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Twin-to-twin transfusion syndrome : from placental anastomoses to long term outcome

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Part 4

Long-term outcome

Chapter 11

Long-term neurodevelopmental outcome
in twin-to-twin transfusion syndrome

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Abstract

Objective: To determine the long-term neurodevelopmental outcome in children after twin-to-twin transfusion syndrome (TTTS).

Methods: Maternal and neonatal medical records of all TTTS-cases admitted to our center between 1990 and 1998 were reviewed. Neurological and mental development at school age was assessed during a home visit in all TTTS survivors.

Results: A total of 33 pregnancies with TTTS were identified. Four couples opted for termination of pregnancy. All other pregnancies were managed conservatively, 18 (62%) with serial amnioreductions and 11 (38%) without intrauterine interventions. Mean gestational age at delivery was 28.6 (range: 20-37) weeks. Perinatal mortality was 50% (29/58). Birth weight of donor twins was less than recipient twins ($p < 0.001$). Systolic blood pressure at birth was lower in donors than in recipients ($p = 0.023$) and donors required more frequently inotropic support postnatally than recipients ($p = 0.008$). The incidence of hypertension at birth was higher in recipients than in donors ($p = 0.038$). Abnormal cranial ultrasonographic findings were reported in 41% (12/29) of the neonates. All long-term survivors ($n = 29$) were assessed during a home visit. Mean gestational age at birth of the surviving twins was 31.6 (range: 25-37) weeks. Mean age at follow-up was 6.2 (range: 4-11) years. The incidence of cerebral palsy was 21% (6/29). Five out of six children with cerebral palsy had an abnormal mental development. The incidence of cerebral palsy in the group of survivors treated with serial amnioreduction was 26% (5/19). Four children were born after intrauterine fetal demise of their co-twin: two of them had cerebral palsy.

Conclusions: The incidence of adverse neurodevelopmental outcome in TTTS survivors is high, especially after intrauterine fetal demise of a co-twin.

Introduction

Cerebral palsy is estimated to occur seven times more often in twins than in singletons¹. The higher relative risk for cerebral damage is not only attributable to the higher incidence of premature birth and low birth weight in twins compared to singletons. Monochorionic twinning predisposes to cerebral damage due to complications caused by twin-to-twin transfusions²⁵⁰. Twin-to-twin transfusion syndrome (TTTS) occurs in approximately 15% of monochorionic pregnancies and results from shunting of blood from one twin, the donor, to the other twin, the recipient. The donor becomes hypovolemic and oliguric, whereas the recipient becomes hypervolemic and polyuric¹¹. The management of TTTS remains a significant challenge in perinatal medicine and the perinatal mortality rate in untreated TTTS is reported to be 75-100%^{112;114}. Treatment of TTTS with serial amnioreductions or with laser coagulation of placental vascular anastomoses has decreased the perinatal mortality rate to an average rate of approximately 40%^{123;124;129}. Nevertheless, the morbidity in surviving twins, which includes mainly neurological, cardiovascular and renal complications, remains high¹¹. Cerebral white-matter lesions have been reported to occur antenatally in up to 35% of TTTS survivors¹⁴⁶. To date, few studies have reported long-term neurodevelopmental outcome in TTTS. The incidence of cerebral palsy and global developmental delay in surviving twins varies from 4% to 23%^{39;133;147;148;150;152}. However, in most studies, follow-up of the surviving twins did not extend beyond a mean age of 2 years corrected for prematurity. Assessment at school age is essential since neurological handicaps and mental retardation may only become evident several years after birth²⁵¹⁻²⁵³. The main purpose of our study was to evaluate long-term neurodevelopmental outcome in school-aged twins after TTTS.

Material and Methods

We identified all cases of TTTS who were admitted at our center from January 1990 to December 1998. Written information on the aims of the study was sent to the parents of all surviving twins. Parents were asked

for consent to examine their children. Neurological outcome was assessed in all children by a single pediatrician during a home visit. Neurological outcome was defined as abnormal when evidence of cerebral palsy was found. Cerebral palsy was classified as diplegia, hemiplegia, quadriplegia, dyskinetic or mixed. We estimated the level of mental development of the children according to their school performance. School entry in the Netherlands starts at four years of age. All children with learning disabilities due to mental retardation or behavioral problems are referred to a school for special education. For the purposes of the study, children in mainstream education with or without special assistance were considered to have a normal mental development, whereas children who needed special education as well as children one or more grades below the appropriate school-level for their age were considered to have an abnormal mental development.

Diagnosis of TTTS was reached according to the following prenatal ultrasound criteria: 1.) monochorionicity established by absence of a “twin peak” sign and the presence of a thin dividing membrane, 2.) oligohydramnios (deepest vertical pocket < 1 cm) in the twin sac of one fetus and 3.) polyhydramnios (deepest vertical pocket > 8cm) in the twin sac of the other fetus. During the study period, the standard treatment at our center for TTTS was serial amnioreduction. Monochorionicity was confirmed after delivery.

The following obstetrical data were extracted from the medical charts: gestational age at the time of diagnosis, number of therapeutic amnioreductions and total volume of amniotic fluid removed, intrauterine fetal death, gestational age at delivery and mode of delivery. We also recorded the stage of TTTS on admission⁹. In short, staging according to Quintero has five stages: stage I, bladder of donor twin still visible; stage II, anuria of donor twin; stage III, critically abnormal Doppler studies; stage IV, hydrops; stage V, demise of one or both twins¹⁹. The following neonatal data were extracted: birth weight, Apgar score at 5 minutes, arterial blood pressure on admission measured with Dinamap, hematocrit on day 1 of life. Growth discordance between recipient and donor was calculated by dividing the difference in birth weights by the birth weight of the recipient twin. Hypotension or hypertension at birth was defined as a systolic blood pressure respectively below the 3rd or above the 97th

percentile for gestational age²⁴⁶. We also recorded the use of inotropic support during the stay in our nursery. Neonatal cranial ultrasound findings were reviewed, such as periventricular leucomalacia (PVL) (grade classification according to de Vries *et al*²²³), intraventricular hemorrhage (IVH) (grade classification according to Volpe *et al*²³⁶), porencephalic or parenchymal cysts, subependymal pseudocysts, ventriculomegaly and lenticulostriate vasculopathy. Other significant neonatal problems were also reviewed, including transient tachypnoea of the newborn, respiratory distress syndrome, chronic neonatal lung disease, patent ductus arteriosus, necrotizing enterocolitis, renal failure, hydrops fetalis, retinopathy of prematurity and congenital malformation.

Analysis of the TTTS group according to whether the twins were donor or recipient was performed in order to detect eventual differences in perinatal mortality and morbidity as well as differences in long-term outcome.

Results of categorical variables were compared using Fisher's exact test, whereas continuous normally distributed variables were examined with paired Student's *t* test. Chi-square test for trend was used in order to evaluate the relationship between stage of TTTS and outcome. A p-value < 0.05 was considered to indicate statistical significance. Analysis was performed using SPSS version 10 (SPSS, Inc., Chicago, Illinois, USA).

Results

Obstetrical results

During the 8-year study period, 33 multiple pregnancies (31 twins and 2 triplets) with TTTS were admitted to our center. The mean gestational age at the time of diagnosis was 22.4 (range: 15-28) weeks. The Quintero stage at admission was I in nine cases, II in eight cases, III in ten cases, IV in three cases and V in three cases. Four couples opted for termination of pregnancy. In the remaining 29 pregnancies, intrauterine fetal demise of both twins occurred in 38% (11/29) of the pregnancies. In four pregnancies, one twin survived while the co-twin died in utero. Caesarean delivery was performed in 9 (31%) of the 29 pregnancies. The mean gestational age at delivery was 28.6 (range: 20-37) weeks. Serial amnioreduction was performed in 18 (62%) of the 29 TTTS-

pregnancies. Mean gestational age at birth of the group of twins treated with serial amnioreduction was 31.3 weeks (range: 28-35). The median number of amnioreductions per case was 1 (range: 1-7) and the mean amount of amniotic fluid removed 2 liters (range: 0.5-15) per pregnancy. Amnioreduction was not performed in the remaining 15 pregnancies either due to intrauterine death of one or both twins at presentation (n = 7), because the patient opted for termination of pregnancy (n = 4), because of mild TTTS (Quintero stage I) (n = 3), or due to imminent delivery (n = 1). We found a direct relationship between stage of TTTS and mortality rate (p = 0.042) as well as stage of TTTS and adverse outcome (cerebral palsy or death) (p = 0.015) (Table 1). Cases in which parents opted for termination of pregnancy (n = 4) and cases with stage V (n = 3) of TTTS were not included in this analysis.

TABLE 1 Mortality rate and adverse outcome (cerebral palsy or death) by stage of TTTS.

Stage	Death ^a	Cerebral palsy or Death ^b
I	31% (5/16)	37% (6/16)
II	33% (4/12)	42% (5/12)
III	61% (11/18)	83% (15/18)
IV	67% (4/6)	67% (4/6)
Total	46% (24/52)	58% (30/52)

Values are percentages (numbers)

Cases in which parents opted for termination of pregnancy (n = 4) and cases with stage V (n = 3) of TTTS were not included in this analysis.

^aChi-square test for trend = 4.1, df = 1, p = 0.042

^bChi-square test for trend = 5.9, df = 1, p = 0.015

Neonatal results

Thirty-six (55%) fetuses were male, 30 (45%) were female. The overall perinatal survival rate was 50% (29/58) and in the subgroup treated with serial amnioreduction, 53% (19/36). Neonatal death occurred in 3 infants, all donor twins, and was caused by terminal renal failure (n = 1), *Escherichia coli* sepsis (n = 1) and severe respiratory distress syndrome (n = 1). There was no difference in overall perinatal mortality between donor and recipient twins (Table 2). The mean birth weight in donors was 1016 gr (range: 220-2740), whereas the mean birth weight in recipients

TABLE 2 Mortality and morbidity in donor and recipient twins.

	Donor (n = 29)	Recipient (n = 29)	p-value
IUFD	41% (12/29)	48% (14/29)	NS
NND	18% (3/17)	0% (0/15)	NS
Overall perinatal death	52% (15/29)	48% (14/29)	NS
Cerebral Palsy	17% (3/17)	17% (3/17)	NS

Cases in which parents opted for termination of pregnancy (n = 4) were not included in this analysis. IUFD, intrauterine fetal demise; NND, neonatal death; NS, not significant.

was 1291 gr (range: 310-2790). The difference in birth weight between donors and recipients was significant ($p < 0.001$). Eight of the seventeen donors (47%) were also small for gestational age as compared to none of the recipients ($p = 0.003$). The mean birth weight discordance between life born recipients and donors was 24% (range: 2%-41%). The median Apgar score at 5 minutes was 8 (range: 4-10). There was no significant difference in Apgar score between donors and recipients. The mean hematocrit at birth in donors was 48.2 (range: 28-68) l/l and in recipients, 51.8 (range: 39-66) l/l. The difference in hematocrit between donors and recipients was not significant. The mean systolic blood pressure at birth in donor twins was 45.6 (range: 30-60) mmHg and in recipients 61.8 (range: 44-94) mmHg. The difference in systolic blood pressure at birth between donors and recipients was significant ($p = 0.023$). Eight of the seventeen donors (47%) also required inotropic support as compared to only one of the recipients ($p = 0.008$). Hypertension at birth was found in 27% (4/15) of the recipients, but in none of the donors ($p = 0.038$). Renal failure occurred in two neonates, both donor twins. One of them died from terminal renal failure, the other child requires hemodialysis. Fetal hydrops was found in two twins at delivery (6%). One of them was a recipient twin. The other case of fetal hydrops occurred in a donor after the co-twin died in utero and was secondary to severe fetal anemia (hemoglobin value of 4.5 g/dL) probably following acute blood loss into the dead co-twin through the vascular anastomoses. An intrauterine blood transfusion raised the hemoglobin to 13 g/dL. The donor twin was born a few days later and was still hydropic. The incidence of respiratory distress syndrome was 31% (10/29). The incidence of chronic lung disease was 10% (3/29). Patent

ductus arteriosus was found in 25% (8/32) of the neonates. Necrotizing enterocolitis was diagnosed in 9% (3/32) of the neonates. None of the neonates had retinopathy of prematurity or congenital malformations. We found no significant differences in neonatal morbidity between donors and recipients. Abnormal cranial ultrasonographic findings were found in 12 of the 29 neonates (41%) in whom a scan was performed (IVH grade I-II: n = 4, unilateral IVH grade III with intraparenchymal echodensity: n = 2, bilateral IVH grade III with intraparenchymal echodensity: n = 1, PVL grade I: n = 3, ventriculomegaly: n = 3, lenticulostriate vasculopathy: n = 1). In 3 neonates no cranial ultrasound scan was performed. We found no significant differences in abnormal ultrasonographic findings between donors and recipients.

Long-term outcome

We were able to follow-up all 29 surviving twins during a home visit. The derivation of the surviving population is shown in a flow diagram in Figure 1. The mean gestational age at birth of the surviving twins was 31.6 (range: 25-37) weeks and the mean age at follow-up was 6.2 (range: 4-11) years. The incidence of cerebral palsy was 21% (6/29) (spastic quadriplegia: n = 2, spastic diplegia: n = 3, spastic hemiplegia: n = 1). The incidence of cerebral palsy in the group treated with serial amnioreduction was 26% (5/19). Five children with cerebral palsy had an abnormal mental development, and one child with left spastic hemiplegia had a normal

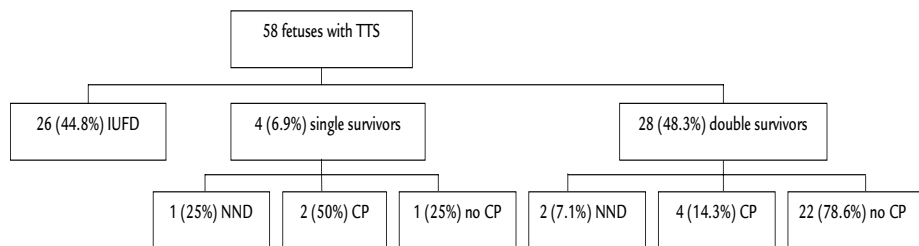


FIGURE 1 Outcome of 58 fetuses in 29 pregnancies with TTS.

Cases in which parents opted for termination of pregnancy (n = 4) were not included in this analysis. IUFD, intrauterine fetal demise; NND, neonatal death; CP, cerebral palsy

mental development. All children with abnormal mental development needed special education. Both infants with quadriplegia were severely mentally retarded. Data regarding the 6 surviving twins with abnormal neurodevelopmental outcome are listed in Table 3. In the group of children without cerebral palsy or abnormal mental development, 22% (5/23) of the children had a mild speech delay and required speech therapy. All of these children were kept in mainstream education with special assistance from a teacher or remedial teaching.

Four survivors were born after intrauterine fetal demise of their co-twin: one of them died in the neonatal period due to sepsis caused by *Escherichia coli*, two survivors have cerebral palsy and only one survivor has a normal outcome. The incidence of adverse long-term neurodevelopmental outcome in twins whose co-twin died in utero was 67% (2/3). The incidence of adverse long-term neurodevelopmental outcome in twins who were both born alive was 15% (4/26). The difference in neurodevelopmental outcome between survivors whose co-twin died in utero compared to twins who were both alive at birth was not significant, probably because study numbers were too small.

Gestational age at birth as well as birth weight was not associated with a significantly higher incidence of adverse neurodevelopmental outcome. We found no significant difference in long-term neurodevelopmental outcome between donors and recipients. In the neonatal period, IVH grade I-II was diagnosed in 4 neonates. All of them have a normal long-term psychomotor outcome. One neonate had a bilateral IVH grade III with intraparenchymal echodensity and died in the neonatal period due to terminal renal failure. Two neonates from the same pregnancy had a unilateral IVH grade III with intraparenchymal echodensity. One of them died two days after birth due to multi-organ failure. Its co-twin had a right-sided IVH grade III with intraparenchymal echodensity and has now spastic hemiplegia on the left side. PVL grade I was diagnosed in 3 neonates. Two of them have an abnormal long-term neurodevelopmental outcome. One of them also had ventriculomegaly but has only mild symptoms (mild speech and motor delay) without further signs of cerebral palsy or abnormal mental development. Another child with ventriculomegaly died two days after birth. The neurodevelopmental outcome of the recipient twin with lenticulostriate vasculopathy was normal.

TABLE 3 Data of the 6 surviving twins with adverse neurodevelopmental outcome.

Case	Twin	No. of amnio-reductions	GA at birth (wk)	BW (gr)	Neonatal cranial ultrasound findings	Age at follow-up	Neurologic outcome	Abnormal mental outcome	Other morbidity	Outcome of co-twin
1	Recipient	3	28	780	PVL I, ventriculomegaly	10,5	quadriplegia	yes	CLD	NND
2	Recipient	3	29	1206	PVL I	10	diplegia	yes	NEC	IUFD
3	Donor	7	32	930	normal	9,5	quadriplegia	yes	renal failure	normal
4	Donor	1	35	1064	normal	6	diplegia	yes	none	normal
5	Donor	4	32	1330	normal	4,5	diplegia	yes	NEC	IUFD
6	Recipient	0	25	801	IVH III + IPE	4	hemiplegia	no	CLD	NND

GA, gestational age; BW, birth weight; IPE, intraparenchymal echodensity; NND, neonatal death; CLD, chronic lung disease; NEC, necrotizing enterocolitis

Comment

In this study we analyzed the perinatal mortality and morbidity in TTTS. We report a high perinatal mortality rate (50%) in TTTS, emphasizing the critical nature of this disease. The perinatal mortality rate in the group treated with serial amnioreduction was slightly lower (47%), and comparable to previously published mortality rates in pregnancies managed similarly^{123;124;129}. We also found a direct relationship between stage of TTTS and mortality rate as well as between stage of TTTS and adverse outcome (cerebral palsy or death), confirming the prognostic significance of the Quintero staging classification. Regarding the neonatal morbidity, this study shows a significant difference in systolic blood pressure at birth between donors and recipients. Hypertension in recipients has previously been reported, and is theoretically more consistent with increased afterload rather than increased preload following volume overload⁸³. Increased afterload may result from a higher endothelin-1 level in recipients⁸⁴. Abnormal cranial ultrasonographic findings were found in 41% of the neonates who underwent cranial ultrasonography. Denbow *et al* reported an even higher incidence, 58%¹⁴⁶, whereas Hecher *et al* reported a lower incidence (range: 6% to 18%, depending on the type of antenatal therapy) of abnormal cranial ultrasound findings¹²³. However, the definition of abnormal ultrasound findings in the study of Hecher *et al* did not include IVH grades I and II.

The main objective of our study was to evaluate the long-term neurodevelopmental outcome in TTTS. We report a high incidence (21%) of cerebral palsy and abnormal mental development in surviving twins with TTTS. This is the first study in which all TTTS survivors were at least 4 years of age at follow-up. Since the incidence of adverse neurodevelopmental outcome is positively correlated to the duration of follow-up, it is important to continue follow-up until school age^{252;253}. The incidence of cerebral palsy and abnormal mental development is similar to most previous publications on long-term neurodevelopmental follow-up. Haverkamp *et al* found a 23% incidence of severe psychomotor retardation in combination with cerebral palsy in a cohort of 40 TTTS survivors who were followed until a mean age of 24 months¹⁴⁷. Cincotta *et al* found a 22% incidence of cerebral palsy and global developmental

delay in 23 surviving twins who were followed to at least 2 years of age corrected for prematurity¹⁴⁸. In a smaller study of 14 TTTS survivors who were followed until 2 years of age, Seng *et al* report a lower incidence (14%) of cerebral palsy with mental retardation³⁹. However, the inclusion criteria for TTTS of Seng *et al* were not based on prenatal ultrasound findings, but rather on postnatal inter-twin hemoglobin and birth weight differences. Other studies, including our study, have shown that the recipient does not necessarily have a higher hemoglobin or a higher hematocrit than the donor. Reaching the correct diagnosis of TTTS is no longer guaranteed by these postnatal criteria. Therefore, some of their patients may not have been affected by TTTS, which would also explain the exceptionally high survival rate (88%) in their study. Mari *et al* also report a much lower incidence (5%) of cerebral palsy in a cohort of 42 surviving twins who were at least 2 years of age at last follow-up¹⁵⁰. However, one infant in their cohort had multilocular encephalopathy but was lost to follow-up. Another infant died at 6 months of age of respiratory as well as neurological complications. Whether this child also had cerebral palsy is not clearly mentioned. Most importantly, the rate of neonatal deaths in their study was high, 16% (8/51). Half of these neonatal deaths occurred in children born at 24 and 25 weeks of gestation. The incidence of neurodevelopmental disability in children born at 24 and 25 weeks' gestation is reported to range from 12% to 45%²³⁹. Two other neonates who died in their study were reported to have abnormal cranial ultrasound findings (respectively brain infarction and IVH). Therefore the suspected incidence of cerebral palsy in the study of Mari *et al* could be higher. In all three neonatal deaths reported in our study, major abnormal cranial ultrasound findings were found (bilateral IVH grade III with intraparenchymal echodensity, n = 1; unilateral IVH grade III with intraparenchymal echodensity, n = 1; ventriculomegaly, n = 1). Therefore, the incidence of cerebral palsy in our study would most certainly have been higher had these three neonatal deaths not occurred. Mari *et al* also found that survivors born after 27 weeks of gestation had an excellent long-term outcome. In our study, 5 of the 6 survivors with adverse neurodevelopmental outcome were born after 27 weeks of gestation. We found that adverse neurodevelopmental outcome was associated with IUFD of a co-twin. This result supports previously published findings in

which a high incidence (27%) of serious neurological morbidity was found in survivors after death of a co-twin¹¹. The major cause of cerebral white-matter damage in surviving twins whose co-twin died in utero is acute cerebral ischemia due to acute exsanguination of the surviving twin into the low-resistance vascular system of the moribund or dead twin through the vascular anastomoses¹¹.

In all previously reported long-term follow-up studies, TTTS pregnancies were treated with serial amnioreduction. In our study, the incidence of adverse neurodevelopmental outcome in twins with TTTS treated with serial amnioreduction was also high (26%). Recent reports suggest that laser ablation therapy of placental vascular anastomoses may be associated with a lower incidence (4-9%) of cerebral palsy in surviving twins compared to serial amnioreduction^{133;152}. To assess the difference in mortality and morbidity between laser ablation therapy and serial amnioreduction, results of the first randomized control trial (www.eurofoetus.org) comparing both treatments must be awaited. Considering the high incidence of adverse neurodevelopmental outcome in TTTS, we recommend that all surviving twins be thoroughly followed up.

