Brain matters in twin-twin transfusion syndrome

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Chapter 5

Behavioral outcome in twin-twin transfusion syndrome survivors treated with laser surgery

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Abstract

Objective
Evaluate the incidence of and risk factors for behavioral problems in twin-twin transfusion syndrome (TTTS) survivors treated with fetoscopic laser coagulation.

Design
Observational cohort study.

Setting
National referral center for fetal therapy, Leiden University Medical Center, the Netherlands.

Patients
Behavioral outcome was assessed in 417 TTTS survivors, at the age of 2 years.

Interventions
Parents completed the Child Behavior Checklist for their twins. Antenatal, neonatal and follow-up data including Bayley-III and a neurological exam were recorded from the medical database.

Main outcome measures
The incidence of risk factors for behavioral problems.

Results
332 twin pregnancies (664 fetuses) were treated with fetoscopic laser for TTTS between 2008 and 2015. For 517 children eligible for follow-up, 417 (81%) Child Behavior Checklist questionnaires were completed. The study group was born at a mean gestational age of 32.8 weeks $\pm$ 3.2. Total behavioral problems within the borderline to clinical range were reported in 8% (95% CI 5.9 to 11.2) of survivors, compared with 10% in the general Dutch population ($p = 0.12$). No difference between donors and recipients was detected ($p = 0.84$). Internalizing and externalizing problems were reported in 9.4% (95% CI 6.9 to 12.6) and 11.5% (95% CI 8.8 to 15.0), respectively. Severe neurodevelopmental impairment was more frequent in the children with behavioral problems. High maternal educational level was associated with lower behavioral problem scores.

Conclusion
Parents of twins treated with fetoscopic laser therapy for TTTS do not report more behavioral problems compared with general population norms. More behavioral problems are reported in children with severe neurodevelopmental impairment.

Introduction

Twin-to-twin-transfusion-syndrome (TTTS) is a severe complication of monochorionic (MC) twin gestations. TTTS develops in approximately 10% of MC twin pregnancies and is the result of an unbalanced net transfusion of blood between one twin, the donor, and the other twin, the recipient, via placental vascular anastomoses. The donor twin becomes hypovolemic, resulting in oliguria and oligohydramnios. The recipient becomes hypervolemic, resulting in polyuria and polyhydramnios.(1) Once TTTS is diagnosed by ultrasound, fetoscopic laser coagulation of the placental vascular anastomoses is the treatment of choice.

Increased survival rate and improved short-term outcome of both donor and recipient has led to a shift in focus towards the long-term neurodevelopmental outcome of TTTS survivors. Long-term follow-up studies report cerebral palsy in 3 to 12% (overall 6%) of survivors and neurodevelopmental impairment (NDI) in 4 to 17% (overall 10%).(2) However, even in children without obvious neurodevelopmental impairment, subtle problems may occur including behavioral and social-emotional problems such as attention problems and rule-breaking behavior. These 'subtle' problems can have a significant impact on care and educational requirements of children. For example, hyperactive/inattentive behavior may result in fewer opportunities to learn in the class room, thereby reducing opportunities to develop age-appropriate academic skills. Up until now, these outcome measures are lacking in the follow-up of TTTS survivors treated with fetoscopic laser surgery. The aim of this study was to assess the behavioral outcome of TTTS survivors treated with laser surgery and to evaluate potential risk factors for long-term problems.

Methods

Participants

All TTTS survivors treated with fetoscopic laser coagulation at the Leiden University Medical Center (LUMC) between March 2008 and March 2015 were eligible for this study. The LUMC is a tertiary medical center and the national referral center for laser treatment in TTTS pregnancies in the Netherlands. TTTS was diagnosed using standard prenatal ultrasound criteria and staged I to V according to Quintero.(3, 4) All parents gave written informed consent for their children.

The following antenatal and neonatal data were recorded: gestational age at laser surgery, Quintero stage, fetal demise, incomplete laser surgery (post-laser twin anemia polycythemia sequence (TAPS) or recurrence of TTTS), gestational age at birth, birth weight, severe neonatal morbidity, cerebral injury and neonatal death (death within 28 days after birth). The presence of TAPS was diagnosed according to previously published antenatal and postnatal criteria.(5)

Severe neonatal morbidity was defined as: respiratory distress syndrome needing surfactant and mechanical ventilation, severe chronic lung disease defined as the need for ≥30% oxygen and/or positive pressure ventilation or nasal continuous positive airway pressure at 36 weeks postmenstrual age or at discharge (whichever comes first), patent ductus arteriosus needing medical therapy or surgical closure, necrotizing enterocolitis ≥ Bell stage 2, retinopathy of prematurity ≥ stage 3, ischemic limb injury, amniotic band syndrome and/or severe cerebral injury. Severe cerebral injury includes: intra-ventricular hemorrhage ≥ grade 3, cystic periventricular leukomalacia ≥ grade 2, ventricular dilatation ≥ 97th percentile, porencephalic or parenchymal cysts, or other severe cerebral lesions associated with adverse neurological outcome. (6-9) Neuroimaging was performed using either fetal or neonatal ultrasound. In case of suspected cerebral injury, MRI was performed. Mild NDI was defined as the presence of at least one of the following: Cerebral Palsy (Gross Motor Functioning Classification System (GMFCS) grade I), cognitive and/or motor test score between 70 (≥ -2 SD) and 84 (< -1 SD) using the Dutch version of the Bayley scales of Infant and Toddler Development (Bayley-III), vision or hearing loss requiring aids.(10, 11) Severe NDI was defined as the presence of at least one of the following: Cerebral Palsy (GMFCS grade ≥ II), Bayley III cognitive and/or motor test score of less than 70 (< -2 SD), bilateral blindness or bilateral deafness requiring hearing aids.(11)

Maternal educational level was recorded and divided into three levels. A score of 1 was given when the mother's education was low (primary school), a score of 2 for an intermediate educational level (secondary school and intermediate vocational school), and a score of 3 for higher levels of education (higher vocational school and university).

Procedure

At 2 years of age (corrected for prematurity), all TTTS survivors treated with fetoscopic laser surgery were invited for a follow-up visit at our outpatient clinic. According to our follow-up protocol a visit includes a physical and neurological examination and an assessment of cognitive and motor development using Bayley-III.(12)

Measures

At follow-up, parents completed a behavioral questionnaire, the Child Behavior Checklist (CBCL/1½-5).(13) The checklist obtains parents' ratings of 99 problem items. Parents are instructed to rate their child's behavior as it occurs now or within the previous 2 months on a 3-point scale (*not true*, *somewhat or sometimes true* and *very true or often true*). Similar problem items are grouped into syndrome scale scores and their scores are summed up to produce a raw score for that syndrome: Emotionally Reactive (e.g. upset by new people or situations), Anxious/Depressed (e.g. too fearful or anxious), Somatic Complaints (e.g. stomachaches without medical cause), Withdrawn (e.g. avoids eye contact), Sleep Problems (e.g. Resists going to bed), Attention Problems (e.g. cannot concentrate) and Aggressive Behavior (e.g. angry moods).

Two broad band scales combine the syndrome scales: Internalizing Problems sums the Emotionally Reactive, Anxious/Depressed, Somatic Complaints and Withdrawn scores. Externalizing problems combines Attention Problems and Aggressive behavior. The Total problems score is the sum of the scores of all the problem items.

The CBCL/1½-5 also produces five DSM-oriented scales consisting of problem items matching the diagnostic criteria for DSM disorders: Depressive Problems, Anxiety Problems, Autism Spectrum Problems, Attention Deficit/Hyperactivity Problems and Oppositional Defiant Problems.

A Dutch normative sample was used to create standard T scores. These scores compare the raw score to what would be 'normal' compared with responses for preschoolers of the same age and gender. The T scores of the normative sample are scaled with a mean of 50 and a standard deviation (SD) of 10. Higher scores indicate greater severity of problems. For each syndrome, T scores can be interpreted as falling in the normal ($T \leq 64$, $\leq 92^{nd}$ percentile), borderline ($T = 65\text{-}69$; $93^{rd}\text{-}97^{th}$ percentile), or clinical range ($T \geq 70$; $\geq 98^{th}$ percentile). For the broadband scales (Internalizing, Externalizing, Total Problems) the cut points are $T = 60\text{-}63$ ($84^{th}\text{-}90^{th}$ percentiles) for the borderline- and $T \geq 64$ ($\geq 91^{st}$ percentile) for the clinical range. Emotional and behavioral problems are reported in approximately 10% of 2- and 3-year-olds in the Dutch population.(14, 15)

The primary aim was to evaluate the incidence of behavioral problems within the borderline to clinical range. We compared the incidence of behavioral problems between donors and recipients. Secondary outcome was to determine potential risk factors associated with behavioral problem scores including Quintero stage, gestational age at laser surgery, post-laser TAPS or recurrent TTTS, gestational age at birth, birth weight, severe neonatal morbidity (including severe cerebral injury) and maternal level of education.

Statistical analysis

Results are presented as median (IQR and/or minimum-maximum), mean ± SD or n (%). For comparisons between donors and recipients, a paired t-test was used. A binomial test was used to compare the incidence of behavioral problems in our study group to the general Dutch population (10%). Potential risk factors contributing to behavioral problems were tested using an univariable linear regression model. Only variables that showed significant association in the univariate analysis were included in a multivariate analysis. Results are expressed as regression coefficients (B) with 95% CI. A p value of less than 0.05 was considered significant. All analyses were conducted using the Generalized Estimated Equation (GEE) to account for the fact that observations between MC twins are not independent. All statistical analyses were executed with SPSS version 23 (IBM).

Results

Between March 2008 and March 2015, a total of 332 TTTS pregnancies were treated with fetoscopic laser therapy at our center. **Figure 1** shows the derivation of the study population. There were 75 (11%) cases of fetal demise and 33 (5%) neonatal deaths. Three children were excluded from follow-up analyses due to Tay Sachs disease (n=1, the co-twin was a fetal demise) and Neurofibromatosis Type 1 (n=2). In total, 517 children were eligible for follow-up and 417 (81%) Child Behavior Checklists were completed by parents. Ninety- seven children were lost to follow-up due to loss of contact address (n=75), refusal (n=6) or language problems (n=16). The study group had a higher birth weight compared with the lost-to follow-up group (B 2.04, 95% CI 0.51 to 3.56; p = 0.01) and a significant larger proportion of children in the study group were born at-term (B 0.08, 95% CI 0.23 to 0.14; p = 0.01). Baseline characteristics of both groups are presented in **table 1**.

Table 2a shows the incidence of behavioral problems in the 417 children included for behavioral follow-up at a corrected median age of 26 months (IQR 25-29 months). Total behavioral problem scores were within the borderline to clinical range in 34/417 (8.2%, 95% CI 5.9 to 11.2) children.

Compared with 10% in the general Dutch population, parents did not report more behavioral problems for their twins (p = 0.12). Internalizing problems and externalizing problems were reported in 39/417 (9.4%, 95% CI 6.9 to 12.6) and 48/417 (11.5%, 95% CI 8.8 to 15.0) children respectively. We found no significant differences between donors and recipients for total behavioral problem score (t (176) = -0.21, p = 0.84), internalizing (t (176) = -0.17, p = 0.86) or externalizing problems (t (176) = 1.09, p = 0.28). Baseline characteristics did not differ between the children with and without behavioral problems (**table 2b**).

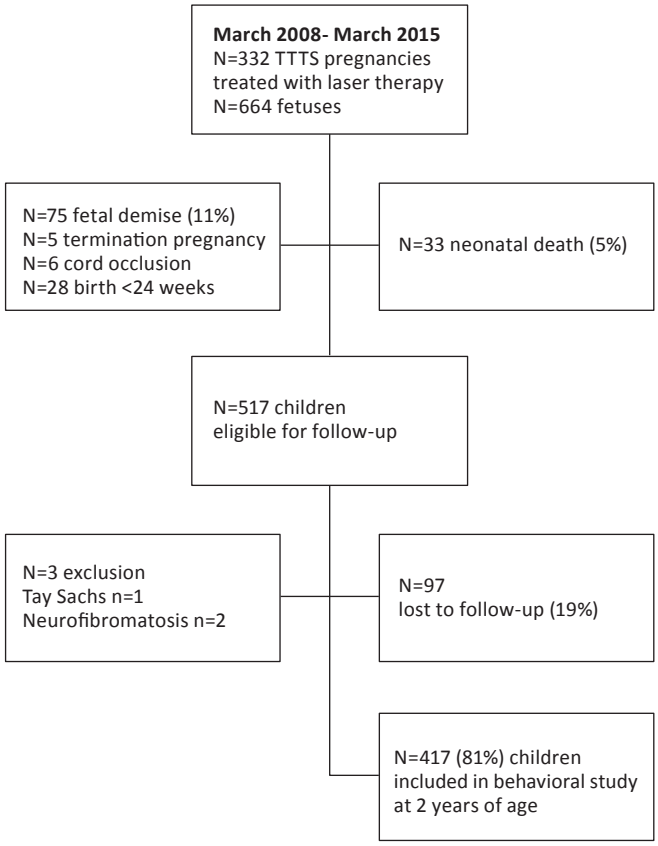

Figure 1. Flow chart showing the derivation of the study population.

Of the 417 children included in our behavioral study, 408 (98%) children had a complete neurodevelopmental assessment according to our follow-up protocol. Severe NDI was detected in 18/408 (4.4%) children. Mean cognitive development score was 99.94 ± 13.5 (55-139). Mean motor development score was 99.22 ± 14.7 (49-138). The incidence of severe NDI including severe cognitive and motor impairment was however more frequent in the children with behavioral problems compared with the children without behavioral problems (**table 3**).

Univariate analysis of potential risk factors associated with total behavioral problem scores was performed (**table 4**). Compared with mothers with a low educational level, mothers with a high educational level reported less behavioral problems (B -5.36, 95% CI -9.56 to -1.15, p = 0.01).

Table 1. Baseline characteristics of the study group and the 97 children lost-to follow-up

Characteristics	Study group N=417	Lost-to follow-up group N=97	p value
TTTS Quintero stage	3 (1-4)	3 (1-4)	0.65
Stage I, n(%)	53 (12.7)	11 (11.3)	
Stage II, n(%)	129 (22.1)	32 (33.0)	
Stage III, n(%)	226 (54.2)	53 (54.6)	
Stage IV, n(%)	9 (2.2)	1 (1)	
Donor, n(%)	210 (50.4)	48 (49.5)	0.46
Gestational age at laser, weeks	20.02 ± 3.44	19.45 ± 2.89	0.11
Recurrent TTTS or TAPS	54 (13)	9 (9)	0.72
Double survivor*, n (%)	354 (85)	86 (89)	0.30
Gestational age at birth, weeks	32.77 ± 3.23	32.0 ± 3.23	0.10
Term 37-40 weeks, n (%)	40 (9.6)	2 (2.1)	0.01
Late preterm 33-36 weeks	182 (43.6)	37 (38.1)	0.65
Very preterm 26-32 weeks	188 (45.1)	55 (56.7)	0.18
Extremely preterm 24-25 weeks	7 (1.7)	3 (3.1)	0.55
Birth weight, grams	1825 ± 597.75	1623 ± 536.26	0.01
Severe neonatal morbidity, n (%)	92/415 (22)	24/91 (26)	0.40
Severe cerebral injury, n (%)	19/415 (5)	3/90 (3.3)	0.71
Female, n (%)	206 (49.4)	46 (47.4)	0.59
Maternal education			
High, n(%)	184 (44)	NA	-
Intermediate, n(%)	184 (44)		
Low, n(%)	49 (12)		

Data are presented as median (minimum-maximum), n (%) or mean ± SD
*Double survivor, survival of both twins beyond the first 28 days of life.
NA, not assessed; TAPS, twin anemia-polycythemia sequence

Table 2a. Behavioral outcome in the 417 TTTS survivors included for follow-up

Child Behavior Checklist	T score ± SD*	Clinical n (%)	Borderline n (%)	Borderline-Clinical n (%)
Behavioral problems, total score	45.27 ± 10.27	25 (6)	9 (2.2)	34 (8.2)
Internalizing behavior	44.70 ± 10.44	22 (5.3)	17 (4.1)	39 (9.4)
Emotionally Reactive	53.49 ± 6.06	10 (2.4)	25 (6)	35 (8.4)
Anxious/Depressed	51.68 ± 4.21	3 (0.7)	8 (1.9)	11 (2.7)
Somatic Complaints	52.85 ± 4.94	11 (2.7)	13 (3.1)	24 (5.8)
Withdrawn behavior	52.64 ± 4.82	6 (1.4)	11 (2.7)	17 (4.1)
Externalizing behavior	46.84 ± 10.32	23 (5.5)	25 (6.0)	48 (11.5)
Attention Problems	53.13 ± 5.22	8 (1.9)	19 (4.6)	27 (6.5)
Aggressive behavior	53.06 ± 5.33	10 (2.4)	13 (3.1)	23 (5.5)
Sleep Problems	52.75 ± 5.67	14 (3.4)	3 (0.7)	17 (4.1)
Stress Problems	53.09 ± 4.82	10 (2.4)	7 (1.7)	17 (4.1)
DSM-V scales				
Depressive Problems	53.02 ± 4.88	10 (2.4)	7 (1.7)	17 (4.1)
Anxiety	52.47 ± 5.27	12 (2.9)	7 (1.7)	19 (4.6)
Autism Spectrum	53.91 ± 6.46	19 (4.6)	25 (6.0)	44 (10.6)
Attention Deficit/Hyperactivity	52.12 ± 3.89	3 (0.7)	7 (1.7)	10 (2.4)
Oppositional Defiant	53.60 ± 5.83	20 (4.8)	11 (2.7)	31 (7.5)

Data are presented as mean ± SD or n (%)
*T scores of the CBCL normative sample have a mean of 50 ± SD 10. For each syndrome score: T = 65-69 for the borderline range and T ≥ 70 for the clinical range. For Internalizing, Externalizing and Total Problems: T = 60-63 for the borderline range and T ≥ 64 for the clinical range.
CBCL, Child Behavior Checklist; DSM-V, Diagnostic and Statistical Manual of Mental Disorders 5th edition

Table 2b. Baseline characteristics of the TTTS survivors with borderline to clinical behavioral problem scores and scores within the normal range

Characteristics	n = 34 children Borderline - clinical range	n = 383 children Normal range	p value
TTTS Quintero stage	3 (1-4)	3 (1-4)	0.89
Stage I, n(%)	2 (5.9)	362 (11.3)	0.39
Stage II, n(%)	15 (44.1)	32 (33.0)	0.34
Stage III, n(%)	15 (44.1)	53 (54.6)	0.54
Stage IV, n(%)	2 (5.9)	1 (1)	0.20
Donor, n(%)	210 (50.4)	48 (49.5)	0.27
Gestational age at laser, weeks	20.38 ± 4.28	19.45 ± 2.89	0.82
Recurrent TTTS or TAPS	54 (13)	9 (9)	0.32
Double survivor, n (%)	354 (85)	86 (89)	0.99
Gestational age at birth, weeks	32.73 ± 3.54	32.0 ± 3.23	0.89
Term 37-40 weeks, n (%)	40 (9.6)	2 (2.1)	0.92
Late preterm 33-36 weeks	182 (43.6)	37 (38.1)	0.69
Very preterm 26-32 weeks	188 (45.1)	55 (56.7)	0.81
Extremely preterm 24-25 weeks	7 (1.7)	3 (3.1)	0.77
Birth weight, grams	1825 ± 597.75	1623 ± 536.26	0.68
Severe neonatal morbidity, n (%)	92/415 (22)	24/91 (26)	0.86
Severe cerebral injury, n (%)	19/415 (5)	3/90 (3.3)	0.57
Female, n (%)	206 (49.4)	46 (47.4)	0.88
Maternal education			0.39
High, n(%)	184 (44)	163/354 (42.6)	0.29
Intermediate, n(%)	184 (44)	155/354 (40.5)	0.40
Low, n(%)	49 (12)	36/354 (9.4)	0.83

TAPS, Twin Anemia Polycythemia Sequence

Table 3. Outcome of the 34 TTTS survivors with behavioral problems in the borderline to clinical range compared with the 383 TTTS survivors with behavioral scores in the normal range

Characteristics	n = 34 children Borderline - clinical range	n = 383 children Normal range	p value
Mild-moderate neurodevelopmental impairment	9/33 (27.3)	59/375 (15.7)	0.15
Severe neurodevelopmental impairment	6/33 (18.2)	12/375 (3.2)	0.00
Cerebral Palsy	1/34 (2.9)	8/383 (2.1)	0.77
CP grade I	-	4/383 (1.0)	
CP grade ≥ II	1/34 (2.9)	4/383 (1.0)	
Cognitive development score	91.6 ± 17.84 (55-129)	100.7 ± 12.77 (55-139)	0.02
Cognitive development <85 and >70 (-1 SD), n (%)	7/33 (21.2)	28/371 (7.5)	0.05
Cognitive development < 70 (-2 SD), n (%)	3/33 (9.1)	2/371 (0.5)	0.01
Motor development score	93.03 ± 16.82 (64-135)	99.7 ± 14.36 (49-138)	0.02
Motor development <-1 SD, n (%)	7/33 (20.6)	45/364 (12.4)	0.08
Motor development <-2 SD, n (%)	4/33 (12.1)	7/364 (1.9)	0.00
Deafness	0/34 (0)	2/383 (0.5)	-

Data are presented as mean ± SD (minimum-maximum) or n/N (%)

Table 4. Analysis of potential risk factors associated with total behavior problem scores

Characteristics	Univariate analysis B (95% CI)	SE	p value
TTTS Quintero			
Stage I	-5.71 (-13.79 – 2.36)	4.12	0.17
Stage II	-3.66 (-11.40 – 4.08)	3.95	0.35
Stage III	-5.07 (-12.61 – 2.46)	3.84	0.19
Stage IV	-		
Gestational age at laser therapy, weeks	0.17 (-0.20 – 0.54)	0.19	0.37
Recurrent TTTS or TAPS	0.36 (-3.06 – 3.79)	1.75	0.84
Fetal demise co-twin	-0.18 (-3.47 – 3.11)	1.68	0.92
Gestational age at birth, weeks	-0.11 (-0.51 – 0.29)	0.20	0.59
Birth weight, grams	-0.05 (-0.23 – 0.12)	0.09	0.55
Severe neonatal morbidity	0.14 (-1.83 – 2.11)	1.00	0.89
Severe cerebral injury	0.49 (-3.07 – 4.04)	1.81	0.79
Maternal education			
High	-5.36 (-9.56 – -1.15)	2.15	0.01
Intermediate	-3.80 (-8.10 – 0.48)	2.18	0.08
Low	-		

Values are regression coefficient B (95% CI), SE and p value.
TAPS, twin anemia-polycythemia sequence

Discussion

This is the first study evaluating the behavioral outcome in over 400 TTTS survivors treated with fetoscopic laser surgery. Despite the improving rate of survival to birth, the neurodevelopmental outcome for TTTS survivors has not been reported consistently, let alone behavior and socio-emotional development.(16, 17) At 2 years of age behavioral problems were reported in 8.2% (95% CI 5.9% to 11.2%) of TTTS survivors. This proportion is comparable to cohorts of 2-year-old children from the general population, with approximately 10% in the general Dutch population.(14, 15, 18) Dickinson and colleagues reported clinical behavior problems in 12% of TTTS survivors treated with serial amnioreduction.(19) In our cohort, donor twins did not differ from recipient twins in long-term behavioral outcome. An important finding of our study is that severe impairment was more frequent in children with

behavioral problems. The association between cognitive impairment and behavioral problems has been reported previously, particularly among preterm born children (below 32 weeks gestational age). For TTTS survivors, often born between 32 to 33 weeks' gestation, this association has not been reported before. This finding suggests that caregivers and health care professionals need to be aware of comorbid behavioral problems in children with severe impairments including cognitive and motor delay. Behavior problems among children with developmental delay are already evident at 2 years of age and seem to increase as children move toward school age.(20) Early identification, evaluation and referral to specialist care is necessary to support parents and to improve outcomes for these children. In addition, TTTS diagnosis and treatment, often followed by complicated neonatal courses due to prematurity and/or other complications constitute traumatic events with an important risk of posttraumatic stress, anxiety and a possible alteration of the prenatal attachment.(21) Insecure attachment to parents is strongly related to externalizing problem behavior in children.(22) Prenatal and postnatal psychological support is therefore important for both mothers and fathers.

In our study group, a relatively large proportion of mothers, 44%, reported a high level of education compared to 30% in the general Dutch population.(23) The mothers with a high educational level reported less behavioral problems in their twins compared to mothers with a low educational level. The strong link between maternal education and children's outcomes is one of the most well-established findings in developmental psychology.(24, 25)

Unfortunately, 19% of the children were lost to follow-up. Comparison of the antenatal and neonatal characteristics showed a significantly lower birth weight and a lower proportion of term born children in the lost-to follow-up group. Preterm born children with low birth weight are at higher risk of developing behavioral problems than term born children with normal birth weight.(26, 27) If these children had been included for follow-up the incidence of behavioral problems may have been higher.

An important limitation is the absence of a control group of uncomplicated MC twins matched for gestational age to assess the effect of TTTS and treatment on outcome. In addition, although we have included over 400 children for behavioral assessment at 2 years of age, assessment at this young age only partially predicts outcome at a later age. At this young age it is possible to discover major developmental abnormalities that require and benefit from early intervention. However, developmental outcomes assessed during early childhood are only moderate predictors of long-term neurodevelopment, particularly for scores on behavioral functioning and academic performance.

Some developmental problems, including learning difficulties or autism spectrum disorder, cannot be detected until later on, once the children start becoming more socially and academically challenged at school age. Follow-up of children treated with laser for TTTS is recommended until at least school age.

Conclusion

In conclusion, parents of twins treated with fetoscopic laser therapy for TTTS do not report more behavioral problems at 2 years of age compared to general populations. Behavioral problems were more frequent in twins with severe developmental delay. This study should be repeated at school age when the academic and social environment becomes more complex and challenging for children.

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