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Perioperative fetal hemodynamic changes in twin-twin transfusion syndrome and neurodevelopmental outcome at two years of age

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Abstract

Objective: To investigate whether perioperative fetal hemodynamic changes in twin-to-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 1 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 > 2SD 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) 1 day after surgery (odds ratio [OR] 4.96; 95% confidence interval [CI]: 1.17-21.05, P = .03), a change from normal umbilical artery pulsatility index (UA-PI) presurgery to UA-PI >p95 postsurgery (OR 4.19; 95% CI: 1.04-16.87, P = .04), a change from normal to MCA-PSV >1.5MoM (OR 4.75; 95% CI: 1.43-15.77, P = .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.

1 | 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% to 87%.[2,3] In TTTS survivors, the incidence of neurodevelopmental impairment (NDI) is on average 10%.[4] Possible risk factors for NDI are advanced

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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 postlaser cerebroplacental ratio (CPR)[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 surgery in relation to neurodevelopmental outcome at the age of two in a large consecutive cohort of TTTS survivors.

What's already known?

- Hemodynamic changes in fetuses may cause fetal developmental abnormalities.
- Hemodynamic changes caused by single fetal demise in monochorionic twins leads to cerebral injury in over a quarter of co-twins.

What does this study add?

- Perioperative fetal hemodynamic changes in TTTS pregnancies treated with laser surgery are associated with poor neurodevelopmental outcome.
- Routine long-term follow-up should be offered to all TTTS twins, especially to those with hemodynamic deterioration after laser surgery.

2 | 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 centre[2,10] and short-term outcome results have previously been reported.[11] 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.

2.1 | 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 1 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 95th 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 CPR was calculated by dividing MCA-PI by UA-PI. An abnormal CPR was categorically defined at <1.0.[17]

2.2 | 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 birthweight <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 ≥97th 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 (2 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 > 2SD below the mean.

2.3 | 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 χ^2 test test or Fisher's exact test for categorical

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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 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 $P < .05$. P values were adjusted for multiple hypotheses testing using the false discovery rate (FDR) correction (FDR threshold of 0.1).[24]

TABLE 1 Perinatal characteristics of 279 TTTS pregnancies treated with laser surgery

Characteristics	Value
Gestational age at laser surgery (weeks)[a]	20.0 (17.4-22.6)
TTTS stage n (%)	
Stage 1	32 (12)
Stage 2	91 (33)
Stage 3	149 (53)
Stage 4	7 (3)
TAPS or recurrent TTTS n (%)	33 (12)
Fetal demise of co-twin n (%)	51 (18)
Gestational age at birth (weeks)[a]	33.1 (30.3-36.0)

[a]Median (IQR).
Abbreviations: IQR, interquartile range; TAPS, twin anemia polycythemia sequence; TTTS, twin-twin transfusion syndrome.

3 | RESULTS

During the study period, 398 consecutive TTTS pregnancies were treated with fetoscopic laser surgery. One hundred nineteen 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 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 ($P < .001$). 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

TABLE 2 Characteristics of 492 TTTS survivors

Characteristic	NDI (n = 24)	No NDI (n = 468)	*P*-value
Recipient n (%)	12 (50)	232 (50)	.97
GA at laser surgery (weeks)[a]	20.3 (17.5-23.2)	20.0 (17.4-22.6)	.75
TTTS stage n (%)			
Stage 1	3 (13)	57 (12)	1.00
Stage 2	10 (42)	149 (32)	.32
Stage 3	10 (42)	250 (53)	.26
Stage 4	1 (4)	12 (3)	.48
TAPS n (%)	3 (13)	50 (11)	.48
Recurrent TTTS n (%)	1 (4)	6 (1)	.30
Fetal demise of co-twin n (%)	2 (8)	49 (11)	.00
GA at birth (weeks)[a]	32.3 (30.0-34.6)	33.1 (30.4-35.9)	.33
37-40 n (%)	3 (13)	33 (7)	.41
33-37 n (%)	7 (29)	220 (47)	.09
26-33 n (%)	12 (50)	207 (44)	.58
24-26 n (%)	2 (8)	8 (2)	.08
Birthweight (g)[a]	1655 (1260-2051)	1822 (1350-2293)	.27
Small for gestational age n (%)	11 (46)	201 (43)	.78
Severe neonatal cerebral injury n (%)	8 (33)	13 (3)	<.001

[a]Median (IQR).
Abbreviations: IQR, interquartile range; NDI, neurodevelopmental impairment; TAPS, twin anemia polycythemia sequence; TTTS, twin-twin transfusion syndrome.

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TABLE 3 Analysis of hemodynamic risk factors for neurodevelopmental impairment

		NDI (n = 24)	No NDI (n = 468)	Crude OR (95% CI)	FDR adjusted *P* value
Absent/reversed UA EDV n (%)	Presurgery	1 (5)	54 (12)	0.38 (0.07-2.06)	.58
	Day 1	0 (0)	19 (5)	0.0	1.00
	Week 1	1 (5)	11 (3)	2.20 (0.34-14.50)	.69
UA PI > p95 n (%)	Presurgery	1 (6)	47 (12)	0.50 (0.07-3.75)	.77
	Day 1	2 (15)	18 (5)	3.29 (0.77-14.11)	.31
	Week 1	4 (20)	33 (8)	3.27 (1.15-9.33)	.11
Change UA from normal to PI to > p95 n (%)		4 (27)	20 (7)	5.23 (1.62-16.89)	.04
MCA PSV > 1.5 MoM n (%)	Presurgery	1 (5)	23 (6)	1.32 (0.30-5.86)	.95
	Day 1	5 (36)	25 (8)	6.49 (2.06-20.46)	.01
	Week 1	4 (24)	20 (5)	5.47 (1.32-22.63)	.10
Change MCA PSV from normal to > 1.5MoM n (%)		6 (43)	28 (10)	6.22 (2.12-18.23)	.02
MCA PI < p5 n (%)	Presurgery	3 (21)	123 (34)	0.59 (0.17-2.02)	.73
	Day 1	1 (8)	83 (29)	0.16 (0.02-1.28)	.28
	Week 1	2 (12)	70 (18)	0.63 (0.12-3.29)	.83
CPR < 1.0 n (%)	Presurgery	8 (50)	156 (45)	0.99 (0.40-2.45)	1.02
	Day 1	3 (27)	81 (31)	1.06 (0.29-3.84)	1.04
	Week 1	1 (6)	80 (22)	0.20 (0.01-2.47)	.50
Absent/reversed DV a-wave n (%)	Presurgery	1 (5)	61 (15)	0.69 (0.15-3.20)	1.27
	Day 1	1 (10)	49 (16)	0.76 (0.12-4.72)	.97
	Week 1	1 (5)	16 (4)	1.17 (0.11-12.98)	1.06

Abbreviations: CI, confidence interval; CPR, cerebroplacental ratio; DV, ductus venosus; EDV, end-diastolic velocity; FDR, false discovery rate; MCA, middle cerebral artery; MoM, multiples of the median; NDI, neurodevelopmental impairment; OR, odds ratio; PI, pulsatility index; PSV, peak systolic velocity; UA, umbilical artery.

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 postlaser TAPS, with reversal of the inter-twin transfusion (the former TTTS donor was the TAPS recipient and vice-versa).

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 >1.5MoM after laser. When adjusted for severe cerebral injury, these parameters remained statistically significant. An MCA-PSV >1.5MoM 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 = .03). Presurgery, 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 1 week), which increased the risk of NDI four times (OR 4.19; 95% CI: 1.04-16.87, P = .04). A change from normal MCA-PSV to MCA-PSV >1.5MoM (either 1 day or 1 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 = .01). Abnormal UA-PI and MCA-PSV were equally distributed between recipients and donors. One of six fetuses with an MCA-PSV >1.5MoM after laser surgery developed TAPS, the remaining five fetuses had only transient increased MCA-PSV without evidence of TAPS.

4 | 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 postlaser CPR and long-term developmental outcomes.[8] Data from our study further increase 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

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deteriorating effect on fetal brain development. The mechanism underlying the elevated MCA-PSV in the recipient postlaser 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 postlaser, indicating normal autoregulation. There was a trend toward higher rates of abnormalities of UA-PI and MCA-PI postlaser in NDI cases, possibly reflecting insufficient autoregulatory capacities in these fetuses. This hypothesis is supported by results from the study by Delabaere et al,[30] 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 midtrimester 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 preoperative and postoperative 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 of 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 2 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]

5 | CONCLUSION

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 NDI at 2 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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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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