Long-Term Neurodevelopmental Outcome in Survivors of Twin-to-Twin Transfusion Syndrome

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Twin–twin transfusion syndrome (TTTS) is a severe complication of monochorionic (MC) twin pregnancies associated with high perinatal mortality and morbidity rates. Management in TTTS is a major challenge for obstetricians and neonatologists. Twins with TTTS are often born prematurely after an extremely distressing and highly hazardous fetal period. Follow-up studies report varying rates of cerebral palsy (CP) and long-term neurodevelopmental impairment (NDI). This review discusses the latest findings on the long-term outcome of TTTS survivors, possible risk factors for long-term impairment, and provides recommendations for future research.

■ **Keywords:** twin–twin transfusion syndrome, monochorionic twins, amnioreduction, laser surgery, neurodevelopmental outcome

TTTS is a severe complication of MC twin pregnancies and one of the most lethal conditions in perinatal medicine. The optimal management is still a major challenge for both obstetricians and neonatologists. TTTS is the result of unbalanced inter-twin blood transfusion through placental vascular anastomoses and is characterized by the presence of oligohydramnion in the donor twin and polyhydramnion in the recipient twin.

Treatment options in TTTS include serial amnioreduction to drain the excess amniotic fluid in the amniotic sac of the recipient, and fetoscopic laser coagulation of placental vascular anastomoses. Twins treated with serial amnioreduction are less likely to survive compared to twins treated with laser surgery (Rossi & D'Addario, 2008) and are born on average at 29 weeks' gestation, compared to 32–33 weeks' gestation after laser surgery. In addition, treatment with amnioreduction is associated with a significant higher risk of severe cerebral injury compared to laser surgery (van Klink et al., 2013). The preferred treatment for TTTS is therefore fetoscopic laser coagulation of the anastomoses, with an overall survival rate increasing in the past decade from 55% to 74% (Senat et al., 2004; Slaghekke et al., 2014).

With this improving survival rate, attention is shifting towards the long-term outcome in surviving children. An increasing number of studies are gradually shedding more light on the wide range of long-term morbidity associated with TTTS. This review will focus on the long-term neurodevelopmental outcome in TTTS survivors treated with either serial amnioreduction or fetoscopic laser surgery.

Cerebral Injury on Neuroimaging in the Neonatal Period

The reported incidence of cerebral injury after amnioreduction ranges from 6% to 38% compared to 8% to 18% following laser surgery (Cincotta et al., 2009; Lenclen et al., 2007; Lopriore et al., 2006; Senat et al., 2004). Several types of cerebral injury have been described, including cystic periventricular leukomalacia (PVL), cerebral white-matter cysts, severe intraventricular hemorrhage (IVH), ventricular dilatation, cerebral atrophy, and arterial ischemic stroke (Lopriore et al., 2006). Donors and recipients appear to be equally at risk (Lopriore et al., 2006). Cerebral injury

may result from antenatal injury and/or postnatal injury, partly due to extreme prematurity, an important risk factor for cystic PVL and IVH. Antenatal injury may result from impaired cerebral perfusion due to hemodynamic imbalance and inter-twin shifts of blood through the vascular anastomoses, leading to hypoxic-ischemic insults. Hypoxic-ischemic damage caused by cerebral hypoperfusion is probably the main cause for cerebral injury in donor twins. Hyperviscosity and polycythemia causing vascular sludging may be an important cause for cerebral injury in recipients.

In a meta-analysis performed by our group, we found a 7-fold higher risk of severe cerebral injury in TTTS twins treated with amnioreduction compared to twins treated with laser surgery (van Klink et al., 2013). Given the high incidence and range of cerebral injuries in TTTS, routine standardized ante- and postnatal cerebral imaging protocols are strongly recommended to accurately evaluate origin, timing, and type of neurological damage. In case of cerebral injury, MRI may play an important role in investigating the correlation between antenatal and postnatal imaging findings. Increased awareness may improve neonatal and pediatric care for these children. The clinical relevance of neuroimaging findings should then be determined using long-term neurodevelopmental outcome data of all TTTS survivors until at least childhood.

Long-Term Neurodevelopmental Outcome in TTTS Survivors

Advancing techniques, increasing survival rates and improving short-term outcome necessitate a greater knowledge on the impact of TTTS and its management on long-term neurodevelopment. A better understanding of the impact on child development over time will allow more accurate counseling of parents and targeted interventions to optimize child development when needed. This requires international collaboration, to obtain large enough sample sizes and statistical power, using a standardized follow-up regimen including uniform and clearly defined criteria for long-term NDI. NDI is a standard composite outcome defined as at least one of the following: CP, severe motor and/or cognitive developmental delay, bilateral blindness, or deafness requiring amplification with hearing aids. Determining NDI involves a follow-up regimen that includes a physical and neurologic examination and an assessment of cognitive and motor development using developmental tests such as the Bayley Scales of Infant and Toddler Development by certified examiners.

The incidence and type of NDI in TTTS survivors treated with amnioreduction or laser surgery reported in the literature is described in the two following sections and summarized in Tables 1 and 2.

Long-Term Neurodevelopmental Outcome in TTTS Treated With Amnioreduction

The reported incidence of CP and NDI after amnioreduction ranges from 5% to 23% and from 6% to 26%, respectively (Cincotta et al., 2000; Dickinson et al., 2005; Frusca et al., 2003; Haverkamp et al., 2001; Lenclen et al., 2009; Lopriore et al., 2003; Mari et al., 2000; Reisner et al., 1993). This large discrepancy is due to considerable differences in methodology between the studies and heterogeneity within the case series. In the majority of studies, cohorts included only a small number of children (range: 20–52 children). As a consequence, the investigators were unable to assess whether NDI was due to confounders such as prematurity or growth restriction (Senat et al., 2004). A clear definition of impairment, in terms of NDI, was often not reported, and detailed information on individual observations of impairment was often lacking. Finally, not all studies included standardized developmental tests (Lenclen et al., 2009; Lopriore et al., 2003; Mari et al., 2000; Reisner et al., 1993). Table 1 summarizes the follow-up studies after amnioreduction.

In the Eurofetus trial, the short-term neurologic outcome of TTTS survivors treated with amnioreduction was less favorable compared to laser surgery. However, the long-term outcome was similar between the two treatment groups (Salomon et al., 2010; Senat et al., 2004). Unfortunately, the long-term evaluation did not take into account that in a relatively large percentage (22%; 20/93) of live-born neonates in the amnioreduction group, intensive care treatment was withdrawn due to severe cerebral injury. Had these children survived, the differences in long-term neurodevelopmental outcome between both groups could have been much more evident (Lopriore et al., 2011).

Long-Term Neurodevelopmental Outcome in TTTS Treated With Laser Surgery

The reported incidence of CP and NDI after laser surgery ranges from 3% to 12% and from 4% to 18%, respectively (Banek et al., 2003; Chang et al., 2012; De Lia et al., 1999; Graef et al., 2006; Graeve et al., 2012; Gray et al., 2011; Lenclen et al., 2009; Lopriore et al., 2009; McIntosh et al., 2014; Salomon et al., 2010; Sutcliffe et al., 2001; Vanderbilt et al., 2014). Table 2 summarizes the follow-up studies after laser surgery. Again, care must be taken when comparing the results of these studies, as this large discrepancy is due to different methodology, differences in (neonatal) death rates, considerable heterogeneity within the small case series and lack of uniform outcome measures and criteria.

In 1999, De Lia et al. reported major impairment in 5% (5/93) of TTTS survivors after laser surgery at a mean age of 14 months (De Lia et al., 1999). No developmental

TABLE 1

Long-Term Neurodevelopmental Outcome in TTTS Treated with Amnioreduction

Author, year	Outcome measure	CP % (n/N)	NDI % (n/N)	Comments
1. Reisner et al. (1993)	Neurologic exam	19 (5/27)	NA	No developmental tests, no controls, 19/27 < 18 months at follow-up
2. Mari et al. (2000)	Clinical record, discussion parent/pediatrician, speech, or physical therapy	5 (2/42)	NA	No developmental tests, inclusion mild TTTS cases, follow-up based on clinical records, no controls, high NND rate (16%)
3. Cincotta et al. (2000)	Neurologic exam, physiotherapy assessment, griffiths scale	13 (3/23)	22 (5/23)	18% NND rate, inclusion gestation matched twin controls
4. Haverkamp et al. (2001)	Neurologic exam, denver screening test, griffiths scale	23 (9/40)	23 (9/40)	18% lost to follow-up, incomplete follow-up, no controls
5. Frusca et al. (2003)	Neurologic exam, griffiths scale	16 (5/31)	26 (8/31)	35% (11/31) < 2 years at follow-up, no controls
6. Lopriore et al. (2003)	Neurologic exam, school functioning	21 (6/29)	NA	No developmental tests
7. Dickinson et al. (2005)	Neurologic exam, general health questionnaire, vineland scales, child behavior checklist, bayley scales, stanford-binet intelligence scale	6 (3/52)	14 (7/52)	Neurologic exam in very pre-terms only, behavioral outcome but only in pre-scholars, inclusion contemporaneous regional cohort
8. Lenclen et al. (2009)	Neurologic exam, ages stages questionnaire	19 (4/21)	NA	No developmental tests, gestation matched DC controls, inclusion twins treated with laser
9. Salomon et al. (2010)	Neurologic exam, ages stages questionnaire, wechsler scales, goodenough draw-a-man-test	13 (6/47)	NA	NDI not reported, 36% NND rate, no controls, inclusion twins treated with laser
10. Li et al. (2011)	Neurologic exam, enjoji development scale, wechsler scales	15 (3/20)	20 (4/20)	Small study size, preponderance mild TTTS cases
Total range		13.9 (46/332) 5–23	19.9 (33/166) 14–26	

Note: The first part of the Eurofetus trial is not included in this table because the children are more fully described in the follow-up of this trial. CP = cerebral palsy; NDI = neuro developmental impairment defined as CP, severe cognitive and/or motor delay (<2 SD), blindness and/ or deafness; NND = neonatal death; DC = dichorionic.

tests were employed. Sutcliffe et al. (2001) found CP in 9% (6/66) of TTTS survivors treated with laser. Details on the number of children with severe cognitive delay were not reported. Two follow-up studies from Germany reported NDI in 11% (10/89) and 8% (13/167) of survivors at 2 years of age (Banek et al., 2003; Graef et al., 2006). NDI was more likely in children born <32 weeks' gestation. In both studies, the definition of impairment did not include severe cognitive delay. Hence, children with severe cognitive delay but without CP were not included in the group with NDI. Neurodevelopmental outcome of 190 of these 256 children was re-evaluated at a median age of 6 years and 5 months (Graeve et al., 2012). NDI, now defined as major neurologic deficiencies (CP) and severe cognitive delay as measured with a standardized intelligence test, was detected in 9% (17/190). The authors concluded that neurodevelopmental outcome at 6 years was not different from outcome at 2 years. Of note, a significantly higher number of children with NDI were born very or extremely preterm, when compared to the children with normal development.

In a long-term follow-up study in France, Lenclen et al. (2009) reported NDI in 11% (10/88; CP: $n = 9$; blindness: $n = 1$). Developmental test scores were similar in TTTS survivors compared to preterm dichorionic twins. Low gestational age at birth was significantly associated with NDI (relative risk [RR]: 1.20 for each week, 95% CI: 1.1–1.4; $p = .02$). In 2009, three European fetal therapy centers (Barcelona, Leuven, and Leiden) performed a multicenter

follow-up study to investigate risk factors for NDI in TTTS treated with laser (Lopriore et al., 2009). Overall, the incidence of NDI was 18% (50/278). Four risk factors were found to be significantly associated with increased risk for NDI: gestational age at laser surgery (odds ratio [OR] 1.30, 95% CI: 1.0–1.7; $p = .05$), Quintero stage (OR 3.55 for each increment in stage, 95% CI: 1.1–11.8; $p = .04$), lower gestational age at birth (OR 1.39 for each week, 95% CI 1.1–1.8; $p = .01$), and lower birth weight (OR 1.18 for each 100-g decrease, 95% CI 1.1–1.3; $p = < .01$; Lopriore et al., 2009). Gray et al. (2011) found a 4% (5/113) incidence of CP and NDI was diagnosed in 12% (14/113) of TTTS survivors. Four children with CP also had severe cognitive delay, whereas nine children without CP were diagnosed with severe cognitive delay, using standardized developmental tests. Advanced Quintero stage was a risk factor for NDI (OR: 13.02; 95% CI: 1.92–88.33; $p = < .001$). At a corrected age of 1 year at follow-up, Chang et al. (2012) reported CP in 5% (3/59) and NDI in 7% (4/59) of TTTS survivors treated with laser. Univariate analyses revealed that low gestational age at birth was a significant predictor of impairment (OR: 0.63; 95% CI not reported; $p = .018$). Although standardized neurological assessment and developmental tests were employed, the timing of follow-up was too early for a reliable diagnosis of CP or developmental delay.

McIntosh et al. (2014) investigated the long-term neurodevelopmental outcome of a cohort of 3- to 5-year-old

TABLE 2

Long-Term Neurodevelopmental Outcome in TTTS Treated With Laser Surgery

Author, year	Outcome measure	CP % (n/N)	NDI % (n/N)	Comments
1. De Lia et al. (1999)	Neurologic exam	3 (3/93)	NA	No developmental tests, mean age follow-up 14 months, no controls
2. Sutcliffe et al. (2001)	Neurologic exam, griffiths scale	9 (6/66)	9 (6/66)	19% lost to follow-up, 47% information GP, 54% incomplete tests, no controls
3. Banek et al. (2003)	Neurologic exam, griffiths scale, snijders-oomen Intelligence test	11 (10/89)	11 (10/89)	Severe developmental delay not included as criterion for NDI, no controls
4. Graef et al. (2006)	Neurologic exam, griffiths scale, snijders-oomen intelligence test	6 (10/167)	8 (13/167)	Suboptimal/incomplete use of developmental tests
5. Lenclen et al. (2009)	Neurologic exam, ages stages questionnaire	10 (9/88)	NA	No developmental tests, preterm DC controls matched for GA at birth
6. Lopriore et al. (2009)	Neurologic exam, bayley scales	6 (17/278)	18 (50/278)	2 TTTS-pregnancies treated >26 weeks' gestation
7. Salomon et al. (2010)	Neurologic exam, ages stages questionnaire, wechsler scale	12 (9/73)	NA	NDI not reported, no controls
8. Gray et al. (2011)	Neurologic exam, griffiths, and bayley scales	4 (5/113)	12 (14/113)	Mixed developmental tests; e.g., second and third version Bayley scales, no controls
9. Chang et al. (2012)	Neurologic exam, bayley scales	5 (3/59)	7 (4/59)	Small study size, corrected age follow-up 1 year
10. Graeve et al. (2012)	Neurologic exam, K-assessment battery, national screening exam, questionnaire parents	NA	9 (17/151)	CP not reported, mixed tests, 89/190 examined personally, 82/190 intelligence test
11. McIntosh et al. (2014)	Wechsler preschool primary scale of intelligence- III, general health questionnaire	2 (1/50)	4 (2/50)	16% lost to follow-up, no neurologic exam, small sample size
12. Vanderbilt et al. (2014)	Amiel tieson neurodevelopmental exam, battelle developmental inventory	3 (3/100)	4 (4/100)	50% lost to follow-up, majority lost to follow-up Quintero stage IV
13. van Klink, Slaghekke et al. (2015a)	Neurologic exam, bayley scales	3 (6/216)	10 (22/216)	Follow-up in two of the five participating centers, limited power to detect difference in long-term outcome
Total Range		6.1% (82/1341) 3–12%	9.8% (120/1228) 4–18%	

Note: Two follow-up studies (Lopriore et al., 2007; van Klink et al., 2014) in TTTS after laser are not included in this table because the included children are more fully described in the multi-center follow-up of this studies (Lopriore et al., 2009; van Klink et al., 2015b). CP = cerebral palsy; NDI = neuro developmental impairment defined as CP, severe cognitive and/or motor delay (<2 *SD*), blindness and/ or deafness; NND = neonatal death; GP = general practitioner; GA = gestational age.

survivors of TTTS treated with laser. NDI was reported in 4% (2/50) children tested with the Wechsler Preschool Primary Scale of Intelligence and a general health questionnaire. Most recently, Vanderbilt et al. (2014) reported NDI in 4% (4/100 TTTS survivors), as one child had a Battelle Developmental Inventory score < 70 and three children were diagnosed with CP. Lower maternal education ($\beta = 0.60$; $p = < .01$), higher Quintero stage ($\beta = -0.36$; $p = < .01$) and lower gestational age at birth ($\beta = 0.30$; $p = < .01$) were associated with worse cognitive scores. The results could, however, be severely hampered due to a 50% lost-to-follow-up rate. High lost-to-follow-up rates can lead to biased reports of impairment, likely resulting in underestimation, since parents with low educational levels and those with children with severe developmental delay are most likely to drop out of follow-up programs (Aylward et al., 1985; Wolke et al., 1995). In addition, in countries where families have to travel long distances to the follow-up clinic, parents are more likely to refrain from participating. Assessments using (web-based) questionnaires such as the Ages and Stages Questionnaire could be more feasible to avoid large lost to follow-up rates.

Randomized Controlled Trials in TTTS

Despite the fact that the preferred treatment for TTTS is fetoscopic laser coagulation, severe postoperative complications can occur when inter-twin vascular anastomoses remain patent, including twin-anemia polycythemia sequence (TAPS) or recurrent TTTS. To minimize the occurrence of residual anastomoses, a modified laser surgery technique, the Solomon technique, was developed, in which the entire vascular equator is coagulated (Slaghekke et al., 2014). In the Solomon randomized controlled trial, this technique was associated with a significant reduction in TAPS and recurrence of TTTS when compared to the standard laser surgery technique (Slaghekke et al., 2014).

In a follow-up study, we evaluated the long-term neurodevelopmental outcome in surviving children with TTTS included in the trial (van Klink, Slaghekke et al., 2015b). Routine, standardized follow-up in survivors, at least 2 years after the estimated date of delivery, was performed at two of the five centers participating in the Solomon trial: Buzzi Hospital Milan (Italy) and Leiden University Medical Center (the Netherlands). The primary outcome, survival without NDI, was detected in 95/141 (67%) in the Solomon group and in 99/146 (68%) in the standard group ($p = .92$).

NDI in long-term survivors included for follow-up was detected in 12/107 (11%) in the Solomon and in 10/109 (9%) in the standard group ($p = .61$; see Table 2).

Several explanations can be considered to explain the lack of difference between the two treatment groups in this follow-up study. First, the Solomon trial was primarily designed and powered to detect a difference in short-term outcome (van Klink, Slaghekke et al., 2015b). Follow-up was only available from two of the five centers participating in the Solomon trial and results cannot be generalized to the total trial population. A second explanation could be that timely detection and adequate management and treatment (intrauterine transfusion, laser surgery re-intervention) in patients with short-term complications (TAPS or recurrent TTTS) in the standard group reduced the risk for long-term impairment. The lack of difference in Bayley scores could also be related to early interventions for children with developmental impairment. However, no difference in the rate of early interventions including physical therapy (39% vs. 41%, $p = .89$), speech-language therapy (9% vs. 12%, $p = .65$) and psychological interventions (4% vs. 7%, $p = .54$), was found between the Solomon and standard group, respectively. In view of the reduction of short-term complications and absence of increased adverse long-term effects, our data support the use of the Solomon technique in the treatment of TTTS.

Other Interventions and Complications in Monochorionic Pregnancies

When fetoscopic laser surgery is not feasible or in cases with severe complications leading to the impending death of one twin, selective reduction can be offered. Up to now, no long-term outcome data of TTTS survivors following selective feticide of the co-twin are available. In a recent follow-up study, long-term NDI was detected in 7% (5/74) of co-twin survivors treated with selective reduction for severe complications, including TTTS, TAPS, twin-reversed arterial perfusion (TRAP), and selective fetal growth restriction (sFGR; van Klink, Koopman et al., 2015a). Of the 25 cases treated with selective reduction for TTTS, 2 (8%) were diagnosed with NDI. Large, multicenter follow-up studies are required to reliably assess long-term outcome in TTTS pregnancies treated with selective reduction.

The optimal management of other severe complications in MC pregnancies, including TAPS, TRAP, and sFGR, is not clear and international consensus on the best treatment strategy is lacking. Multicenter efforts are of utmost importance to study the natural history in complicated pregnancies with fetal disorders and the effect of interventions to determine optimal management (timing and type of intervention). The ideal study design to evaluate new interventions in fetal therapy is an adequately powered randomized controlled trial with 'survival without NDI' as a primary outcome. Long-term follow-up, at a minimum of 2 years

of age, should be an integrated component of fetal therapy in all fetal medicine centers around the world. In addition, worldwide registries to record and evaluate the outcome in large groups of children after fetal therapy are of paramount importance to increase current knowledge in specific subgroups. It is crucial to continuously assess child development, including formal psychological testing and standardized measures of well documented psychometric quality, with increasing reliability of results with increasing age of surviving children following fetal therapy.

Conclusions

TTTS is associated with an increased risk of neonatal mortality and morbidity, including severe cerebral injury. Twins treated with amnioreduction are less likely to survive compared to twins treated with laser surgery. The incidence of long-term NDI in TTTS treated with amnioreduction is high, on average 20%. The long-term outcome in TTTS treated with laser is more favorable; NDI is reported in 10%. This significant difference in outcome is partly due to the higher rate of severe prematurity in TTTS treated with amnioreduction. The association between low gestational age at birth and NDI is not surprising, as prematurity is a well-recognized risk factor for adverse neurodevelopmental outcome. Other important risk factors are advanced gestational age at intervention, higher Quintero stage, severe cerebral injury, low birth weight, and low parental educational level (Lopriore et al., 2009; van Klink et al., 2014). However, special care must be taken when comparing the results of long-term, follow-up studies, as discrepancies exist at least partly due to different methodology, differences in neonatal death rates, the considerable heterogeneity within small case series, and lack of uniform outcome criteria.

In conclusion, regardless of antenatal treatment, all TTTS survivors are at increased risk for NDI and require long-term follow-up. The age of follow-up assessment in most studies is 2 years, which is still of limited value since developmental problems often become more apparent at a later age, especially at school age. Therefore, follow-up until at least school age is recommended. Continuing close collaboration between obstetricians, neonatologists and child developmental specialists is crucial in order to improve care of children with TTTS (Lopriore et al., 2005).

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