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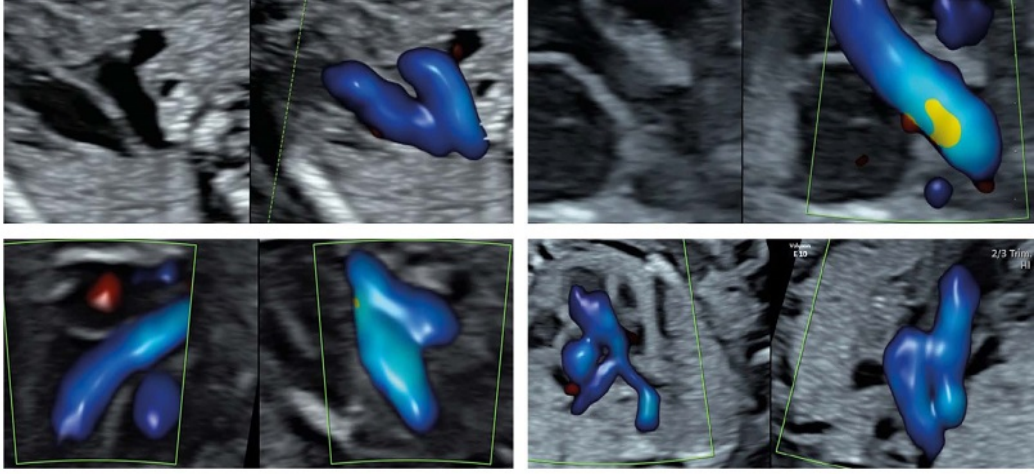

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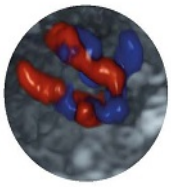

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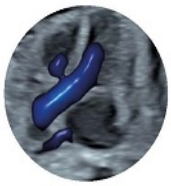

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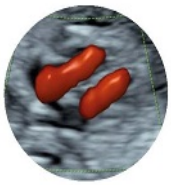

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Ultrasound Obstet Gynecol 2020; **55**: 39–46
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.20846

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

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KEYWORDS: anemia; long-term outcome; monochorionic twins; neurodevelopmental impairment; twin anemia–polycythemia sequence

CONTRIBUTION

What are the novel findings of this work?
Donor twins of pregnancies complicated by spontaneous twin anemia–polycythemia sequence (TAPS) have four-fold higher odds of neurodevelopmental impairment compared with their recipient cotwins, are at increased risk of cognitive delay and have a high rate of deafness.

What are the clinical implications of this work?
Based on our findings, we strongly advise that routine long-term follow-up, including testing for hearing loss, should be an essential part of care of twins diagnosed with spontaneous TAPS.

ABSTRACT

Objectives *To evaluate the long-term neurodevelopmental and behavioral outcomes in surviving infants of pregnancies with spontaneous twin anemia–polycythemia sequence (TAPS), to compare outcome between donors and recipients, and to investigate potential risk factors for neurodevelopmental impairment (NDI).*

Methods *This was a retrospective study of a consecutive cohort of spontaneous-TAPS survivors delivered between 2005 and 2017 at the Leiden University Medical Center, The Netherlands. Neurological, motor, cognitive and behavioral development were assessed at a median age of 4 years. The primary outcome was 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 *Forty-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 30% (22/74) of TAPS survivors, and was found more often in donors (44%; 15/34) than in recipients (18%; 7/40) (odds ratio (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) vs 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 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 delivery (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 cotwins, are at increased risk of cognitive delay and have a high rate of deafness.*

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Accepted: 9 August 2019

INTRODUCTION

Twin anemia–polycythemia sequence (TAPS) is a form of chronic imbalanced fetofetal 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 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 for 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 of 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 on quality of life. Only one previous study in a cohort of post-laser TAPS twins 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 counseling. Moreover, knowledge of the long-term outcome is of paramount importance for designing future randomized controlled trials to determine the best treatment option for TAPS.

The aims of the current study were to evaluate long-term neurodevelopmental and behavioral 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 twin pregnancies with spontaneous TAPS evaluated at our center between 2005 and 2017 were eligible for this study. The Leiden University Medical Center (LUMC) is the national referral center 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 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 the presence of change in fetal middle cerebral artery (MCA) peak systolic velocity (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) intertwin difference in hemoglobin with at least one of the following criteria: reticulocyte count ratio > 1.7 and the presence of only minuscule (diameter < 1 mm) 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; birth weight < 3rd centile), 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 1 day 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 need for blood transfusion at birth. Severe neonatal morbidity was defined as 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 ≥ 2[10], or severe cerebral injury. Severe cerebral injury was diagnosed in cases with one of the following abnormalities detected on cerebral imaging: intraventricular hemorrhage grade ≥ 3[11], cystic periventricular leukomalacia grade ≥ 2[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 neurological and cognitive assessment and a behavioral 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 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. For those aged between 3 and 6 years, the Wechsler Preschool and Primary Scale of Intelligence, third edition (WPPSI-III-NL)[15], was used. For children aged 7 years or older, the Wechsler Intelligence Scale for Children, third edition (WISC-III-NL)[16], was used. To investigate behavioral problems, parents completed the Child's Behavior 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 1 was given when the mother's education level was low (primary school), a score of 2 for intermediate level (secondary school and intermediate vocational school) and a

score of 3 for higher levels (higher vocational school and university).

The primary outcome 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 (composite score < 85 (−1 SD)), vision loss, hearing loss or cerebral palsy (Gross Motor Function Classification System (GMFCS) Level 1[19]). Severe NDI was diagnosed in case of at least one of the following: severe cognitive or motor delay (composite score < 70 (−2 SD)), 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 behavioral problems and risk factor analysis for NDI. The presence of behavioral problems was defined as a CBCL T-score of ≥ 64 in one of the following broadband scales: total problems, internalizing problems (anxious/depressed, withdrawn, somatic complaints), or externalizing problems (rule-breaking, aggressive behavior). 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 analyzed for NDI: management strategy, donor status, severe fetal anemia, gestational age at delivery, 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 median and interquartile range (IQR), as appropriate. A *P*-value < 0.05 was considered to indicate statistical significance. To compare outcomes between TAPS donors and recipients, a paired-samples Student's *t*-test and generalized estimating equations were performed for continuous and categorical variables, respectively. As 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 correlation coefficient (*r*). An *r*-value of > 0.7 or < −0.07 was considered to indicate a strong correlation between the variables. Potential risk factors for NDI were assessed in a univariate logistic regression model. A multivariate logistic regression model was applied to the variables that showed a significant association on univariate analysis. Results of regression analyses 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 ($n = 4$). Long-term follow-up assessment was therefore 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.

Pregnancy characteristics and neonatal outcome in the total population are shown in Tables 1 and 2, respectively. TAPS was detected antenatally in 71% (29/41) of 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%) pregnancies were managed expectantly and in two (17%) of these, spontaneous resolution occurred after 3 and 6 weeks, respectively. In 50% (6/12) of 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 was diagnosed postnatally. Overall, median gestational age at delivery was 33.0 (IQR, 30.1–35.7) weeks. Donors and recipients differed significantly in birth weight ($P < 0.001$). In addition, 53% of donors were affected by FGR compared with 8% of recipients ($P < 0.001$). There was no difference in the rate of severe neonatal morbidity

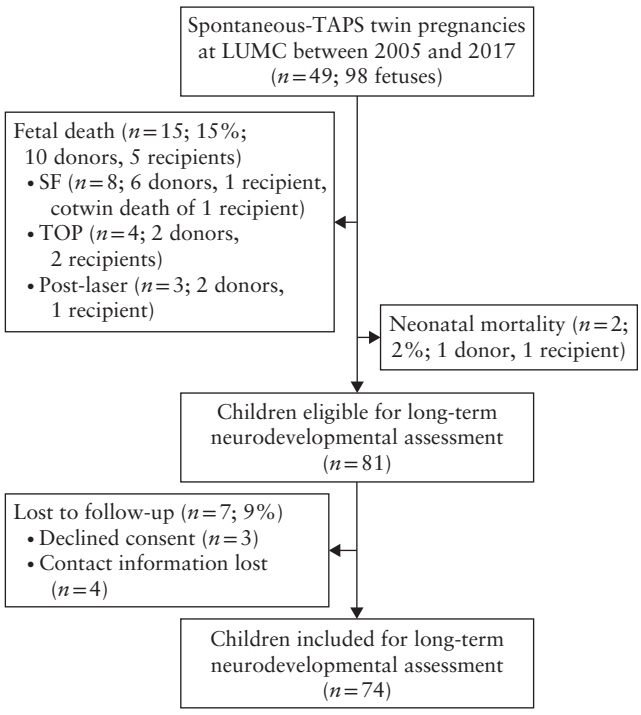

Figure 1 Flowchart summarizing derivation of study population of surviving children of pregnancies complicated by spontaneous twin anemia–polycythemia sequence (TAPS). LUMC, Leiden University Medical Center; SF, selective feticide; TOP, termination of pregnancy.

between donors and recipients. Within 1 day after delivery, TAPS donors received a blood transfusion for anemia in 65% of cases, while 38% of recipients were treated with partial exchange transfusion for polycythemia.

Long-term neurodevelopmental outcome in the 74 TAPS survivors was assessed at a median age of 4 (IQR, 2–6) years. Twenty-seven (37%) children were tested using Bayley-III-NL, 33 (45%) using WPPSI-III-NL and in 14 (19%), assessment was performed using WISC-III-NL.

Table 1 Characteristics of 41 pregnancies complicated by spontaneous twin anemia–polycythemia sequence (TAPS)

Characteristic	*TAPS pregnancies (n = 41)*
Antenatal diagnosis	29 (71)
GA 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	0/29 (0)
Stage 5	0/29 (0)
Management	
Expectant	12/29 (41)
IUT (with PET)	4/29 (14)
Laser surgery	8/29 (28)
Selective feticide	5/29 (17)
GA at delivery (weeks)	33.0 (30.1–35.7)
Postnatal diagnosis only	12 (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 (15)
Maternal education level	
Low	4 (10)
Intermediate	13 (32)
High	24 (59)

Data are presented as *n* (%), median (interquartile range) or *n*/*N* (%). GA, gestational age; IUT, intrauterine transfusion; PET, partial exchange transfusion.

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 odds of NDI compared with their recipient cotwins ($P = 0.001$). The incidence of severe NDI was 9% (7/74), occurring in 6/34 (18%) donors and 1/40 recipients (3%) ($P = 0.056$). Further details of the cases with severe NDI are displayed in Table 4. Mild-to-moderate NDI was found in 20% (15/74) of all children, occurring 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; $P = 0.011$). 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 ($P = 0.056$). Behavioral problems were reported in 10% (7/72) of the total group, with no difference between TAPS donors and recipients. Parental concern regarding development was reported more often for donor than for recipient twins ($P = 0.001$).

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 delivery (OR, 0.8; 95% CI, 0.6–1.0; $P = 0.024$) (Table 5). 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 delivery (OR, 0.7; 95% CI, 0.5–0.9; $P = 0.003$) were independent risk factors for NDI (Table 5). For each incremental week of gestation, the risk of NDI therefore decreases by 30%, and children with severe fetal anemia have a 6.4-fold increased risk.

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

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

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

Table 3 Long-term outcome in 74 survivors of 41 pregnancies complicated by spontaneous twin anemia–polycythemia sequence, overall and according to donor or recipient status

Outcome	*Total (n = 74)*	*Donors (n = 34)*	*Recipients (n = 40)*	P
Cognitive score	97 (87–105)	95 (87–105)	101 (90–106)	0.011
Cognitive delay				
Mild (score < 1 SD)	19 (26)	12 (35)	7 (18)	0.006
Severe (score < 2 SD)	2 (3)	2 (6)	0 (0)	0.265
Motor delay*				
Mild (score < 1 SD)	1/26 (4)	1/12 (8)	0/14 (0)	0.471
Severe (score < 2 SD)	0/26 (0)	0/12 (0)	0/14 (0)	—
Bilateral blindness	1 (1)	0 (0)	1 (3)	0.657
Bilateral deafness	5 (7)	5 (15)	0 (0)	0.056
Cerebral palsy (GMFCS Level 1)	2 (3)	2 (6)	0 (0)	0.265
NDI	22 (30)	15 (44)	7 (18)	0.001
Mild to moderate	15 (20)	9 (26)	6 (15)	0.093
Severe	7 (9)	6 (18)	1 (3)	0.056
NDI-free survival	52/82 (63)	19/41 (46)	33/41 (80)	< 0.001
Behavioral 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), *n* (%) or *n*/*N* (%). *26 children had complete motor assessment with Bayley (BSID III) test. †Child behavior 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)*	*ΔHb* (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 behavioral problems
Donor	26 + 5	Stage 1	Expectant management	36 + 2	FGR	9.5	14.2	3	Severe cognitive delay, externalizing behavioral problems
Donor	28 + 2	Stage 3	IUT, induced delivery	29 + 1	RDS, PDA	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 behavioral 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 ΔHb 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*		
Risk factor	*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 PET)	3/8 (38)	5/8 (63)	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 fetal 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
Maternal education level†			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.

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 four-fold 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 score 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 studies in TTTS or post-laser TAPS cohorts, no difference has been reported between donors and recipients[5,20]. In these cohorts, gestational age at delivery 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 donors and recipients. 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 loss of erythrocytes 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 donor 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. SGA is known to be associated with long-term impairment in singletons[21], which is likely caused by decreased white and gray 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 the present study, FGR was a significant risk factor for NDI on univariate regression analysis, but failed to show significance on multivariate analysis, suggesting an association between FGR and other factors. A relationship between fetal anemia and FGR in TAPS is not unlikely. Selective FGR (based on birth-weight discordance ≥ 25%) has been described previously in 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 do recipients. In TAPS donors it might therefore be caused by other factors, such as chronic loss of erythrocytes, albumin and/or protein through placental anastomoses[25].

Parental concern regarding 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 behavioral problems was 10%, which is comparable to that (10%) in children from the general Dutch population[26].

Surprisingly, TAPS donors were more often affected by deafness than were TAPS recipients. The limited sample size and statistical adjustment for non-occurring events in paired groups prevented this difference from reaching statistical significance, but clinically, we found this noteworthy and warranting more attention. Notably, deafness in all five affected donors was due to 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 fetus could have damaged not only the brain, but also the developing auditory nerve system. Interestingly, the high incidence of deafness has not been reported previously in TTTS survivors or in children who experienced 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 found that fetuses surviving spontaneous TAPS had a more detrimental outcome than did survivors of post-laser TAPS in a previous study[5]. Although the incidence of severe NDI was 9% in both groups, post-laser TAPS twins had an overall better outcome. They showed a lower rate of mild cognitive delay (17% *vs* 26%), did not have bilateral deafness and did not demonstrate differences in outcome between donors and recipients[5]. Two different theories may be considered to explain this discrepancy. Firstly, post-laser TAPS donors are less frequently growth restricted than are spontaneous TAPS donors. This is because TAPS donors are often former TTTS recipients, who generally have a higher birth weight than TTTS donors[32]. Thus, post-laser TAPS donors might be protected by a relatively higher fetal weight when they start to develop anemia. Alternatively, spontaneous TAPS might develop earlier in gestation than 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 the study. In our cohort, TAPS pregnancies varied in TAPS stage, gestational age at onset and management, making it difficult to draw reliable conclusions with regard to the true effect of the natural course of TAPS. Furthermore, the sample size of the cohort was small, but it is nonetheless the largest cohort of spontaneous TAPS survivors reported to date.

In conclusion, this study has shown that spontaneous TAPS is characterized by a high rate of NDI and that donors have an increased risk of cognitive delay compared with donors and a high rate of deafness. To date, spontaneous TAPS has been thought to be a relatively benign form of fetofetal 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 started, which is 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 participating 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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