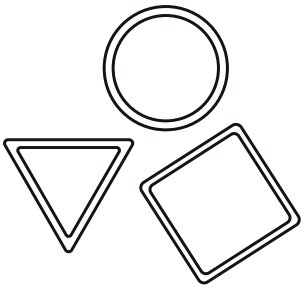
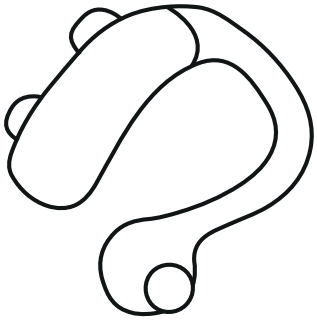
Next steps towards improved care for twin anemia polycythemia sequence

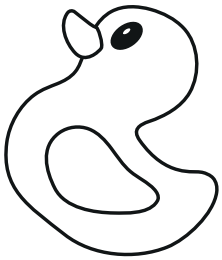
Tollenaar, L.S.A.

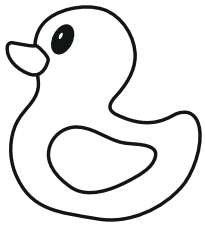
PART 9

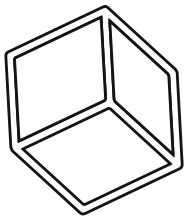
long-term outcome

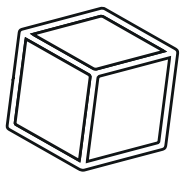












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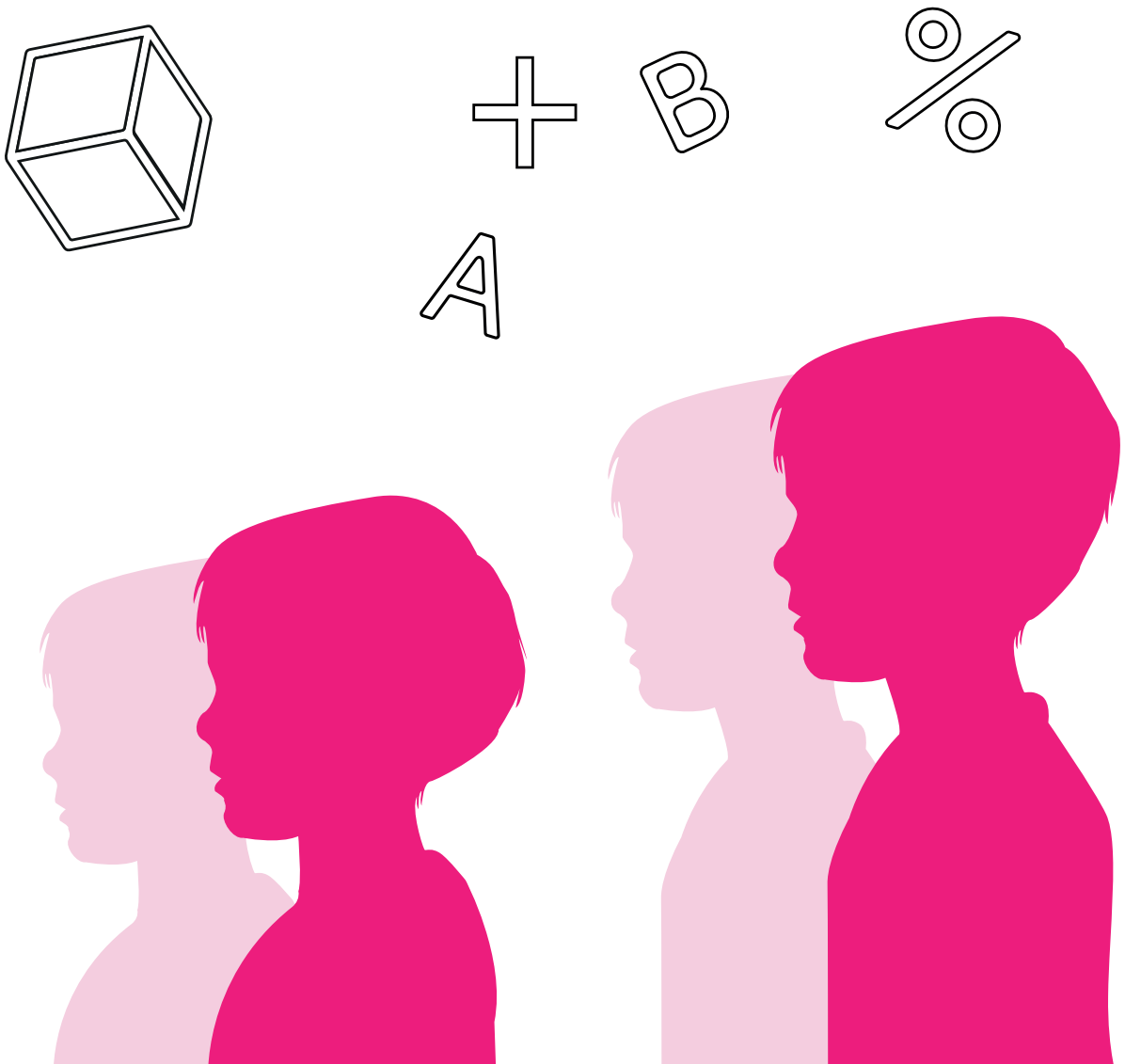
Ultrasound in Obstetrics and
Gynecology, 2020; 55 (1): 39-46

Chapter 11

High risk of long-term neurodevelopmental impairment in donor twins with spontaneous twin anemia polycythemia sequence



Abstract

Objective

The aim of this study was to evaluate the long-term neurodevelopmental and behavioural outcome in survivors of twin anemia polycythemia sequence (TAPS).

Methods

This was a retrospective study of a consecutive cohort of spontaneous TAPS survivors delivered between2005 and 2017 at the Leiden University Medical Center, The Netherlands. Neurological, motor, cognitive, and behavioural development was assessed at median age of 4 years. The primary outcome was neurodevelopmental impairment (NDI), which was a composite outcome of cerebral palsy, deafness, blindness and motor and/or cognitive delay. NDI was subdivided into two grades of severity: mild-to-moderate and severe NDI. Outcome was compared between surviving donor and recipient twins. Logistic regression analysis was used to assess risk factors for NDI

Results

Fourty-nine twin pregnancies complicated by spontaneous TAPS were eligible for inclusion. The perinatal survival rate was 83% (81/98) of twins. Neurodevelopmental assessment was performed in 91% (74/81) of surviving twins. NDI occurred in 31% (22/74) of the TAPS survivors, and was found more often in donors (44%; 15/34) than in recipients (18%; 7/40) (OR 4.1, 95%CI 1.8-9.1, p = 0.001). Severe NDI was detected in 9% (7/74) of survivors and was higher in donors compared with recipients, 18% (6/34) versus 3% (1/40), although the difference did not reach statistical significance (p = 0.056). Donors demonstrated lower cognitive scores compared with recipients (p = 0.011). Bilateral deafness was identified in 15% (5/34) of the donors compared with 0% (0/40) of recipients (p = 0.056). Parental concern regarding development was reported more often for donor than for recipient twins (p = 0.001). On multivariate analysis, independent risk factors for NDI were gestational age at birth (OR = 0.7, 95%CI 0.5-0.9, p = 0.003) and severe anemia (OR = 6.4, 95%CI 2.4-17.0, P < 0.001).

Conclusion

Surviving donor twins of pregnancies complicated by spontaneous TAPS have four-fold higher odds of NDI compared with recipient co-twins. TAPS donors have a fourfold higher risk of NDI compared with recipient co-twins and are at increased risk of cognitive delay and deafness.

Introduction

Twin anemia polycythemia sequence (TAPS) is a form of chronic imbalanced foeto-foetal transfusion through minuscule placental anastomoses in monochorionic twin pregnancies, leading to anemia in the donor twin and polycythemia in the recipient twin.[1] Unlike twin-to-twin transfusion syndrome (TTTS), TAPS is not associated with amniotic fluid discordance. TAPS occurs spontaneously in 3-5% of the monochorionic twin pregnancies (spontaneous TAPS) and can develop iatrogenically due to residual anastomoses in 2-16% of pregnancies treated with laser surgery for TTTS (post-laser TAPS). [2, 3] While the optimal antenatal management in TAPS is not known, management options include expectant management, induced preterm delivery, intrauterine blood transfusion (IUT) with or without partial exchange transfusion (PET), fetoscopic laser coagulation of the placental anastomoses and selective feticide.

Short-term outcome in TAPS varies from isolated hemoglobin differences to severe cerebral injury and neonatal death.[4] Due to an increasing number of monochorionic twins being liveborn after a complicated pregnancy, attention is shifting from short-term perinatal outcome to long-term neurodevelopmental outcome, focusing more on survival without impairment and quality of life. Only one previous study in a cohort of post-laser TAPS evaluated the long-term outcome of TAPS and showed that severe neurodevelopmental impairment (NDI) occurs in 9% of survivors.[5] However, in spontaneous TAPS the long-term neurodevelopmental outcome is unknown, which hampers adequate parent counselling. Moreover, knowledge of the long-term outcome is of paramount importance for designing future RCT's to determine the best treatment option for TAPS.

The aims of the current study were to evaluate the long-term neuro-developmental and behavioural outcomes in a large cohort of children of pregnancies complicated by spontaneous TAPS, to compare outcome between donors and recipients, and to identify potential risk factors for NDI.

Methods

All consecutive monochorionic twins with spontaneous TAPS evaluated at our center between 2005 and 2017 were eligible for this study. The Leiden University Medical Centre (LUMC) is the national referral centre for complicated twin

pregnancies and fetal therapy. The study was approved by the institutional ethics review board and all parents gave written informed consent for their children to participate. Monochorionic twin pregnancies identified as having TAPS either antenatally and/or postnatally were eligible for inclusion. Antenatal diagnosis was based on the recently updated ultrasound Doppler criteria for TAPS.[6] In brief, TAPS was diagnosed in presence of change u delta middle cerebral artery peak systolic velocity (MCA-PSV) > 0.5 multiples of the median (MoM), which is suggestive of the imbalanced chronic fetofetal transfusion leading to fetal anemia and polycythemia. Postnatal diagnosis was based on a large (> 8 g/dL) inter-twin difference in hemoglobin with at least one of the following criteria: reticulocyte count ratio > 1.7 and the presence of only minuscule (diameter < 1mm) anastomoses at the placental surface detected by color dye injection.[7] TAPS was classified antenatally and postnatally from stages 1 to 5, in accordance with the previously published staging systems for TAPS.[6, 8]

The following perinatal data were retrieved from our databases: gestational age at diagnosis, antenatal TAPS stage, antenatal treatment, gestational age at birth, sex, birth weight, small-for-gestational age (SGA: birth weight < 10th percentile) or fetal growth restriction (FGR; birthweight < 3rd percentile, according to the charts of Hoftiezer et al.[9], severe fetal anemia, hemoglobin and reticulocyte values at birth, need for blood transfusion or partial exchange transfusion on day 1 after delivery, severe neonatal morbidity, severe cerebral injury, and perinatal death. Severe fetal anemia was defined as the need for IUT, fetal MCA-PSV value > 1.7 MoM or a blood transfusion at birth. The definition of severe neonatal morbidity is based on the presence of at least one of the following conditions: respiratory distress syndrome requiring mechanical ventilation or surfactant, patent ductus arteriosus requiring medical therapy or surgical closure, necrotizing enterocolitis ≥ grade two[10], or severe cerebral injury. Severe cerebral injury was diagnosed in case of the presence of one of the following abnormalities detected on cerebral imaging: intraventricular haemorrhage ≥ grade three[11] cystic periventricular leukomalacia ≥ grade two[12], ventricular dilatation ≥ 97th percentile[13], porencephalic cysts, or arterial or venous infarction.

A follow-up appointment was scheduled at a minimum age of 24 months and consisted of a neurologic and cognitive assessment and a behavioural questionnaire. Cognitive development was assessed using three standardized

psychometric age-appropriate tests, providing cognitive scores with a normal distribution with a mean of 100 and a SD of 15. For children aged 2-3 years, the Dutch version of the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III-NL)[14] was used. When children were aged between three and six years the Wechsler Preschool and Primary Scale of Intelligence third Edition (WPPSI-III-NL) was used.[15] For children aged 7 years or older, the Wechsler Intelligence Scale for Children third edition (WISC-III-NL)[16], was used. To investigate behavioural problems, parents completed the Child's Behaviour Checklist (CBCL) for 1.5-5 years or 6-18 years, as appropriate.[17, 18] In cases in which the child presented with hearing loss, vision loss, or cerebral palsy, additional medical information from our center or peripheral hospitals was requested to determine the grade of severity of the impairment. Maternal educational level was recorded and divided into three levels. A score of one was given when the mother's education was low (primary school), a score of two for intermediate level (secondary school and intermediate vocational school), and a score of three for higher levels (higher vocational school and university).

The primary outcome of this study was NDI, which was defined as a composite outcome consisting of four different domains: motor and/or cognitive impairment, vision loss, hearing loss, and cerebral palsy. NDI was subdivided into two grades of severity: mild-to-moderate and severe NDI. For mild-to-moderate NDI at least one of the following criteria needed to be fulfilled: mild cognitive or motor delay (IQ score < 85 (-1SD)), vision loss, hearing loss, or cerebral palsy (Gross Motor Functioning Classification System (GMFCS)[19], Level 1). Severe NDI was diagnosed in case of at least one of the following: severe cognitive or motor delay (IQ score < 70 (-2SD)), bilateral blindness, bilateral deafness (requiring amplification), or severe cerebral palsy (GMFCS Level ≥ 2). The incidence of NDI was compared between TAPS donors and recipients. The secondary outcomes included behavioural problems and a risk factor analysis for NDI. The presence of behavioural problems was defined as a T-score ≥ 64 in one of the following broadband scales: total problems, internalizing problems (anxious/depressed, withdrawn, somatic complaints), or externalizing problems (rule-breaking, aggressive behaviour). A specific item of the CBCL open field regarding parental concerns about their child's development, was included as a separate secondary outcome. The following risk factors were analysed for NDI: management strategy, donor status, severe fetal anemia, FGR and maternal educational level.

Statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Data are reported as mean ± SD or as median and interquartile ranges (IQR), as appropriate. A P-value < 0.05 was considered to indicate statistical significance. To compare outcomes between TAPS donors and recipients, a paired sampled T-test and generalized estimating equations was performed for continuous or categorical outcomes, respectively. As a generalized estimating equations cannot be used in case of non-occurring events in one of the groups, an adjustment to the data was applied in which an unaffected child was changed into an affected child, for both groups. This correction generates more conservative P-values. Potential risk factors were checked for correlation using Pearson's square (*r*). An *r*-value of > 0.7 or < -0.7 was considered to indicate a strong relationship between the factors. Potential risk factors for NDI were assessed in a univariate logistic regression model. A multivariate logistic regression model was applied on the variables that showed significant association in the univariate analysis. Results are expressed as odds ratios (OR) with 95% CI.

Results

Between 2005 and 2017, 49 monochorionic twin pregnancies were diagnosed with spontaneous TAPS at the LUMC. Demise occurred in 15 fetuses, which was in all cases related to or preceded by an intervention, including selective feticide (n = 8), laser surgery (n = 3), or termination of pregnancy (n = 4). Neonatal mortality occurred in two infants, yielding a total population of 81 TAPS survivors eligible for long-term follow up. Seven (9%) children were lost to follow-up due to declined consent (n= 3) or loss of contact information (n = 4). In total, long-term follow-up assessment was performed in 91% (74/81) of TAPS survivors, including 34 donors and 40 recipients, from 41 TAPS pregnancies. The derivation of the study population is summarized in Figure 1.

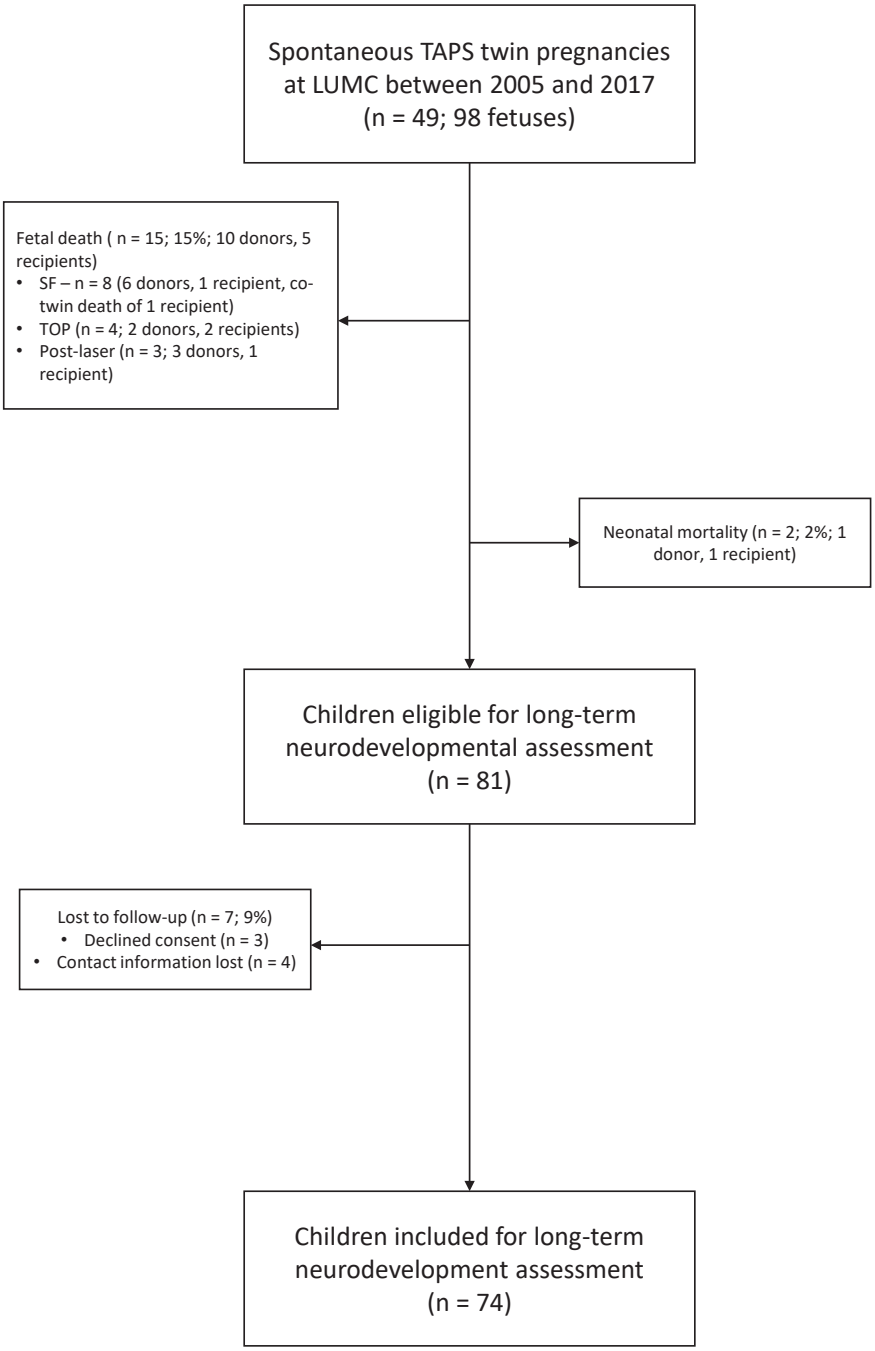


Figure 1. Derivation of the study population. TAPS. Twin anemia polycythemia sequence, LUMC: Leiden University Medical Centre, SF: selective feticide, TOP: termination of pregnancy.

Pregnancy characteristics and neonatal outcome in the total population are shown in Table 1 and 2, respectively. TAPS was detected antenatally in 71% (29/41) of the cases, with TAPS stage ranging from 1 to 3. Fetal therapy was performed in 59% of this group and consisted of IUT/PET (14% (4/29)), laser surgery (28% (8/29)), and selective feticide (17%, (5/29)). Twelve (41%) TAPS pregnancies were managed expectantly and in two (17%), spontaneous resolution occurred after 3 and 6 weeks, respectively. In 50% (6/12) of the cases managed expectantly, preterm delivery was induced due to fetal distress or progression of the disease. In 29% (12/41) of the total population, TAPS was not detected antenatally and diagnosed postnatally. Overall, median gestational age at birth was 33.0 weeks (IQR: 30.1-35.7).

Table 1. Characteristics for 41 pregnancies complicated by twin anemia polycythemia sequence (TAPS)

	TAPS pregnancies (N = 41)
Antenatal diagnosis	29/41 (71)
Gestational age at diagnosis (weeks)	20.4 (18.0-27.0)
Antenatal TAPS stage	
Stage 1	5/29 (17)
Stage 2	11/29 (38)
Stage 3	13/29 (45)
Stage 4	-
Stage 5	-
Management	
Expectant	12/29(41)
IUT (with PET)	4/29(14)
Laser Surgery	8/29 (28)
Selective Foeticide	5/29 (17)
Gestational age at birth (weeks)	33.0 (30.1-35.7)
Postnatal diagnosis (only)	12/41 (29)
Postnatal TAPS stage	
Stage 1	3/27 (11)
Stage 2	10/27 (37)
Stage 3	5/27 (19)
Stage 4	5/27 (19)
Stage 5	4/27 (14)
Maternal education	
Low	4/41 (10)
Intermediate	13/41 (32)
High	24/41 (58)

Data are presented as median (IQR) or n/N (%)
TAPS: twin anemia polycythemia sequence, IUT: intrauterine transfusion, PET: partial exchange transfusion

Donors and recipients differed significantly in birth weight (p < 0.001). In addition, 53% of the donors were affected by FGR compared with 8% of the recipients (p < 0.001). There was no difference in rate of severe neonatal morbidity between donors and recipients. Within 1 day after delivery, TAPS donors received a blood transfusion for anemia in 65% of cases, whereas 38% of recipients were treated with a partial exchange transfusion for polycythemia.

Table 2. Neonatal outcome in 74 survivors of 41 pregnancies complicated by spontaneous twin anemia polycythemia sequence, overall and according to donor or recipient status

	Total (N = 74)	**Donors (N = 34)**	**Recipients (N = 40)**	**p-value**
Female sex	37/74 (50)	17/34 (50)	20/40 (50)	1.000
Birth weight (g)	1835 (1295-2238)	1733 (1160-1980)	2042 (1396-2424)	**< 0.001**
SGA	32/74 (43)	24/34 (71)	8/40 (20)	**< 0.001**
FGR	21/74 (28)	18/34 (53)	3/40 (8)	**< 0.001**
Severe neonatal morbidity				
Respiratory distress	21/74 (28)	8/34 (24)	13/40 (33)	0.116
syndrome	21/74 (28)	8/34 (24)	13/40 (33)	0.116
Patent ductus arteriosus	5/74 (7)	3/34 (9)	2/40 (5)	0.218
Necrotizing enterocolitis	2/74 (3)	1/34 (3)	1/40 (3)	0.905
Severe cerebral injury	1/74 (1)	0/34 (0)	1/40 (3)	0.668
Severe fetal anemia	30/74 (41)	30/34 (88)	0/40 (0)	-
Blood transfusion*	22/74 (30)	22/34 (65)	0/40 (0)	-
Partial exchange transfusion*	15/74 (20)	0/34 (0)	15/40 (38)	-

Data are presented as n/N (%) or median (interquartile range). *Within 1 day after delivery. FGR, fetal growth restriction (birth weight < 3rd percentile); SGA, small-for-gestational age (birth weight < 10th percentile)

Long-term neurodevelopmental outcome in the 74 TAPS survivors was assessed at a median age of 4 years (IQR: 2-6). Twenty-seven (37%) children were tested with a Bayley-III-NL, 33 (45%) children using WPPSI-III-NL and in 14 (19%) children, assessment was performed using WISC-III-NL. Table 3 shows long-term outcome. NDI was detected in 30% of the total group, affecting 15/34 (44%) donors and 7/40 (18%) recipients (p = 0.001). Donors had 4.1 (95%CI, 1.8-9.1)-fold higher risk for NDI compared to their recipient co-twins (p = 0.001). The incidence of severe NDI was 9% (7/74), occurring in 6/34 (18%) donors and in 1/40 recipient (3%) (p = 0.056). Further details on the cases with severe NDI are displayed in Table 4. Mild-to-moderate NDI was found in 20% (15/74) of all children, occuring in 26% (9/34) of donors and 15% (6/40) of recipients (p = 0.093). In addition,

donors had significantly lower cognitive scores compared with recipients (95 vs. 101; p = 0.001). Bilateral deafness was observed in 5/34 (15%) TAPS donors, which was in all cases due to auditory neuropathy spectrum disorder (ANSD), while none of the recipients had deafness (p = 0.056). Behavioural problems were reported in 10% (7/72) of the total group, with no difference between TAPS donors and recipients. Parents concern regarding development was reported more often for donor than for recipient twins (p = 0.001).

Table 3. Long-term outcome in 74 spontaneous TAPS survivors

	Total (N =74)	**Donors (N = 34)**	**Recipients (N = 40)**	**P-value**
Cognitive score	97 (87-105)	95 (87-105)	101 (90-106)	**0.011**
Cognitive delay				
Mild (score < 1 SD)	19/74 (26)	12/34 (35)	7/40 (18)	**0.006**
Severe (score < 2 SD)	2/74 (3)	2/34 (6)	0/40 (0)	0.265
Motor delay				
Mild (score < 1 SD)	1/26 (4)	1/12 (8)	0/14 (1)	0.471
Severe (score < 2 SD)	0/26 (0)	0/12 (0)	0/14 (0)	-
Bilateral blindness	1/74 (1)	0/34 (0)	1/40 (3)	0.657
Bilateral deafness	5/74 (7)	5/34 (15)	0/40 (0)	**0.056**
Cerebral Palsy (GMFCS Level 1)	2/74 (3)	2/34 (6)	0/40 (0)	0.265
NDI	22/74 (30)	15/34 (44)	7/40 (18)	**0.001**
Mild-to-moderate	15/74 (20)	9/34 (26)	6/40 (15)	0.093
Severe	7/74 (9)	6/34 (18)	1/40 (3)	**0.056**
NDI-free survival	52/82 (63)	19/41 (46)	33/41 (80)	**< 0.001**
Behavioural problems†				
Total	7/72 (10)	3/33 (9)	4/39 (10)	0.435
Internalizing	6/72 (8)	2/33 (6)	4/39 (10)	0.264
Externalizing	8/72 (11)	4/33 (12)	4/39 (10)	0.417
Parental concern regarding child's development	33/72 (46)	20/33 (61)	13/39 (33)	**0.001**

Data are presented as median (interquartile range) or n/N(%).*26 children had complete motor assessment with Bayley (BSID III) † Child Behaviour Checklist was not completed for one twin pair
GMFCS: Gross Motor Function Classification System, NDI: neurodevelopmental impairment

Table 4. Characteristics of seven survivors of pregnancies complicated by spontaneous twin anemia polycythemia sequence (TAPS) that had severe neurodevelopmental impairment

TAPS donor / recipient	GA at diagnosis (weeks)	Antenatal TAPS stage	Antenatal Treatment	GA at birth (weeks)	Neonatal morbidity	Hb at birth (g/dL);	Δ Hb (g/dL)	Postnatal TAPS stage	Long-term outcome
Recipient	15^{+2}	Stage 2	Expectant management	25^{+2}	RDS PDA IVH stage 2 ROP stage 3	21.6	NA†	NA	Bilateral blindness Mild cognitive delay Internalizing and externalizing behavioural problems
Donor	26^{+5}	Stage 1	Expectant management	36^{+2}	FGR	9.5	14.2	3	Severe cognitive delay Externalizing behavioural problems
Donor	28^{+2}	Stage 3	IUT, induced delivery	29^{+1}	RDS, PDAPDA	4.8	15.6	3	Bilateral deafness (ANSD) CP (GMFCS Level 1) Severe cognitive delay
Donor	30^{+1}	Stage 1	Induced delivery	30^{+1}	RDS, FGR	3.1	16.3	3	Bilateral deafness (ANSD) Mild cognitive delay
Donor	25^{+9}	Stage 1	Expectant management, Induced delivery	28^{+6}	RDS	8.1;	13.5	2	Bilateral deafness (ANSD)
Donor	28^{+3}	Stage 2	Laser surgery	28^{+4}	RDS	4.0	22.2	5	Bilateral deafness (ANSD)
Donor	Postnatal	-	-	35^{+5}	FGR	6.4	16.1	3	Bilateral deafness (ANSD) CP (GMFCS Level 1) Externalizing behavioural problems

*Difference in hemoglobin (Hb) level between twin and cotwin. †Neonatal mortality occurred within 1 day after birth in donor cotwin due to low birth weight (430 g, < 3rd centile) so Hb level was not available and Hb could not be calculated. ANSD, auditory neuropathy spectrum disorder; CP, cerebral palsy; FGR, fetal growth restriction; GA, gestational age; GMFCS, Gross Motor Function Classification System; IUT, intrauterine transfusion; IVH, intraventricular hemorrhage; NA, not available; PDA, patent ductus arteriosus; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity.

Table 5. Univariate and multivariate logistic regression analysis of potential risk factors for neurodevelopmental impairment in 74 surviving twins of 41 pregnancies complicated by spontaneous twin anemia polycythemia sequence

			Univariate analysis			Multivariate analysis		
	NDI (n = 22)	**No NDI (n = 52)**	**OR (95% CI)**	**SE**	**P**	**OR (95% CI)**	**SE**	**P**
Management								
Postnatal diagnosis	5/24 (21)	19/24 (79)	-	-	-			
Expectant management	11/22 (50)	11/22 (50)	3.8 (0.9-15.3)	0.7	0.061			
IUT (with or without PET)	3/8 (38)	5/8 (62)	2.3 (0.3-15.0)	1.0	0.177			
Laser surgery	2/15 (13)	13/15 (87)	0.6 (0.1-4.0)	1.0	0.577			
Selective feticide	1/5 (20)	4/5 (80)	1.0 (0.1-10.9)	1.2	0.967			
Severe anemia	16/30 (53)	14/30 (47)	6.2 (2.6-14.8)	0.4	**<0.001**	6.4 (2.4-17.0)	0.5	**<0.001**
Donor*	15/34 (44)	19/34 (56)	4.1 (1.8-9.1)	0.4	**0.001**			
GA at birth (completed weeks)	31 ± 3.4	33 ± 2.8	0.8 (0.6-1.0)	0.1	**0.024**	0.7 (0.5-0.9)	0.1	**0.003**
FGR	10/21 (48)	11/21 (52)	3.1 (1.1-8.4)	0.5	**0.030**	2.1 (0.7-6.9)	0.6	0.211
Level of education mother			0.8 (0.3-2.2)	0.5	0.802			
Low	1/4 (25)	3/4 (75)						
Intermediate	5/13 (38)	8/13 (62)						
High	6/24 (25)	18/24 (75)						

Data are given as n/N (%) or mean ± SD, unless stated otherwise. *Donor status was excluded from multivariate analysis due to strong correlation with severe anemia (R = 0.84, P < 0.001). †Odds ratio (OR) for maternal education level based on score in which 1 = low (primary school), 2 = intermediate (secondary school and intermediate vocational school) and 3 = high (high vocational school and university). FGR, fetal growth restriction (birth weight < 3rd centile); GA, gestational age; IUT, intrauterine transfusion; NDI, neurodevelopmental impairment; PET, partial exchange transfusion; SE, standard error.

Univariate logistic regression analysis of potential risk factors for NDI showed a significant association with severe fetal anemia (OR = 6.2, 95%CI 2.6-14.8, p < 0.001), donor status (OR = 4.1, 95%CI 1.8-9.1, p = 0.001), FGR (OR = 3.1, 95%CI 1.1-8.4, p = 0.030) and gestational age at birth (OR = 0.8, 95%CI 0.6-1.0, p = 0.024). All significant risk factors were included in the multivariate analysis. As severe fetal anemia was correlated strongly with donor status (r = 0.84, p < 0.001), donor status was excluded from the multivariate analysis. There was no strong significant association between other risk factors. Multivariate analysis demonstrated that severe anemia (OR = 6.4, 95%CI 2.4-17.0, p < 0.001) and gestational age at birth (OR = 0.7, 95%CI 0.5-0.9, P = 0.003) were independent risk factors for NDI. So, for each incremental week of gestation, the risk of NDI decreases by 30%, and children with severe fetal anemia have a 6.4-fold increased risk for NDI (Table 5).

Discussion

This is the first study to investigate long-term neurodevelopmental outcome in surviving infants of pregnancies complicated by spontaneous TAPS. TAPS donors had a fourfold higher risk of NDI compared with TAPS recipients. We also observed an unexpected high risk of bilateral deafness (15%) in TAPS donors, with no cases observed in recipients. In addition, there was a higher rate of mild cognitive delay and lower cognitive scores in TAPS donors compared with TAPS recipients.

The reason for the large discrepancy in long-term outcome between TAPS donors and recipients is unknown. To date, in the vast majority of long-term follow-up in TTTS or post-laser TAPS cohorts, no difference has been reported between donors and recipients.[5, 20] In these cohorts, gestational age at birth was the main predictor of adverse outcome. As twins, including those with TAPS, are born at the same gestational age, we need to look for other factors to explain the differences between donor and recipient. Given that TAPS twins are monochorionic and therefore monozygotic, genetic factors cannot play a role. Typically, in TAPS pregnancies, donors and recipients are exposed to different intrauterine environments. In TAPS, chronic erythrocyte loss from the donor into the recipient's circulation, gradually leading to fetal anemia, may result in a chronic hypoxic environment, impairing fetal brain development in the donors over time. Notably, donors with severe fetal anemia had a six-fold increased risk

for NDI. Alternatively, FGR could also be an important contributor to long-term adverse outcome in donors. In our population, FGR affected 53% of donors. FGR is known to be associated with long-term impairment in singletons[21], likely caused by decreased white and grey matter in the hippocampus and frontal lobe.[22, 23] These cerebral areas are responsible for memory, learning skills and executive functioning and therefore play a crucial role in cognitive impairment. In our study, FGR was a significant risk factor for NDI in univariate analysis, but failed to show significance in multivariate analysis, suggesting an association between FGR and other factors. A relation between fetal anemia and FGR in TAPS is not unlikely. Selective FGR (based on birth-weight discordance ≥ 25%) has previously been described in spontaneous TAPS twins and complicated 30% of the population.[24] Interestingly, growth restriction in TAPS is not related to unequal placental sharing; on the contrary, donors often have larger placental territories than recipients. FGR in TAPS donors might therefore be caused by other factors, such as chronic erythrocyte, albumin and/or protein loss through placental anastomoses.[25]

Parental concern regarding the development of their child was reported more often for donor than for recipient twins. It is reassuring for the validity of our findings that the impairment observed by standardized assessment coincides with parental concerns in daily life. The overall incidence of behavioural problems was 10%, which is comparable to that (10%) in children from the general Dutch population.[26]

Surprisingly, TAPS donors were more affected by deafness than TAPS recipients. The limited sample size and statistical adjustment for non-occurring events in paired groups prevented this difference to reach statistical significance, but clinically we found this striking and warranting more attention. Notably, deafness in all five affected donors was based on ANSD. In ANSD, the cochlea and outer hair cells are unaffected, but the inner hair cells, which connect synapses and/or the auditory nerve itself are damaged, resulting in compromised transmission of sound to the brain.[27] The pathogenesis of ANSD is multifactorial, including prematurity and perinatal hypoxia.[28] In theory, the chronic hypoxic state of the anemic foetus could have damaged not only the brain, but the developing auditory nerve system as well. Interestingly, the high incidence of deafness is not reported before in TTTS survivors or in children suffering from chronic fetal anemia based on erythrocyte alloimmunization.[29,30]

Moreover, the incidence of deafness in TAPS donors is higher compared with that in infants admitted to the neonatal intensive care unit (1-3%) [31]. To further explore the pathogenesis behind deafness in spontaneous TAPS, more elaborate studies are needed; for example, using neonatal brain magnetic resonance imaging.

Our study also revealed that spontaneous TAPS survivors showed a more detrimental outcome than did survivors of post-laser TAPS in a previous study.[5] Although the incidence of severe NDI was 9% for both groups, post-laser TAPS twins had overall a better outcome. They showed a lower rate of mild cognitive delay (17% vs. 26%), did not have bilateral deafness, and did not demonstrate differences between donor and recipient.[5] Two different theories may be considered to explain this discrepancy. Firstly, post-laser TAPS donors are less frequently growth restricted than spontaneous TAPS donors. This is because TAPS donors often have been former TTTS recipients, who generelly have a higher birth weight than TTTS donors.[32] Thus, post-laser TAPS donors might be protected by the relatively higher fetal weight when they start to develop anemia. Alternatively, spontaneous TAPS might develop earlier in gestation compared to post-laser TAPS, leading to a more chronic exposure to anemia during pregnancy.

Caution should be taken when interpreting our results due to the retrospective nature of this study. In our cohort, TAPS pregnancies varied in TAPS stage, gestational age at onset and management, making it hard to draw reliable conclusions with regard to the true effect of the natural course of TAPS. Furthermore, the sample size of this group was small, but it is nonetheless the largest group of spontaneous TAPS survivors reported to date.

In conclusion, this study has shown that spontaneous TAPS is characterized by a high impairment rate and that donors have an increased risk of cognitive impairment and deafness. To date, spontaneous TAPS has been thought to be a relatively benign form of feto-fetal transfusion, but these results show that the long-term consequences of this condition should not be underestimated. These findings necessitate further research into the best antenatal therapy for TAPS. Recently, the TAPS Trial has started, a study that will compare laser treatment with standard care for TAPS.[33] Finally, this study reinforces the importance of long-term follow-up for complicated monochorionic twin pregnancies. Although TAPS survivors have few severe neonatal problems, the true impact of this

condition seems to manifest in childhood. Therefore, routine long-term follow-up including screening for hearing loss should be an essential part of care for TAPS twins.

Acknowledgment

We thank all parents and children for their time and effort. We give special thanks to the psychologists of the department of Pediatrics, in particular Michelle de Mol and Carolien van Kerkhoven, for their dedicated work in performing follow-up assessments and writing outcome reports.

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