



Universiteit
Leiden
The Netherlands

Follow-up studies in prenatal medicine

Nagel, H.T.C.

Citation

Nagel, H. T. C. (2007, February 14). *Follow-up studies in prenatal medicine*.
Retrieved from <https://hdl.handle.net/1887/9762>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/9762>

Note: To cite this publication please use the final published version (if applicable).

CHAPTER 6

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

E Lopriore

HTC Nagel

FPHA Vandenbussche

F Walther

Based on: Am J Obstet Gynecol 2003;189:1314-19

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 death of their co-twin: two of them had cerebral palsy.

Conclusion

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

Introduction

Cerebral palsy is estimated to occur seven times more often in twins than in singletons. 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 transfusions.² 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 polyuric.³ 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%.^{4,5} 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%.⁶⁻⁸ Nevertheless, the morbidity in surviving twins, which includes mainly neurological, cardiovascular and renal complications, remains high.³ Cerebral white-matter lesions have been reported to occur antenatally in up to 35% of TTTS-survivors.⁹ 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%.¹⁰⁻¹⁵ 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 birth.¹⁶⁻¹⁸ The main purpose of our study was to evaluate long-term neurodevelopmental outcome in school-aged twins after TTTS.

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 < 1cm) 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 centre 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 death, gestational age at delivery and mode of delivery. We also recorded the stage of TTTS on admission.¹⁹ 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, death of one or both twins.¹⁹ 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 age.²⁰ We also recorded the use of inotropic support during the stay in our nursery. Neonatal cranial ultrasound findings were reviewed, such as periventricular leukomalacia (PVL) (grade classification according to de Vries *et al.*), intraventricular hemorrhage (IVH) (grade classification according to Volpe *et al.*), porencephalic or parenchymal cysts, subependymal pseudocysts, ventriculomegaly and lenticulostriate vasculopathy.^{21,22} Other significant neonatal problems were also reviewed, including transient tachypnea of the newborn, respiratory distress syndrome, chronic neonatal lung disease, patent ductus arteriosus, necrotising 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-squared test for trend was used to evaluate the relationship between the stage of TTTS and outcome. A probability-value <0.05 was considered to indicate statistical significance. Analysis was performed with SPSS software (version 10; SPSS, Inc., Chicago, Illinois, USA).

Results

Obstetric 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 death 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 litres (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*	Cerebral palsy or Death†
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 (n/N)

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.

*Chi-squared test for trend = 4.1, $df = 1$, $P = .042$

†Chi-squared test for trend = 5.9, $df = 1$, $P = .015$

Table 2. Mortality and morbidity rates in donor and recipient twins

	Donor (n=29)	Recipient (n=29)	P-value
Intrauterine fetal death	41.4% (12/29)	48.3% (14/29)	NS
Neonatal death	17.6% (3/17)	0% (0/15)	NS
Overall perinatal death	51.7% (15/29)	48.3% (14/29)	NS
Cerebral Palsy	17% (3/17)	17% (3/17)	NS

Values are percentages (n/N)

Cases in which parents opted for termination of pregnancy (n = 4) were not included in this analysis.
NS, not significant.

Neonatal results:

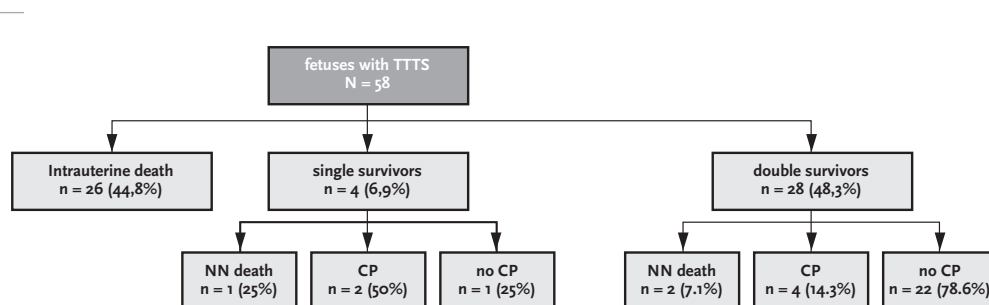
Thirty-six (55%) fetuses were male, 30 (45%) were female. The overall perinatal survival rate was 50% (29/58) and in the subgroup treated with serial amnioreduction, 53% (19/36). Neonatal death occurred in 3 infants, all donor twins, and was caused by terminal renal failure (n = 1), *Escherichia coli* 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 1,016 g (range: 220-2,740), whereas the mean birth weight in recipients was 1,291 g (range: 310-2,790). The difference in birth weight between donors and recipients was significant ($P < 0.001$). Eight of the 17 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) and in recipients, 51.8% (range: 39-66). 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 17 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 of whom were donor twins. One of them died of 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 due to severe fetal anaemia

(hemoglobin value of 4.5 g/dL) probably after 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 neonates). The incidence of chronic lung disease was 10% (3/29 neonates). Patent ductus arteriosus was found in 25% (8/32) of the neonates. Necrotising 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: 4 neonates, unilateral IVH grade III with intraparenchymal echodensity: 2 neonates, bilateral IVH grade III with intraparenchymal echodensity: 1 neonate, PVL grade I: 3 neonates, ventriculomegaly: 3 neonates, 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**.

Figure 1. Outcome of 58 fetuses in 29 pregnancies with TTTS.



Cases in which parents opted for termination of pregnancy (n = 4) were not included in this analysis.
NN, neonatal ; CP, cerebral palsy

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 infants). Five children with cerebral palsy had abnormal mental development, and one child with left spastic hemiplegia had a normal mental development. All children with abnormal mental development needed special education. Both infants with quadriplegia were severe 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.

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

Case	Twin	Number of amnioreductions (n)	GA at birth (wk)	Birth weight (g)	Neonatal cranial ultrasound findings	Age at follow-up (y)	Neurologic outcome	Abnormal mental outcome	Other morbidity	Outcome of co-twin
1	Recipient	3	28	780	PVL I, ventriculomegaly	10 ^{1/2}	Quadriplegia	Yes	CLD	NN death
2	Recipient	3	29	1206	PVL I	10	Diplegia	Yes	NEC	IU death
3	Donor	7	32	930	Normal	9 ^{1/2}	Quadriplegia	Yes	renal failure	Normal
4	Donor	1	35	1064	Normal	6	Diplegia	Yes	none	Normal
5	Donor	4	32	1330	Normal	4 ^{1/2}	Diplegia	Yes	NEC	IU death
6	Recipient	0	25	801	IVH III + IPE	4	Hemiplegia	No	CLD	NN death

GA, gestational age; PVL, periventricular leukomalacia; CLD, chronic lung disease; NN, neonatal; NEC, necrotising enterocolitis; IU, intrauterine; IPE, intraparenchymal echodensity

Four survivors were born after intrauterine death 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 children). 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 with twins who were both alive at birth was not significant, probably because study numbers were too small.

Gestational age at birth as well and birth weight were 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 four 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 of 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 of 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.

Discussion

We analysed the perinatal mortality and morbidity in TTTS. We report a high perinatal mortality rate (50%) in TTTS, which emphasizes the critical nature of this disease. The perinatal mortality rate in the group that was treated with serial amnioreduction was slightly lower (47%), and comparable to previously published mortality rates in pregnancies treated similarly.⁶⁻⁸ We also found a direct relationship between stage of TTTS and mortality rate and between stage of TTTS and adverse outcome (cerebral palsy or death), which confirms the prognostic significance of the Quintero staging classification. Regarding the neonatal findings, this study shows a significant difference in systolic blood pressure at birth between donors and recipients. Hypertension at birth in recipients has been reported previously, and is theoretically more consistent with increased afterload rather than increased preload after volume overload.²³ Increased afterload may result from a higher endothelin-1 level in recipients.²⁴ Abnormal cranial ultrasonographic findings were found in 41% of the neonates who underwent cranial ultrasonography. Denbow *et al.* reported an even higher incidence, 58%, whereas Hecher *et al.* reported a lower incidence (range: 6% to 18%, depending on the type of antenatal therapy) of abnormal cranial ultrasound findings.^{8,9} 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.^{17,18} 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 survivors of TTTS who were followed until a mean age of 24 months.¹³ 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 prematurity.¹² 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 retardation.¹¹ 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-up.¹⁰ 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 infants). One half of these neonatal deaths occurred in children who were born at 24 and 25 weeks of gestation. The incidence of neurodevelopmental disability in children who were born at 24 and 25 weeks gestation is reported to range from 12% to 45%.²⁵ 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 who were 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. However, because our study was not a case-control study, we could not conclude whether cerebral palsy was prematurity related or TTTS related. We found that

adverse neurodevelopmental outcome was associated with intrauterine fetal death of a co-twin. This result supports previously published findings in which a higher incidence of serious neurological morbidity was found in survivors after death of a co-twin.^{3,26,27} 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 anastomoses.³

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.^{14,15}

Conclusion

To assess whether cerebral palsy in TTTS is treatment related, the results of the first randomised control trial (www.eurofoetus.org) that compared both laser ablation therapy and serial amnioreduction must be awaited. Considering the high incidence of adverse neurodevelopmental outcome in TTTS, we recommend that all surviving twins undergo thorough follow-up visits.

References

1. Blickstein I. Cerebral palsy in multifoetal pregnancies. *Dev Med Child Neurol* 2002;44:352-5.
2. Minakami H, Honma Y, Matsubara S, Uchida A, Shiraishi H, Sato I. Effects of placental chorionicity on outcome in twin pregnancies. A cohort study. *J Reprod Med* 1999;44:595-600.
3. Lopriore E, Vandenbussche FP, Tiersma ES, de Beaufort AJ, de Leeuw JP. Twin-to-twin transfusion syndrome: new perspectives. *J Pediatr* 1995;127:675-80.
4. Gonsoulin W, Moise KJ, Jr., Kirshon B, Cotton DB, Wheeler JM, Carpenter RJ, Jr. Outcome of twin-twin transfusion diagnosed before 28 weeks of gestation. *Obstet Gynecol* 1990;75:214-6.
5. Urig MA, Clewell WH, Elliott JP. Twin-twin transfusion syndrome. *Am J Obstet Gynecol* 1990;163:1522-6.
6. Hecher K, Plath H, Bregenzner T, Hansmann M, Hackeloer BJ. Endoscopic laser surgery versus serial amniocenteses in the treatment of severe twin-twin transfusion syndrome. *Am J Obstet Gynecol* 1999;180:717-24.
7. Mari G, Roberts A, Detti L, Kovanci E, Stefos T, Bahado-Singh RO et al. Perinatal morbidity and mortality rates in severe twin-twin transfusion syndrome: results of the International Amnioreduction Registry. *Am J Obstet Gynecol* 2001;185:708-15.
8. Hecher K, Diehl W, Zikulnig L, Vetter M, Hackeloer BJ. Endoscopic laser coagulation of placental anastomoses in 200 pregnancies with severe mid-trimester twin-to-twin transfusion syndrome. *Eur J Obstet Gynecol Reprod Biol* 2000;92:135-9.
9. Denbow ML, Battin MR, Cowan F, Azzopardi D, Edwards AD, Fisk NM. Neonatal cranial ultrasonographic findings in preterm twins complicated by severe fetofetal transfusion syndrome. *Am J Obstet Gynecol* 1998;178:479-83.
10. Mari G, Detti L, Oz U, Abuhamad AZ. Long-term outcome in twin-twin transfusion syndrome treated with serial aggressive amnioreduction. *Am J Obstet Gynecol* 2000;183:211-7.
11. Seng YC, Rajadurai VS. Twin-twin transfusion syndrome: a five year review. *Arch Dis Child Fetal Neonatal Ed* 2000;83:F168-F170.
12. Cincotta RB, Gray PH, Phythian G, Rogers YM, Chan FY. Long term outcome of twin-twin transfusion syndrome. *Arch Dis Child Fetal Neonatal Ed* 2000;83:F171-F176.
13. Haverkamp F, Lex C, Hanisch C, Fahnenstich H, Zerres K. Neurodevelopmental risks in twin-to-twin transfusion syndrome: preliminary findings. *Eur J Paediatr Neurol* 2001;5:21-7.
14. Ville Y, Hecher K, Gagnon A, Sebire N, Hyett J, Nicolaides K. Endoscopic laser coagulation in the management of severe twin-to-twin transfusion syndrome. *Br J Obstet Gynaecol* 1998;105:446-53.
15. Sutcliffe AG, Sebire NJ, Pigott AJ, Taylor B, Edwards PR, Nicolaides KH. Outcome for children born after in utero laser ablation therapy for severe twin-to-twin transfusion

- syndrome. *BJOG* 2001;108:1246-50.
16. Ornstein M, Ohlsson A, Edmonds J, Asztalos E. Neonatal follow-up of very low birthweight/extremely low birthweight infants to school age: a critical overview. *Acta Paediatr Scand* 1991;80:741-8.
17. Escobar GJ, Littenberg B, Petitti DB. Outcome among surviving very low birthweight infants: a meta-analysis. *Arch Dis Child* 1991;66:204-11.
18. McCormick MC. Long-term follow-up of infants discharged from neonatal intensive care units. *JAMA* 1989;261:1767-72.
19. Quintero RA, Morales WJ, Allen MH, Bornick PW, Johnson PK, Kruger M. Staging of twin-twin transfusion syndrome. *J Perinatol* 1999;19:550-5.
20. Anonymous. Systolic blood pressure in babies of less than 32 weeks gestation in the first year of life. Northern Neonatal Nursing Initiative. *Arch Dis Child Fetal Neonatal Ed* 1999;80:F38-F42.
21. de Vries LS, Eken P, Dubowitz LM. The spectrum of leukomalacia using cranial ultrasound. *Behav Brain Res* 1992;49:1-6.
22. Volpe JJ. Intracranial hemorrhage: germinal matrix-intraventricular hemorrhage of the premature infant. In: Volpe JJ, editor. *Neurology of the newborn*. 4th Edition. Philadelphia: Saunders; 2001. p. 428-93.
23. Tolosa J. E., Zoppini, C., Ludomirsky, A., Bhutani, S., Weil, R., and Huhta, J. C. Fetal hypertension and cardiac hypertrophy in the discordant twin syndrome. *Am J Obstet Gynecol* 1993;169:292.
24. Bajoria R, Sullivan M, Fisk NM. Endothelin concentrations in monochorionic twins with severe twin-twin transfusion syndrome. *Hum Reprod* 1999;14:1614-8.
25. Hack M, Fanaroff AA. Outcomes of children of extremely low birthweight and gestational age in the 1990's. *Early Hum Dev* 1999;53:193-218.
26. Scher AI, Petterson B, Blaier E, Ellenberg JH, Grether JK, Haan E *et al*. The risk of mortality or cerebral palsy in twins: a collaborative population based-study. *Pediatr Res* 2002 ;52:671-81.
27. Glinianaia SV, Pharoah POD, Wright C, Rankin JM. Fetal or Infant death in twin pregnancy: neurodevelopmental consequence for the survivor. *Arch Dis Child* 2002 ;86:F9-15.

