 66.4-100)	20/27 (74.1, 53.7-88.9)	4/9 (44.4, 13.7-78.8)
Our study*	1996-2015	18 (15-23)	33	30 (90.9)	32/33 (97.0, 84.2-100)	72/99 (72.7, 62.9-81.2)	22/32 (68.8, 50.0-83.9)
Pooled analysis, %, (95% CI)			132		126/132 (94.4, 90.1-97.6)	301/393 (76.1, 71.9-80.2)	43/73 (56.7, 43.1-69.8)
Cochrane's Q (P value)					4.3230 (0.7419)	2.0919 (0.9546)	6.8491 (0.2321)
I^2 statistic, [(%), 95% CI]					0 (0-56.3)	0 (0-56.3)	27 (0-70.7)

* Including data from Sepulveda *et al* [10]; CI = Confidence intervals.

Table 3. Studies reporting on endoscopic laser surgery for fetofetal transfusion syndrome in monochorionic triamniotic triplet pregnancy

Author	**Period**	**Gestation at laser, median (range)**	**Total (n)**	**Stage 3/4, n (%)**	**Survival of ≥1 baby, n/N (%, 95% CI)**	**Overall survival n/N (%, 95% CI)**	**Live birth at <32w n/N (%, 95% CI)**
De Lia *et al.,* 2009 [11]	1992-2008	21 (18-25)	2	1 (50.0)	1/2 (50.0, 1.3-98.7)	3/6 (50.0, 11.8-88.2)	1/2 (50.0, 1.3-98.7)
Chmait *et al.,* 2010 [12]	1998-2008	19 (17-22)	6	2 (33.3)	5/6 (83.3, 35.9-99.6)	11/18 (61.1, 35.7-82.7)	4/5 (80.0, 28.4-99.5)
Diemert *et al.,* 2010 [13]	2004-2008	19 (18-20)	3	1 (33.3)	2/3 (66.7, 9.4-99.2)	5/9 (55.6, 21.2-86.3)	1/2 (50.0, 1.3-98.7)
Ishi *et al.,* 2014 [15]	2007-2013	20 (17-22)	7	4 (57.1)	7/7 (100, 59.0-100)	18/21 (85.7, 63.7-97.0)	5/7 (71.4, 29.0-96.3)
Our study*	1996-2015	18 (16-23)	11	11 (100.0)	9/9 (81.8, 48.2-97.7)	11/33 (33.3, 18.0-51.8)	6/9 (66.7, 29.9-92.5)
Pooled analysis, %, (95% CI)			29		24/29 (80.6, 64.9-92.4)	48/87 (57.5, 36.2-77.4)	17/25 (65.4, 47.7-81.1)
Cochrane's Q (P value)					4.3804 (0.3570)	15.9245 (0.0031)	0.9285 (0.9204)
I^2 statistic, [(%), 95% CI]					8.7 (0-67.1)	74.9 (6.1-87.9)	0 (0-64.4)

* Including data from Sepulveda *et al* [10]; CI = Confidence intervals.