Cardiovascular compromise in monochorionic twins

Gijtenbeek, M.

Author: Gijtenbeek, M.
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CHAPTER 5

PERIOPERATIVE FETAL HEMODYNAMIC CHANGES IN TWIN-TWIN TRANSFUSION SYNDROME AND NEURODEVELOPMENTAL OUTCOME AT TWO-YEARS OF AGE

M. Gijtenbeek
M.C. Haak
T.J.P. Huberts
J.M. Middeldorp
F.J.C.M. Klumper
F. Slaghekke
E. Lopriore
D. Oepkes
J.M.M. van Klink

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ABSTRACT

Objective: To investigate whether perioperative fetal hemodynamic changes in twin-twin transfusion syndrome (TTTS) are associated with neurodevelopmental impairment (NDI) at two-years.

Methods: Doppler parameters of three sonograms (day before, first day after and one week after laser surgery for TTTS) were assessed for correlation with neurodevelopmental outcome at two-years (2008-2016). NDI was defined as: cerebral palsy, deafness, blindness, and/or a Bayley-III cognitive/motor developmental test-score > 2 SD below the mean.

Results: Long-term outcome was assessed in 492 TTTS survivors. NDI was present in 5% (24/492). After adjustment for severe cerebral injury (present in 4%), associated with NDI were: middle cerebral artery peak systolic velocity (MCA-PSV) > 1.5 multiples of the median (MoM) one day after surgery (odds ratio [OR] 4.96, 95% confidence interval [CI] 1.17-21.05, p = 0.03), a change from normal umbilical artery pulsatility index (UA-PI) pre-surgery to UA-PI > p95 post-surgery (OR 4.19, 95% CI 1.04-16.87, p = 0.04), a change from normal to MCA-PSV > 1.5 MoM (OR 4.75, 95% CI 1.43-15.77, p = 0.01).

Conclusion: Perioperative fetal hemodynamic changes in TTTS pregnancies treated with laser are associated with poor neurodevelopmental outcome. Prospective research on the cerebrovascular response to altered hemodynamic conditions is necessary to further understand the cerebral autoregulatory capacity of the fetus in relation to neurodevelopmental outcome.

INTRODUCTION

Twin-twin transfusion syndrome (TTTS) is a severe complication of monochorionic twin pregnancies and is caused by an unbalanced blood flow between the donor and recipient twin. The risk of fetal death is approximately 90% if left untreated.[1] The best possible outcome is achieved with fetoscopic laser surgery of the vascular anastomoses, which has an overall survival rate of 74-87%.[2, 3] In TTTS survivors, the incidence of neurodevelopmental impairment (NDI) is on average 10%.[4] Possible risk factors for NDI are advanced gestational age (GA) at intervention, advanced TTTS stage, lower GA at birth, lower birth weight and severe neonatal cerebral injury.[4, 5]

Hemodynamic changes in fetuses may cause fetal developmental abnormalities, for example malformation of cortical development.[6] In case of single fetal demise in monochorionic twin pregnancies, 26% of co-twins suffer from severe cerebral injury,[7] which is thought to be caused by acute fetal exsanguination into the low pressure circulation of the demised fetus through the placental vascular anastomoses. In TTTS, ablation of the vascular anastomoses also results in hemodynamic changes in both the donor and the recipient fetus, with a possible effect on the fetal brain. Whether there is a direct effect on neurodevelopment is unknown. One study showed that a post-laser cerebroplacental ratio[8] < 1.0 was a risk factor for slightly lower developmental test-scores at the age of two.[9]

The aim of this study was to evaluate perioperative fetal hemodynamic changes in TTTS pregnancies treated with fetoscopic laser coagulation (FLC) in relation to neurodevelopmental outcome at the age of two in a large consecutive cohort of TTTS survivors.

METHODS

The Leiden University Medical Center (LUMC) serves as the national referral center for fetal therapy in the Netherlands. Surviving children of consecutive monochorionic twin pregnancies with TTTS treated with fetoscopic laser surgery between March 2008 and April 2016 were eligible for this study. Details on the laser technique at our center[8, 10] and short-term outcome results have previously been reported.[11] The selective laser technique was applied between January 2008 and March 2008. From March 2008 until July 2012 either the selective or the Solomon technique was used, as part of the Solomon trial.[2] After conclusion of the trial, the Solomon technique became the standard technique for all procedures. For this study we retrieved antenatal and neonatal data from our databases. The study was approved by the institutional review board of the LUMC.

Antenatal parameters

TTTS was diagnosed using standard European diagnostic ultrasound criteria[12] and pregnancies were staged prospectively according to the Quintero staging system.[13] We recorded GA at laser surgery, TTTS stage, antenatal and/or postnatal twin anemia polycythemia sequence (TAPS), recurrence of TTTS and fetal demise of the co-twin. The presence of TAPS was identified according to previously published criteria.[14] Doppler parameters of three antenatal sonograms (day before laser surgery, first day after laser surgery and approximately one week after laser surgery) were obtained and evaluated for abnormalities in: umbilical artery (UA) pulsatility index (UA-PI) and end-diastolic velocity (UA-EDV), middle cerebral artery PI (MCA-PI) and peak systolic velocity (MCA-PSV), and pattern of the ductus venosus (DV). UA Doppler was defined as abnormal when EDV was absent or reversed, or the PI was above the 95^{th} percentile (> p95).[15] Blood flow during the atrial contraction in the DV was classified as normal (positive a-wave) or abnormal (absent or reversed a-wave). MCA-PSV was converted to multiples of the median (MoM), and > 1.5 MoM was considered abnormal.[16] The cerebroplacental ratio (CPR) was calculated by dividing MCA-PI by UA-PI. An abnormal CPR was categorically defined at < 1.0.[17]

Postnatal parameters

The following neonatal data were recorded: GA at birth, birth weight and severe cerebral injury. Small for gestational age (SGA) was defined as birth weight < p10. Severe neonatal cerebral injury was defined as at least one of the following: intraventricular hemorrhage ≥ Grade III,[18] cystic periventricular leukomalacia ≥ Grade II,[19] ventricular dilatation ≥ 97^{th} percentile,[20] porencephalic cysts or arterial or venous infarction detected on cerebral imaging.

Since 2008, TTTS survivors have been routinely assessed in our long-term follow-up outpatient clinic at the age of two, corrected for prematurity (two years after the estimated date of delivery). Previous results on neurodevelopmental outcome up to 2016 have been reported.[5, 21] In short: a standardized follow-up evaluation included a physical and neurological examination and an assessment of cognitive and motor development with use of the Dutch version of the Bayley Scales of Infant and Toddler Development III (Bayley-III).[22] NDI was defined as the presence of: cerebral palsy (≥ Grade II),[23] deafness, blindness, and/or a Bayley-III cognitive or motor developmental test-score > 2 SD below the mean.

Statistical analysis

Data are reported as n (%), mean (standard deviation [SD]) or median (interquartile range [IQR]), as appropriate. Baseline characteristics were compared with the use of the Mann-Whitney U test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables, as appropriate. An analysis of risk factors (perioperative Doppler parameters) possibly predicting adverse long-term outcome (NDI) was conducted using univariate and multivariate logistic regression models with a generalized estimated equation (GEE) module to account for the effect that observations of twin pairs are not independent. The multivariable model included variables that showed a significant association in the univariable analysis. The results are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Data were analyzed using SPSS v23 (IBM, USA) and the level of significance was set at $p < 0.05$. P values were adjusted for multiple hypotheses testing using the false discovery rate (FDR) correction (FDR threshold of 0.1).[24]

RESULTS

During the study period, 398 consecutive TTTS pregnancies were treated with fetoscopic laser surgery. 119 pregnancies were excluded (no follow-up n = 51 (13%), double fetal/ neonatal death n = 50 (13%), incomplete follow-up n = 16 (4%), Tay Sachs disease n = 1, neurofibromatosis type I n = 1). Of the remaining 279 pregnancies, 492 children were enrolled in this study.

Table 1 presents the baseline characteristics and Table 2 presents the perinatal characteristics of the children included in this study. Extreme prematurity (< 28 weeks gestation) occurred in 26 out of 279 (9.3%) pregnancies. NDI was detected in 24/492 survivors (4.9%, 95% CI 3.3-8.9). Among the perinatal characteristics, only severe cerebral injury, detected in 21/492 (4.3%, 95% CI 2.8-8 4) live-born neonates, was significantly associated with the occurrence of NDI (OR 17.15, 95% CI 6.24-47.20). Severe cerebral injury was detected in 8/24 (33%) cases with NDI and in 13/468 (3%) cases without NDI ($p < 0.001$). Of the twins with NDI, two donors (2/12) and six recipients (6/12) had severe cerebral injury, of whom one donor was suspected of intracranial hemorrhage on ultrasound and MRI after FLC. There was no difference in GA at laser, TTTS stage, incomplete laser, fetal demise of the co-twin, GA at birth or birth weight between cases with NDI and those without. Pregnancies of three of the cases with NDI (two donors and one recipient) were complicated by post-laser TAPS, with reversal of the intertwin transfusion (the former TTTS donor was the TAPS recipient and vice-versa).

Table 1. Perinatal characteristics of 279 TTTS pregnancies treated with laser surgery

Characteristics	Value
Gestational age at laser surgery (weeks)	20.0 (17.4 - 22.6)
TTTS stage	
I	32 (12)
II	91 (33)
III	149 (53)
IV	7 (3)
TAPS or recurrent TTTS	33 (12)
Fetal demise of co-twin	51 (18)
Gestational age at birth (weeks)	33.1 (30.3 - 36.0)

Data are presented as median (IQR) or n (%). TTTS, twin twin transfusion syndrome; TAPS, twin anemia polycythemia sequence.

Table 2. Characteristics of 492 TTTS survivors

Characteristics	NDI (n = 24)	No NDI (n = 468)	p-value
Recipient	12 (50)	232 (50)	0.97
GA at laser surgery (weeks)	20.3 (17.5 - 23.2)	20.0 (17.4 - 22.6)	0.75
TTTS stage			
I	3 (13)	57 (12)	1.00
II	10 (42)	149 (32)	0.32
III	10 (42)	250 (53)	0.26
IV	1 (4)	12 (3)	0.48
TAPS	3 (13)	50 (11)	0.48
Recurrent TTTS	1 (4)	6 (1)	0.30
Fetal demise of co-twin	2 (8)	49 (11)	1.00
GA at birth (weeks)	32.3 (30.0 - 34.6)	33.1 (30 4 - 35.9)	0.33
37-40	3 (13)	33 (7)	0.41
33-37	7 (29)	220 (47)	0.09
26-33	12 (50)	207 (44)	0.58
24-26	2 (8)	8 (2)	0.08
Birth weight (grams)	1655 (1260 - 2051)	1822 (1350 - 2293)	0.27
Small for gestational age	11 (46)	201 (43)	0.78
Severe neonatal cerebral injury	8 (33)	13 (3)	**<0.001**

Data are presented as median (IQR) or n (%). TTTS, twin-twin transfusion syndrome; NDI, neurodevelopmental impairment; TAPS, twin anemia polycythemia sequence.

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Table 3. Analysis of hemodynamic risk factors for neurodevelopmental impairment

		NDI (n = 24)
Absent/reversed UA EDV	Pre-surgery	1 (5)
	Day 1	0 (0)
	Week 1	1 (5)
UA PI > p95	Pre-surgery	1 (6)
	Day 1	2 (15)
	Week 1	4 (20)
Change UA from normal to PI to > p95		4 (27)
MCA PSV > 1.5 MoM	Pre-surgery	1 (5)
	Day 1	5 (36)
	Week 1	4 (24)
Change MCA PSV from normal to > 1.5 MoM		6 (43)
MCA PI < p5	Pre-surgery	3 (21)
	Day 1	1 (8)
	Week 1	2 (12)
CPR < 1.0	Pre-surgery	8 (50)
	Day 1	3 (27)
	Week 1	1 (6)
Absent/reversed DV a-wave	Pre-surgery	1 (5)
	Day 1	1 (10)
	Week 1	1 (5)

Data are presented as n (%). NDI, neurodevelopmental impairment; OR, odds ratio; FDR, false discovery rate; CI, confidence interval; UA, umbilical artery; EDV, end-diastolic velocity;

The main study findings are summarized in Table 3. After correction for multiple hypotheses testing, NDI was associated with MCA-PSV > 1.5 MoM the first day after surgery and a change from normal UA-PI to UA-PI > p95 and normal MCA-PSV to MCA-PSV > 1.5 MoM after laser. When adjusted for severe cerebral injury, these parameters remained statistically significant. An MCA-PSV > 1.5 MoM the first day after surgery, detected in five cases, increased the risk of NDI almost five times (OR 4.96, 95% CI 1.17-21.05, p = 0.03). Pre-surgery, these five infants had normal MCA-PSV Dopplers. Of the NDI cases, 27% had a normal UA-PI prior to laser and an abnormal UA-PI after surgery (first day after or after one week), which increased the risk of NDI four times

No NDI (n = 468)	Crude OR (95% CI)	FDR- adjusted p value
54 (12)	0.38 (0.07 - 2.06)	0.58
19 (5)	0.0	1.00
11 (3)	2 20 (0.34 - 14.50)	0.69
47 (12)	0.50 (0.07 - 3.75)	0.77
18 (5)	3 29 (0.77 - 14.11)	0.31
33 (8)	3 27 (1.15 - 9.33)	0.11
20 (7)	5 23 (1.62 - 16.89)	**0.04**
23 (6)	1.32 (0.30 - 5.86)	0.95
25 (8)	6.49 (2.06 - 20 46)	**0.01**
20 (5)	5 47 (1.32 - 22.63)	0.10
28 (10)	6.22 (2.12 - 18.23)	**0.02**
123 (34)	0.59 (0.17 - 2.02)	0.73
83 (29)	0.16 (0.02 - 1.28)	0.28
70 (18)	0.63 (0.12 - 3 29)	0.83
156 (45)	0.99 (0.40 - 2 45)	1.02
81 (31)	1.06 (0 29 - 3.84)	1.04
80 (22)	0.20 (0.01 - 2.47)	0.50
61 (15)	0.69 (0.15 - 3.20)	1 27
49 (16)	0.76 (0.12 - 4.72)	0.97
16 (4)	1.17 (0.11 - 12.98)	1.06

PI, pulsatility index; MCA, middle cerebral artery; PSV, peak systolic velocity; MoM, multiples of the median; CPR, cerebroplacental ratio; DV, ductus venosus.

(OR 4.19, 95% CI 1.04-16.87, p = 0.04). A change from normal MCA-PSV to MCA-PSV > 1.5 MoM (either one day or one week after FLC) occurred in 43% of children with NDI, and increased the risk of NDI almost five times (OR 4.75, 95% CI 1.43-15.77, p = 0.01). Abnormal UA-PI and MCA-PSV were equally distributed between recipients and donors. One of six fetuses with an MCA-PSV > 1.5 MoM after laser surgery developed TAPS, the remaining five fetuses had only transient increased MCA-PSV without evidence of TAPS.

DISCUSSION

This study shows that perioperative fetal hemodynamic changes in TTTS pregnancies treated with laser surgery are associated with poor neurological outcome. Hemodynamic changes, leading to increased MCA-PSV or UA-PI after laser surgery, were found to be a risk factor for NDI. Since 5% of children were affected by NDI, we advise routine long-term follow-up for all TTTS twins, especially for those with deterioration of Doppler flows.

The fetal hemodynamic changes in TTTS pregnancies undergoing laser surgery has been the subject of debate in a few studies.[8, 25-28] In only one small cohort, studying 99 children, a correlation was found between an abnormal post-laser cerebroplacental ratio and long-term developmental outcomes.[8] Data from our study further increases the awareness regarding the potential relationship between fetal perioperative hemodynamic changes and NDI.

It has been suggested that the temporary elevation in MCA-PSV is a benign condition.[28] An elevated MCA-PSV may however reflect fetal anemia, as part of a TTTS/TAPS spectrum, at time of diagnosis. Fetal anemia may result in a hypoxic environment and may have a deteriorating effect on fetal brain development. The mechanism underlying the elevated MCA-PSV in the recipient post-laser in the absence of TAPS is not fully understood. Possibly, there is a period of (mal)adaptation in these fetuses, resulting in increased brain vulnerability. Another suggestion is that amnioreduction, which is performed to relieve pressure at the end of the laser surgery, leads to the so called 'placental steal phenomenon'.[29] Brief episodes of hemodynamic imbalance, which may cause hyper- and hypoperfusion of the fetal brain, might result in (transient) cerebral lesions that remain undetected by routine monitoring techniques.[26] In the group without NDI, the majority of fetuses had a normal UA-PI and MCA-PI post-laser, indicating normal autoregulation. There was a trend towards higher rates of abnormalities of UA-PI and MCA-PI post-laser in NDI cases, possibly reflecting insufficient autoregulatory capacities in these fetuses. This hypothesis is supported by results from the study by Delabaere *et al.*,[20] in which cases with fetal demise had a higher mean UA-PI and lower mean MCA-PI, indicating a detrimental effect of cerebroplacental redistribution. Even though the number of SGA fetuses was similar between NDI and no-NDI cases, we cannot rule out a possible effect of fetal growth restriction (and therefore an increased UA-PI) on neurodevelopment.[31] Future prospective studies investigating the cerebrovascular response to altered hemodynamic conditions and its effect on neurodevelopment are necessary to further understand the cerebral autoregulatory capacity of the mid-trimester human fetus.

In accordance with a recent report from our group,[21] we did not find an association between TTTS stage, incomplete laser, fetal demise of the co-twin or GA at birth and NDI, factors previously thought to be associated with NDI. The lack of correlation between GA at birth and NDI can be explained by improvement in neonatal intensive care treatment for premature neonates in combination with the low absolute number of TTTS survivors with severe NDI.

The primary strength of this study lies in the number of TTTS survivors to identify risk factors for neurodevelopment. The use of an extensive dataset with perioperative Doppler parameters and perinatal variables allowed for a robust assessment of risk factors. All pre-operative and post-operative sonograms were performed by a limited number of sonographers experienced in the management of monochorionic twin pregnancies. Routine neonatal cerebral imaging was performed to rule out severe cerebral injury. And lastly, neurodevelopmental assessments were conducted by independent and experienced personnel. Despite these strengths, our findings may be limited by several factors. This was a retrospective study, although the data were collected prospectively. Ultrasound data were not complete in all cases. Prenatal detailed neurosonography or fetal MRI is not routinely performed at our center; possible transient cerebral abnormalities could, therefore, not be ruled out. The question remains whether cerebral injury occurred during pregnancy, as a result of the TTTS or FLC, or after delivery. Another important limitation of long-term follow-up studies, including ours, is the inability to obtain 100% inclusion. However, less than 15% was lost to follow-up, which is lower than generally encountered in the literature. Even though this study includes a large number of subjects, the absolute number of NDI cases was still limited. Furthermore, a control group of uncomplicated monochorionic or dichorionic twins was not available. Although generally applied in twin studies,[8, 32, 33] the cut-off value of < 1.0 for abnormal CPR results from studies in singletons.[17, 34] And lastly, the follow-up evaluation was at two-years of age. Although this age allows for strong cognitive, language, personal-social and motor assessment, some developmental problems become more apparent at a later age such as attention-deficit disorder or speech language problems.[35]

CONCLUSIONS

Our study indicates that perioperative fetal hemodynamic changes in TTTS twins treated with laser surgery are associated with poor neurological outcome. We advise routine long-term follow-up for all TTTS twins, especially for those with signs of hemodynamic deterioration after laser surgery. Parents can be informed that the risk of neurodevelopmental impairment at two-years of age is approximately 5%. Since 4% of the children were affected by severe cerebral injury, large prospective studies are required to examine the impact of preoperative fetal cranial imaging and progressive changes on neurodevelopment after laser surgery.

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PART III

POSTNATAL CIRCULATION