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Behavioural 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 behavioural 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 Behavioural 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 and risk factors for behavioural 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±3.2. Total behavioural 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 ($p=0.84$). Internalising and externalising 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 behavioural problems. High maternal educational level was associated with lower behavioural problem scores.

Conclusion Parents of twins treated with fetoscopic laser therapy for TTTS do not report more behavioural problems compared with general population norms. More behavioural 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.

What is already known on this topic?

- ▶ Since the introduction of fetoscopic laser coagulation of the placental vascular anastomoses survival rate has increased and short-term outcome of both donor and recipient has improved.
- ▶ Long-term follow-up studies report cerebral palsy in 3%–12% (overall 6%) of survivors and neurodevelopmental impairment (NDI) in 4%–17% (overall 10%).
- ▶ In children without obvious NDI, 'subtle' problems including attention problems may occur which already have a significant impact on care and educational requirements of children.

What this study adds?

- ▶ Behaviour problems were reported in 8.2% (95% CI 5.9% to 11.2%) of twin–twin transfusion syndrome (TTTS) survivors which is comparable to cohorts of 2 year old children from the general population.
- ▶ Behavioural problems were more frequent in twins with severe impairment.
- ▶ Early identification and referral to specialist care is necessary to support parents and to improve outcomes for TTTS survivors with behavioural problems.

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%–12% (overall 6%) of survivors and neurodevelopmental impairment (NDI) in 4%–17% (overall 10%).² However, even in children without obvious neurodevelopmental impairment, subtle problems may occur including behavioural and social–emotional problems such as attention problems and rule-breaking behaviour. These 'subtle' problems can have a significant impact on care and educational requirements of children. For example, hyperactive/inattentive behaviour 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



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with fetoscopic laser surgery. The aim of this study was to assess the behavioural 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 centre and the national referral centre 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 (postlaser twin anaemia 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 $\geq 30\%$ oxygen and/or positive pressure ventilation or nasal continuous airway pressure at 36 weeks postmenstrual age or at discharge (whichever comes first), patent ductus arteriosus needing medical therapy or surgical closure, necrotising enterocolitis \geq Bell stage 2, retinopathy of prematurity \geq stage 3, ischaemic limb injury, amniotic band syndrome and/or severe cerebral injury. Severe cerebral injury includes: intraventricular haemorrhage \geq grade 3,⁶ cystic periventricular leukomalacia \geq grade 2,⁷ ventricular dilatation ≥ 97 th percentile,⁸ porencephalic or parenchymal cysts, or other severe cerebral lesions associated with adverse neurological outcome.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),¹⁰ 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.¹¹ Severe NDI was defined as the presence of at least one of the following: Cerebral Palsy (GMFCS grade \geq 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 behavioural 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 behaviour 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 (eg, upset by new people or situations), Anxious/Depressed (eg, too fearful or anxious), Somatic Complaints (eg, stomachaches without medical cause), Withdrawn (eg, avoids eye contact), Sleep Problems (eg, Resists going to bed), Attention Problems (eg, cannot concentrate) and Aggressive Behaviour (eg, angry moods).

Two broad band scales combine the syndrome scales: Internalising Problems sums the Emotionally Reactive, Anxious/Depressed, Somatic Complaints and Withdrawn scores. Externalising problems combines Attention Problems and Aggressive behaviour. 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.

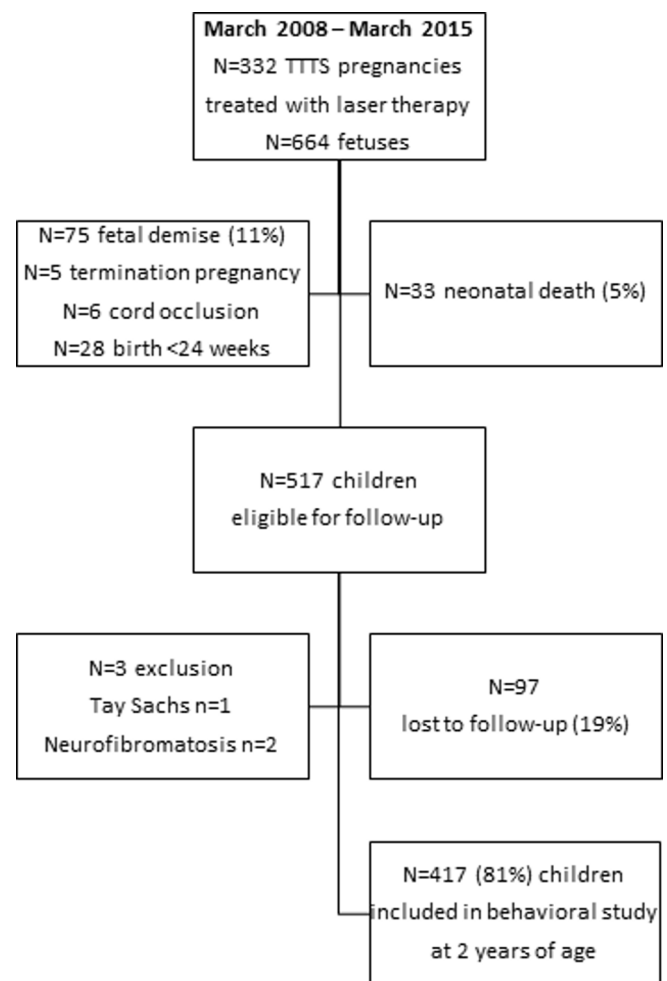


Figure 1 Flow chart showing the derivation of the study population. TTTS, twin–twin transfusion syndrome.

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; TTTS, twin–twin transfusion syndrome.

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 SD of 10. Higher scores indicate greater severity of problems. For each syndrome, T scores can be interpreted as falling in the normal ($T \leq 64$, ≤ 92 nd percentile),

borderline ($T = 65–69$; 93rd–97th percentile), or clinical range ($T \geq 70$; ≥ 98 th percentile). For the broadband scales (Internalising, Externalising, Total Problems) the cut points are $T = 60–63$ (84th–90th percentiles) for the borderline- and $T \geq 64$ (≥ 91 st percentile) for the clinical range. Emotional and behavioural problems are reported in approximately 10% of 2-year-olds and 3-year-olds in the Dutch population.^{14 15}

The primary aim was to evaluate the incidence of behavioural problems within the borderline to clinical range. We compared the incidence of behavioural problems between donors and recipients. Secondary outcome was to determine potential risk factors associated with behavioural problem scores including Quintero stage, gestational age at laser surgery, postlaser 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 behavioural problems in our study group to the general Dutch population (10%). Potential risk factors contributing to behavioural 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 Generalised Estimated Equation (GEE) to account for the fact that observations between MC twins are not independent. All statistical analyses were executed with SPSS V.23 (IBM).

RESULTS

Between March 2008 and March 2015, a total of 332 TTTS pregnancies were treated with fetoscopic laser therapy at our centre. **Figure 1** shows the derivation of the study population.

Table 2A Behavioural outcome in the 417 TTTS survivors included for follow-up

Child Behavior Checklist	T score±SD*	Clinical n (%)	Borderline n (%)	Borderline-Clinical n (%)
Behavioural problems, total score	45.27±10.27	25 (6)	9 (2.2)	34 (8.2)
Internalising behaviour	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 behaviour	52.64±4.82	6 (1.4)	11 (2.7)	17 (4.1)
Externalising behaviour	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 behaviour	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 $T \geq 70$ for the clinical range. For Internalising, Externalising and Total Problems: $T = 60–63$ for the borderline range and $T \geq 64$ for the clinical range.

CBCL, Child Behavior Checklist; DSM-V, Diagnostic and Statistical Manual of Mental Disorders fifth edition; TTTS, twin–twin transfusion syndrome.

Table 2B Baseline characteristics of the TTTS survivors with borderline-clinical behavioural 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 anaemia polycythemia sequence; TTTS, twin-twin transfusion syndrome.

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 behavioural problems in the 417 children included for behavioural follow-up at a corrected median age of 26 months (IQR 25–29 months). Total behavioural 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 behavioural problems for their twins (p=0.12). Internalising problems and externalising 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 behavioural problem score (t (176)=−0.21, p=0.84), internalising (t (176)=−0.17, p=0.86) or externalising problems (t (176)=1.09, p=0.28). Baseline characteristics did not differ between the children with and without behavioural problems (table 2B).

Of the 417 children included in our behavioural 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

Table 3 Outcome of the 34 TTTS survivors with behavioural problems in the borderline to clinical range compared with the 383 TTTS survivors with behavioural 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 (%).
TTTS, twin-twin transfusion syndrome.

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 behavioural problems compared with the children without behavioural problems (table 3).

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

DISCUSSION

This is the first study evaluating the behavioural outcome in over 400 TTTS survivors treated with fetoscopic laser surgery. Despite the improving rate of survival to birth, the

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

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

Values are regression coefficient B (95% CI), SE and p value.

TAPS, twin anemia polycythemia sequence; TTTS, twin-twin transfusion syndrome.

neurodevelopmental outcome for TTTS survivors has not been reported consistently, let alone behaviour and socio-emotional development.^{16 17} At 2 years of age behavioural 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 behaviour problems in 12% of TTTS survivors treated with serial amnioreduction.¹⁹ In our cohort, donor twins did not differ from recipient twins in behavioural outcome. An important finding of our study is that severe impairment was more frequent in children with behavioural problems. The association between cognitive impairment and behavioural 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 healthcare professionals need to be aware of comorbid behavioural problems in children with severe impairments including cognitive and motor delay. Behaviour 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 externalising problem behaviour 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 with 30% in the general Dutch population.²³ The mothers with a high educational level reported less behavioural problems in their twins compared with 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 behavioural problems than term born children with normal birth weight.^{26 27} If these children had been included for follow-up the incidence of behavioural 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 behavioural 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 behavioural 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 behavioural problems at 2 years of age compared with general populations. Behavioural 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.

Contributors JvK and EL made substantial contributions to the conception and design of the work; JvK and FLB made substantial contributions the acquisition, analysis and all authors (FLB, MSS, MR, RINGBT, DO, EL and JvK) made substantial contributions to the interpretation of data for the work; JvK and FLB drafted the work and all authors (FLB, MSS, MR, RINGBT, DO, EL and JvK) revised it critically for important intellectual content; all authors (FLB, MSS, MR, RINGBT, DO, EL and JvK) approved the final version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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