Next steps towards improved care for twin anemia polycythemia sequence

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PART 8

short-term outcome

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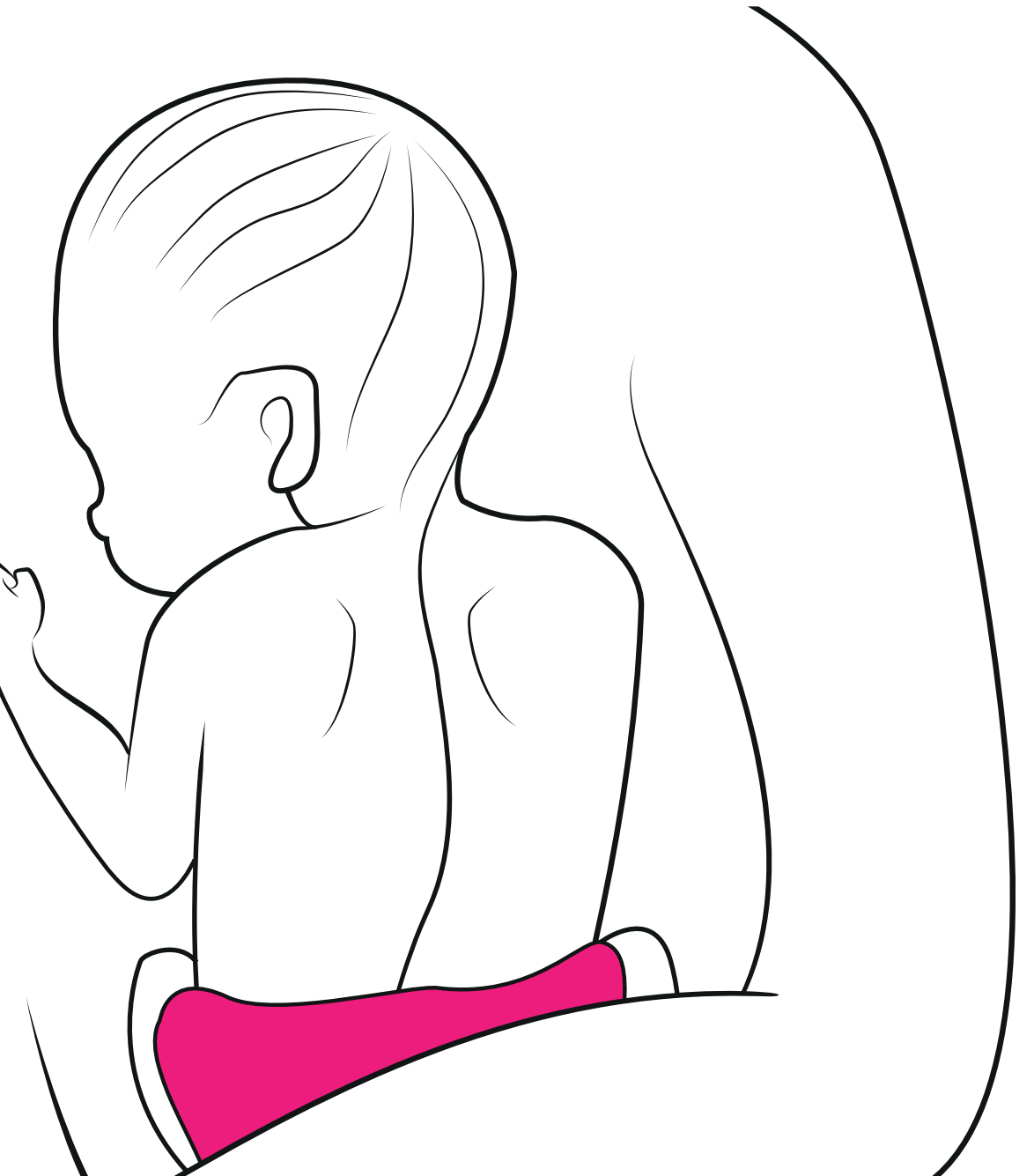
Chapter 9

Spontaneous twin anemia polycythemia sequence: management and outcome in an international cohort of 249 cases



Abstract

Objective

To investigate the management and outcome in spontaneous twin anemia polycythemia sequence (TAPS).

Methods

Data of the international TAPS Registry, collected between 2014-2019, were used for this study. The primary outcomes were perinatal mortality and severe neonatal morbidity. Secondary outcomes included a risk factor analysis for perinatal mortality and severe neonatal morbidity.

Results

A total of 249 spontaneous TAPS cases were included in this study, of which 219 (88%) were diagnosed antenatally and 30 (12%) postnatally. TAPS was diagnosed antenatally at a median gestational age (GA) of 23.7 weeks (IQR: 19.7-28.8; range: 15.1-35.3). Antenatal management included laser surgery in 39% (86/219), expectant management in 23% (51/219), delivery in 16% (34/219), intrauterine transfusion (with partial exchange transfusion) in 12% (26/219), selective feticide in 8% (18/219) and termination of pregnancy in 1% (3/219). Median gestational age at birth was 32.3 weeks (IQR: 30.1-34.9, range: 18.7-39.6). Perinatal mortality rate was 15% (72/493) for the total group; 22% (54/243) for donors and 7% (18/242) for recipients ($p < 0.001$). Severe neonatal morbidity occurred in 33% (141/432) of TAPS twins, being similar for donors (32%; 63/196) and recipients (33%; 75/228), $p= 0.628$. Independent risk factors for spontaneous perinatal mortality were donor status (OR = 3.8, 95%CI 1.9-7.5, $p < 0.001$), antenatal TAPS stage (stage 2: OR = 6.3, 95%CI 1.4-27.8, $p = 0.016$; stage 3: OR 9.6, 95%CI 2.1-45.5, $p = 0.005$; stage 4: OR 20.9, 95%CI 3.0-146.4, $p = 0.002$) and GA at birth (OR = 0.8, 95%CI 0.7-0.9, $p = 0.001$). Independent risk factors for severe neonatal morbidity were antenatal TAPS stage 4 (OR = 7.9, 95%CI 1.4-43.3, $p = 0.018$) and GA at birth (OR = 1.7, 95%CI 1.5-2.1, $p < 0.001$).

Conclusions

Spontaneous TAPS can develop at any time in pregnancy, from the beginning of the second trimester to the end of the third. Management for TAPS varies considerably, with laser surgery being the most frequent intervention. Perinatal mortality and severe neonatal morbidity were high, the former especially in donor twins.

Introduction

Twin anemia polycythemia sequence (TAPS) is a chronic form of unbalanced feto-fetal transfusion through minuscule placental anastomoses in monochorionic twins, leading to anemia in the TAPS donor and polycythemia in the TAPS recipient.[1] In contrast to twin-twin transfusion syndrome (TTTS), TAPS develops in the absence of twin oligohydramnios-polyhydramnios sequence (TOPS). TAPS can occur spontaneously in up to 5% of monochorionic twins.[2] The optimal antenatal treatment for TAPS has yet to be determined, but options include expectant management, preterm delivery, intrauterine transfusion (IUT) with or without a partial exchange transfusion (PET), fetoscopic laser surgery and selective feticide.[3, 4] Perinatal outcome in TAPS may vary between isolated hemoglobin differences to severe cerebral injury and perinatal death.[5, 6] Due to the low incidence of TAPS, studies investigating perinatal outcome are scarce with current data based on small cohort studies. Limited knowledge on optimal management and short- and long-term outcome restricts adequate parental counseling and informed decision-making. To improve our knowledge on TAPS, we set up the TAPS Registry, a large international collaboration aimed at collecting data on diagnosis, treatment and outcome in TAPS twins.

In the current study, the data from this TAPS Registry were used to (1) examine characteristics of diagnosis, management and outcome in twins with spontaneous TAPS, (2) to compare perinatal outcome between donors and recipients and (3) to investigate potential risk factors for adverse perinatal outcome.

Methods

The TAPS Registry was established in 2014 and utilised a web-based registry for anonymous data collection (www.tapsregistry.org). Fetal therapy centers across the world were invited to participate. Participating centers were supplied with personal credentials to enter data of their TAPS cases into the online registry. Between 2014 and 2019, 17 specialized fetal therapy centers contributed to data collection (see Appendix 1).

Monochorionic twin pregnancies diagnosed with spontaneous TAPS were eligible for this study. Cases with post-laser TAPS (TAPS after incomplete laser for TTTS) were excluded from this study and are described in a separate study.[7]

The antenatal diagnosis for TAPS was based on discordant fetal middle cerebral artery peak systolic velocity (MCA-PSV) measures, with an increased MCA-PSV being defined as > 1.5 Multiples of the Median (MoM) in the TAPS donor, suggestive of fetal anemia, combined with a decreased MCA-PSV measure (< 1.0 MoM) in the TAPS recipient, suggestive of fetal polycythemia, and without signs of TOPS.[8] TAPS was diagnosed postnatally in cases with an inter-twin hemoglobin difference > 8.0 g/dL in conjunction with least one of the following: a reticulocyte count ratio > 1.7 or the presence of only minuscule vascular anastomoses (diameter < 1 mm) detected through color dye injection of the placenta.[9, 10]

The following data were retrieved from local medical records: gravidity, parity, location of the placenta, moment of diagnosis (antenatal or postnatal), gestational age (GA) at diagnosis, TAPS stage at diagnosis and the presence of additional ultrasound findings including starry-sky liver in the recipient and/or difference in placental echogenicity, and mode of delivery. The severity of antenatal TAPS was assessed in agreement with the previously published staging system by Slaghekke et al.[11] For antenatal management for TAPS, the type of management was recorded: expectant management, delivery (defined as a delivery within 7 days after diagnosis), IUT (± PET), fetoscopic laser surgery, selective feticide, termination of pregnancy (TOP). Additionally, information on placental color dye injection was collected, including the type (arterio-venous (AV), veno-arterial (VA), arterio-arterial (AA), veno-venous (VV)), number and size of (residual) anastomoses. For perinatal outcome, the following parameters were obtained: donor/recipient status, birth weight, hemoglobin and reticulocyte values, treatment with blood transfusion or partial exchange transfusion on day one, presence of severe neonatal morbidities and/or severe cerebral injury and occurrence of perinatal mortality.

The primary outcomes were perinatal mortality and severe neonatal morbidity. Perinatal mortality was defined as fetal demise or neonatal death within 28 days after birth. As a part of fetal demise is intentional in the context of selective feticide or TOP, a distinction is made between spontaneous fetal demise and intended fetal demise. Severe neonatal morbidity was a composite measure and defined as the presence of at least one of the following, detected within 28 days after birth or before discharge to home: respiratory distress syndrome requiring mechanical ventilation and surfactant, patent ductus

arteriosus requiring treatment, necrotizing enterocolitis ≥ stage 2,[12] retinopathy of prematurity ≥ stage 3,[13] amniotic band syndrome, ischemic limb injury or severe cerebral injury. Severe cerebral injury was diagnosed in case of one of the following abnormalities were detected on cerebral imaging: intraventricular hemorrhage ≥ stage 3,[14] ventricular dilatation (including post-hemorrhagic ventricular dilatation)[15], cystic periventricular leukomalacia ≥ grade 2,[16] porencephalic or parenchymal cysts, arterial infarction or other severe cerebral lesions associated with adverse outcome.

Secondary outcomes included diagnosis- and therapy-related characteristics, hematological and placental characteristics, and a risk factor analysis for spontaneous perinatal mortality and severe neonatal morbidity. For the risk factor analysis for spontaneous mortality, cases with intentional fetal demise due to selective feticide or TOP were excluded. Since TAPS cases can be managed according to different strategies in the same pregnancy, management group assignment was based on the first treatment strategy that was performed. The following parameters were investigated in the univariate risk analysis for spontaneous perinatal mortality: GA at diagnosis TAPS, antenatal TAPS stage, TAPS donor/recipient status, type of antenatal management and GA at birth (weeks). For antenatal TAPS stage, the highest antenatal TAPS stage that was seen during pregnancy was selected. In case of TAPS stage 5, the highest TAPS stage before stage 5 was used. For the risk factor analysis for severe neonatal morbidity, two more parameters were added: severe growth restriction defined as birth weight < 3rd centile and the presence of postnatal TAPS.

The following additional parameters were determined: inter-twin hemoglobin difference (highest hemoglobin value – lowest hemoglobin value), reticulocyte count ratio (highest reticulocyte value (‰)/ lowest reticulocyte value (‰)), the presence of severe or mild growth restriction (defined as a birth weight < 3rd or < 10th centile respectively, according to Hoftiezer[17]), postnatal TAPS stage (according to Slaghekke[11]) and the configuration of anastomosis type per TAPS placenta.

Statistical analyses were performed using SPSS version 25.0 (IBM, Armonk, NY, USA). Data are reported as means ± standard deviation (SD) or as medians and/ or interquartile ranges (IQR) or ranges (minimum-maximum), as appropriate. A p-value < 0.05 was considered to indicate statistical significance. Differences between donors and recipients were calculated using the paired t-test for

normally distributed continuous outcomes and the Generalized Estimated Equation module for categorical outcomes. Potential risk factors were checked for correlation using Spearman's Rank test (R). Correlation coefficient R > (-)0.7 was considered to indicate a strong relationship between the factors. Potential risk factors for perinatal mortality and severe neonatal morbidity were studied in a univariate logistic regression model. A multivariate logistic regression model was applied to the variables that showed significant association in the univariate analysis. Results are expressed as odds ratios (OR) with 95% confidence intervals (CI).

Results

Out of the 422 TAPS cases entered in the TAPS Registry, 249 (59%) were spontaneous TAPS and included in this study, while 173 (41%) were post-laser TAPS and excluded from the study. The number of spontaneous TAPS cases per fetal therapy center is shown in Appendix 1. TAPS was diagnosed antenatally in 88% (219/249) of the group and postnatally in 12% (30/249). Further baseline characteristics of the population are presented in Table 1.

Table 1. Baseline characteristics of spontaneous TAPS twins

	Spontaneous TAPS (N = 249 pregnancies, 498 fetuses)
Gravidity	2 (1-3)
Parity	1 (0-1)
Antenatal diagnosis of TAPS	219/249 (88)
Location of placenta†	
Anterior	127/236 (54)
Posterior	104/236 (44)
Other	5/236 (2)

Data are presented as n/N (%) or median (IQR).
† In 13 cases, position of the placenta was unknown. Other types of placental position included: partly anterior and partly posterior (n=2), lateral left (n=2) and lateral right (n=1).

The median GA at diagnosis was 23.7 weeks (IQR: 19.7-28.8) with a wide range from 15.1 weeks to 35.3 weeks (Figure 1). In antenatally detected TAPS, 39% (86/219) was treated with laser surgery, 24% (52/219) was managed expectantly, 16% (34/219) had a delivery, 13% (26/219) received IUT (± PET), 8% (18/219) was

treated with selective feticide and in 1% (3/219) a TOP was performed. Table 2 further details diagnosis- and management-related characteristics.

Table 2. Diagnosis- and management related characteristics

	Spontaneous TAPS (N = 249 pregnancies, 498 fetuses)
GA at diagnosis (weeks)	23.7 (19.7-28.8; 15.1-35.3)
TAPS stage at diagnosis	
1	80/219 (37)
2	91/219 (42)
3	38/219 (17)
4	10/219 (5)
5	0/219 (0)
Highest TAPS stage during pregnancy	
1	64/219 (29)
2	88/219 (40)
3	52/219 (24)
4	12/219 (6)
5	3/219 (1)
Presence of additional ultrasound markers†	
Starry sky liver (recipient)	93/200 (47)
Difference in placental echogenicity	96/220 (44)
Antenatal management	
Expectant management	51/219 (23)
Delivery‡	34/219 (16)
IUT (± PET)	26/219 (12)
Laser surgery	86/219 (39)
Selective feticide	18/219 (9)
Termination of pregnancy	3/219 (1)
Female§	251/468 (53)
Cesarean¶	330/488 (68)

Data are median (IQR) or n/N(%)
†The presence of a starry sky liver and difference in placental echogenicity was assessed in 200 and 220 cases, respectively.‡ 1 case that had a delivery at 27 weeks based on TAPS stage 3 was a monoamniotic twin § In 30 fetuses, gender is unknown. One case was a male-female pair. ¶ In 10 fetuses mode of delivery is unknown. TAPS, twin anemia polycythemia; GA, gestational age; IUT, intrauterine transfusion; PET, partial exchange transfusion

Color-dye injection of the placenta was performed in 44% (109/249) of the cases (Table 3). In total, 24% (26/109) of injected placentas belonged to TAPS cases treated with laser surgery and 76% (83/109) belonged to TAPS cases that were not treated with laser surgery. In placentas not treated with laser, the median total number of anastomoses was 3 (1-6) and 84% (70/83) of the placentas demonstrated AV and/or VA anastomoses. AA and VV anastomoses

were detected in 19% (16/83) and 7% (6/83) of the group, respectively. In three TAPS cases, the placenta demonstrated only one AA or VV anastomoses at the vascular equator. Seven placentas did not show any anastomoses after placental injection: three cases had spontaneous resolution of TAPS during pregnancy, one case had normal hemoglobin values despite an antenatal diagnosis of TAPS, and the three remaining cases presented with severe postnatal TAPS (≥ stage 4) and a reticulocyte count ratio > 1.7. In total, 94% (74/76) of the placentas with anastomoses, showed only minuscule anastomoses (diameter < 1mm). Residual anastomoses were detected in 11% (3/26) of placentas treated with laser. In all three cases, the residual anastomoses were small and the twins had evidence of antenatal and postnatal TAPS.

Table 3. Characteristics of spontaneous TAPS placentas (not treated with laser)

	Injected TAPS placentas (N = 83)
Total number of anastomoses	3 (1-6)
Number of AV anastomoses	2 (1-3)
Number of VA anastomoses	1 (0-2)
Number of AA anastomoses	0 (0-0)
Number of VV anastomoses	0 (0-0)
Presence of anastomoses	
Presence of AV/VA anastomoses	70/83 (84)
Presence of AA anastomoses	16/83 (19)
Presence of VV anastomoses	6/83 (7)
Type of anastomoses per placenta	
No anastomoses	7/83(8)
AV (one direction)	21/83 (25)
AVs (both directions)	34/83 (41)
AV/VA and AA	13/83 (16)
AV/VA and VV	4/83 (5)
Only AA	2/83 (2)
Only VV	1/83 (1)
AV/VA, AA and VV	1/83 (1)
All anastomoses diameter < 1 mm†	74/76 (97)

Data are median (IQR) or n/N(%)
† Reported only in cases with anastomoses, the 10 cases without anastomoses were excluded.
TAPS, twin anemia polycythemia; TTTS, twin-twin transfusion syndrome; AV, arterio-venous; VA, veno-arterial; AA, arterio-arterial; VV, veno-venous; mm, millimetre

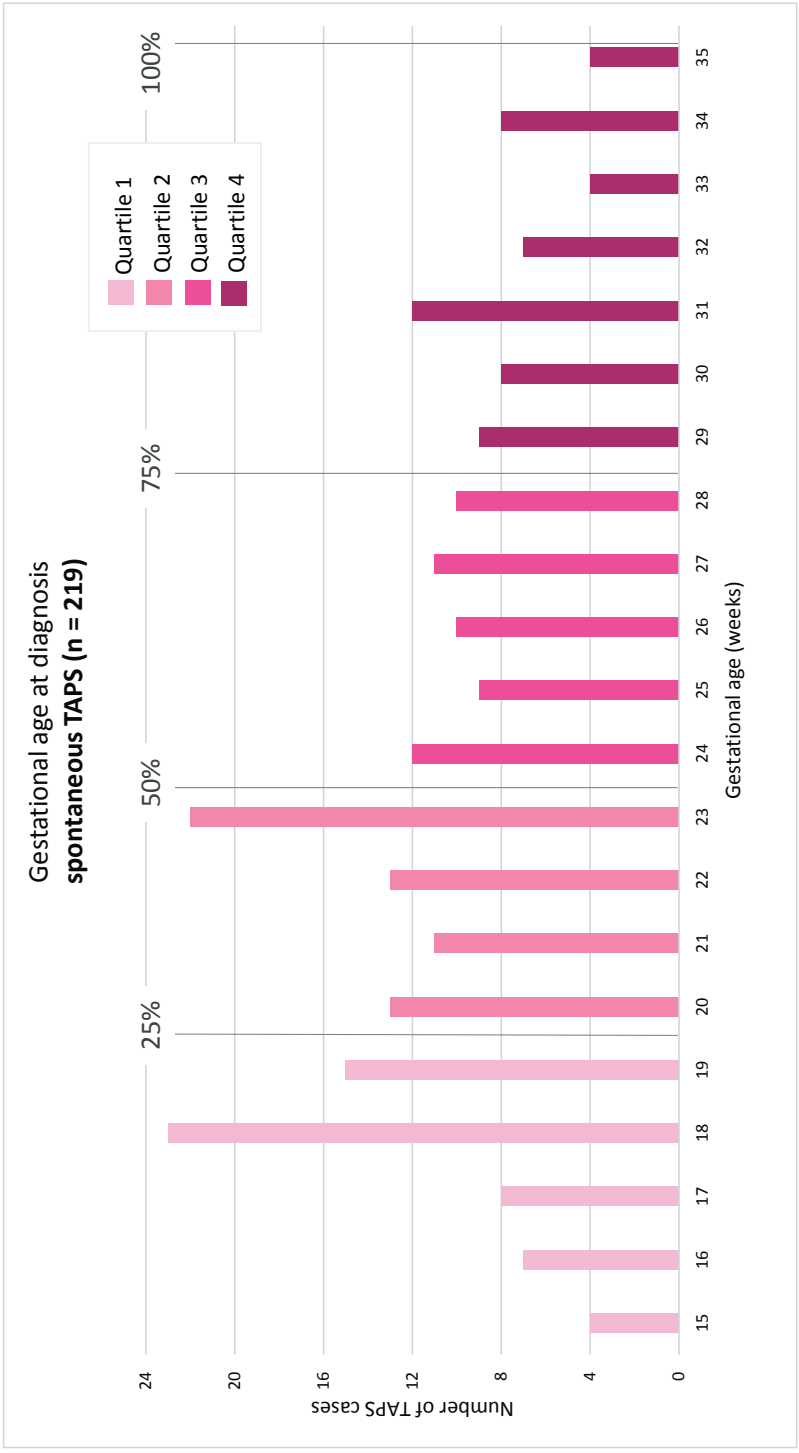


Figure 1. Gestational age at diagnosis in twins with spontaneous twin anemia polycythemia sequence

Table 4 shows perinatal outcome for the total group of TAPS twins, and for donors and recipients separately. The median gestational at birth for TAPS twins was 32.3 weeks (IQR: 30.1-34.9; range: 18.7-39.6). Donors had significantly lower birth weights than recipients, 1483g ± 566g vs. 1765g ± 620g, p < 0.001. In addition, donors were more often severely growth restricted than recipients 49% (98/200) vs. 11% (26/228), p < 0.001. Fetal demise occurred in 11% (54/494) of the group, either spontaneously in 5% (24/494) or intended in 6% (30/494). Donors had a higher risk for fetal demise than recipients, both for spontaneous fetal demise (8%; (19/242) vs. 2% (5/241); p = 0.002) and intended fetal demise (10%; (24/242) vs 3% (6/242) p < 0.001). Overall perinatal mortality (including intended demise) occurred in 15% (72/493) of TAPS twins, in 22% (54/243) of the donors and 7% (18/242) of the recipients, respectively (p < 0.001). Spontaneous perinatal mortality was observed in 9% (42/493) of the group, in 12% (30/243) of donors and in 5% (12/242) of recipients (p < 0.001). The rate of neonatal mortality was 4% (18/439) and was comparable between donors and recipients, 6% (11/200) vs. 3% (7/231), respectively (p = 0.159). Severe neonatal morbidity was diagnosed in 33% (141/432) of live-born TAPS twins, and was similar for donors (32%; 63/196) and recipients (33%; 75/228), p = 0.628. Severe cerebral injury was identified in 4% (15/432) of live-born TAPS twins, in 2% (4/196) of donors and 5% (11/228) of recipients (p = 0.11). Type of severe cerebral injury included intraventricular hemorrhage ≥ grade 3 (n = 9), cystic periventricular leukomalacia ≥ grade 2 (n = 4), (post-hemorrhagic) ventricular dilatation (n = 2), arterial infarction (n = 2) and other severe lesions associated with adverse outcome (n = 3). Amniotic band syndrome and ischemic limb injury did not occur in this cohort of spontaneous TAPS twins. In twins that were diagnosed with TAPS at birth (43%; 108/249) –and did not have a successful laser or spontaneous resolution– inter-twin hemoglobin difference was 14.3 mmol/L (IQR: 11.7-17.8) and reticulocyte count ratio was 3.9 (IQR: 2.5-5.3). Donors needed a blood transfusion at birth in 76% (81/108) and recipients a PET in 51% (51/108). In twins diagnosed with TAPS at birth, 17% (18/108) had postnatal TAPS stage 1, 28% (30/108) stage 2, 24% (26/108) stage 3, 19% (21/108) stage 4, and 12% (13/108) stage 5.

Table 4. Perinatal outcome for spontaneous twin anemia polycythemia sequence

	Spontaneous TAPS (N = 249 pregnancies, 498 fetuses)	TAPS donors† (N = 244 fetuses)	TAPS recipients† (N = 244 fetuses)	p-value
GA at birth (weeks)	32.3 (30.1-34.9; 18.7-39.6)	-	-	-
Fetal demise‡	54/494 (11)	43/243 (18)	11/243 (5)	< 0.001
Spontaneous	24/494 (5)	19/243 (8)	5/243 (2)	0.002
Intended	30/494 (6)	24/243 (10)	6/243 (3)	< 0.001
Neonatal mortality§	18/439 (4)	11/200 (6)	7/231 (3)	0.161
Perinatal mortality (overall)§	72/493 (15)	54/243 (22)	18/242 (7)	< 0.001
Perinatal mortality (spontaneous)§	42/493 (9)	30/243 (12)	12/242 (5)	< 0.001
Severe neonatal morbidity¶	141/432 (33)	63/196 (32)	74/228 (33)	0.652
Respiratory distress syndrome	118/432 (27)	51/196 (26)	64/228 (28)	0.413
Patent ductus arteriosus	34/432 (8)	15/196 (8)	19/228 (8)	0.671
Necrotizing enterocolitis	15/432 (4)	7/196 (4)	8/228 (4)	0.905
Retinopathy of prematurity	7/432 (2)	3/196 (2)	4/228 (2)	0.778
Severe cerebral injury	15/432 (4)	4/196 (2)	11/228 (5)	0.109
Birth weight (gram)¥	1645 ± 609	1483 ± 566	1765 ± 620	< 0.001
Severe growth restriction (bw < p3)¥	126/434 (29)	98/200 (49)	26/228 (11)	< 0.001
Mild growth restriction (bw < p10)¥	211/434 (49)	135/200 (68)	71/228 (31)	< 0.001

Data are presented as mean ± (SD) medians (IQR) or n/N (%).
† in 5/249 cases, the donor-recipient status was unknown
‡ 4 missing values
§ 5 missing values (same as '‡' plus 1 missing value from a liveborn recipient with unknown neonatal mortality information).
¶ 12 missing values (same as '§', plus 4 cases with unknown neonatal morbidity info and 3 cases that died shortly after birth)
¥ 9 missing values (as in '‡' plus 5 cases with unknown birth weights)
TAPS, twin anemia polycythemia sequence; GA, gestational age; bw, birth weight

Univariate risk factor analysis demonstrated that spontaneous perinatal mortality was significantly associated with donor status (OR = 3.0, 95% CI 1.7-5.4, p < 0.001) and antenatal TAPS stage (stage 2: OR = 7.2, 95%CI 1.5-32.2, p = 0.009; stage 3: OR = 11.3, 95%CI 2.5-50.5, p = 0.002; stage 4: OR = 32.5 95%CI 5.7-146.4, p < 0.001) and GA at birth (OR = 0.8, 95%CI 0.7-0.9, p < 0.001). Antenatal TAPS stage, donor status and GA at birth were not correlated (antenatal TAPS stage – donor status (R < 0.000, p = 0.998), antenatal TAPS stage – GA at birth (R < 0.001 p = 1.000), GA at birth – donor status (R < 0.000 p =0.997)), so all parameters were included in multivariate analysis. Multivariate analysis demonstrated that donor status (OR = 3.8, 95%CI 1.9-7.5, p < 0.001) and antenatal TAPS stage (stage 2: OR = 6.3, 95%CI 1.4-27.8, p = 0.016; stage 3: OR 9.6, 95%CI 2.1-45.5, p = 0.005; stage 4: OR 20.9, 95%CI 3.0-146.4, p = 0.002) and GA at birth (OR = 0.8, 95%CI 0.7-0.9, p = 0.001) were independent risk factors for spontaneous perinatal mortality.

Univariate risk factor analysis revealed that antenatal TAPS stage 4 (OR = 4.4, 95%CI 1.2-16.0, p = 0.026), antenatal management with delivery (OR = 2.3 95%CI 1.0-5.6, p = 0.046), GA at birth (OR = 1.7, 95%CI 1.5-1.9, p < 0.001) and the presence of postnatal TAPS (OR = 1.9, 95%CI 1.0-3.3, p = 0.039) were significant risk factors for severe neonatal morbidity. There was no strong correlation between the four parameters (GA at birth – postnatal TAPS (R < 0.001, p = 1.000), antenatal TAPS stage – postnatal TAPS (R = -0.155, p = 0.006), antenatal management (R = -0.493, p < 0.001), GA at birth – antenatal TAPS stage (R = -0.209, p < 0.001), GA at birth – antenatal management (R = 0.154, p = 0.002), antenatal management – antenatal TAPS stage (R = 0.307, p < 0.001), so all were included in multivariate analysis. In the multivariate analysis, antenatal TAPS stage 4 (OR = 7.9, 95%CI 1.4-43.3, p = 0.018), GA at birth (OR = 1.7, 95%CI 1.5-2.1, p < 0.001) independently associated with severe neonatal morbidity. More details on univariate and multivariate risk analysis for perinatal mortality and severe neonatal morbidity are presented in Table 2a and 2b of Appendix 2.

Appendix 1. Spontaneous TAPS cases per center.

Center	Country	Spontaneous TAPS Cases
Leiden University Medical Center	The Netherlands	70
Leuven University Hospital	Belgium	30
Necker-Enfants Malades Hospital Paris	France	23
Hospital Universitari Vall d'Hebron Barcelona	Spain	16
University Medical Center Hamburg-Eppendorf	Germany	15
Center Medico-Chirurgical Obstetrical Strasbourg	France	13
Medical University of Graz	Austria	13
Mount Sinai Hospital Toronto	Canada	12
Children's Hospital V. Buzzi Milan	Italy	11
University of Texas McGovern Medical School at Houston	United States of America	10
Saint George's Hospital London	United Kingdom	9
Mater Hospital Brisbane	Australia	8
Brugmann University Hospital	Belgium	7
Yale New Haven Hospital	United States of America	6
Karolinska University Hospital Stockholm	Sweden	3
V.I. Kulakov National Medical Research Center of Obstetrics, Gynecology and Perinatology Moscow	Russia	2
Birmingham Women's and Children's NHS Foundation Trust	United Kingdom	1

APPENDIX 2 a Univariate and multivariate risk analysis for spontaneous perinatal mortality in spontaneous twin anemia polycythemia sequence.

	Death† (n = 42/463)	**Alive† (n = 421/463)**	**Univariate analysis OR (95% CI)**	**SE**	**P**	**Multivariate analysis OR (95% CI)**	**SE**	**P**
GA at diagnosis TAPS	22.7 ± 4.8	24.7 ± 5.4	0.9 (0.8-1.0)	0.05	0.124			
Antenatal TAPS stage								
1	2/126 (2)	124/126 (98)	-*					
2	17/162 (11)	145/162 (89)	7.2 (1.5-32.2)	0.8	**0.009**	6.3 (1.4-27.8)	0.8	**0.016**
3	14/91 (15)	77/91 (85)	11.3 (2.5-50.5)	0.8	**0.002**	9.6 (2.1-45.5)	0.8	**0.005**
4	8/15 (35)	18/15 (65)	32.5 (5.7-186.7)	0.9	**< 0.001**	20.9 (3.0-146.4)	1.0	**0.002**
Recipient‡	12/236 (5)	224/236 (95)	-*					
Donor‡	30/219 (14)	189/219 (86)	3.0 (1.7-5.4)	0.3	**< 0.001**	3.8 (1.9-7.5)	0.3	**< 0.001**
Antenatal therapy								
Expectant management	12/101 (10)	89/101 (88)	-*					
Delivery	5/68 (7)	63/68 (93)	0.6 (0.2-1.8)	0.6	0.334			
IUT (± PET)	2/52 (4)	50/52 (96)	0.3 (0.1-1.4)	0.9	0.118			
Laser surgery	21/163 (13)	142/163 (87)	1.1 (0.5-2.5)	0.4	0.865			
Selective feticide (co-twin)	2/17 (11)	17/19 (89)	0.9 (0.2-4.3)	0.8	0.855			
GA at birth	29.5 ± 4.7	32.6 ± 2.9	0.8 (0.7-0.9)	0.1	**< 0.001**	0.8 (0.7-0.9)	0.1	**0.001**

Values are odds ratios (OR) (95% confidence intervals (CI)), standard error (SE) and p-value. *was set as a reference. † 30 cases were excluded as mortality occurred in context of selective feticide or termination of pregnancy, from the 648 cases 5 cases have missing values ‡ In 5 cases, donor-recipient status was unknown

GA, gestational age; TAPS, twin anemia polycythemia sequence; IUT, intrauterine transfusion; PET, partial exchange transfusion

APPENDIX. 2b Univariate and multivariate risk analysis for severe neonatal morbidity in spontaneous twin anemia polycythemia sequence.

	SNM† (N=141/432)	No SNM† (N= 291/432)	Univariate analysis OR (95% CI)	SE	P	Multivariate analysis OR (95% CI)	SE	P
GA at diagnosis TAPS	25.4 ± 5.2	24.5 ± 5.6	1.0 (0.9-1.0)	0.02	0.300	-	-	-
Antenatal TAPS stage								
1	40/123 (33)	83/123 (67)	-*					
2	44/148 (30)	104/148 (70)	0.9 (0.5-1.7)	0.3	0.651	0.7 (0.3-1.6)	0.4	0.414
3	31/82 (38)	51/82 (62)	1.1 (0.6-2.4)	0.4	0.749	1.0 (0.4-3.0)	0.5	0.953
4	14/19 (74)	5/19 (26)	4.4 (1.2-16.0)	0.7	**0.026**	7.9 (1.4-43.3)	0.8	**0.018**
Recipient‡	74/226 (33)	153/226 (67)	-*					
Donor‡	63/196 (32)	133/196 (68)	1.1 (0.8-1.3)	0.1	0.628	-	-	-
Antenatal therapy								
Expectant management	26/93 (28)	67/93 (72)	-*					
Delivery	32/68 (47)	35/68 (53)	2.3 (1.0-5.6)	0.4	0.046	0.5 (0.1-1.5)	0.5	0.252
IUT (± PET)	22/50 (44)	28/50 (56)	1.9 (0.8-4.6)	0.5	0.150	1.3 (0.4-4.0)	0.6	0.695
Laser surgery	44/145 (31)	108/145 (69)	1.2 (0.5-2.4)	0.4	0.661	1.6 (0.6-4.9)	0.6	0.370
Selective feticide	4/17 (24)	13/17 (76)	0.8 (0.2-2.8)	0.6	0.710	- §		
GA at birth	30.1 ± 2.7	33.6 ± 2.3	1.7 (1.5-1.9)	0.1	**< 0.001**	1.7 (1.5-2.1)	0.1	**< 0.001**
Severe growth restriction, no	99/304 (33)	205/304 (67)	-*					
Severe growth restriction, yes	41/122 (34)	81/122 (66)	1.0 (0.7-1.5)	0.2	0.842	-	-	-
Postnatal TAPS, no	40/156 (26)	116/156 (74)	-*					
Postnatal TAPS, yes	81/211 (38)	130/211 (62)	1.9 (1.0-3.3)	0.3	**0.039**	2.1 (0.9-5.0)	0.4	0.068

Values are odds ratios (OR) (95% confidence intervals (CI)), standard error (SE) and p-value. *was set as a reference † 12 neonates with missing neonatal outcome. ‡In 5 cases, donor-recipient status was unknown. §Group too small to calculate OR in multivariate analysis.
SNM, severe neonatal morbidity; GA, gestational age; TAPS, twin anemia polycythemia sequence; IUT, intrauterine transfusion; PET, partial exchange transfusion

Discussion

This is the first large international study investigating management and outcome in spontaneous TAPS. We found that TAPS can develop across a wide range of gestation. Management in all 17 centers varied considerably, with fetoscopic laser surgery being the most frequent intervention. In this cohort, perinatal outcome was poor, particularly due to a high perinatal mortality rate in donor twins. These findings stress the need for increased awareness by clinicians concerning the severity of TAPS. Adaptation of guidelines to ensure early diagnosis is needed, as well as prospective, well-controlled studies to determine the most optimal diagnostic criteria and management strategy.

Until now, information regarding time of onset of TAPS was scarce and mostly based on small cohort studies. To develop adequate TAPS screening guidelines, using routine MCA-PSV Doppler measurements, knowledge concerning the time of onset of TAPS is essential. This study shows that TAPS can develop from 15 weeks to 35 weeks' gestation. As three of the four cases detected at 15 weeks were stage 2 or higher, it is likely that TAPS manifested even earlier. Currently, there is no consensus on when to start with MCA-PSV surveillances to check for the presence of TAPS. The ISUOG twin guideline recommends bi-weekly MCA-PSV screening starting from 20 weeks' gestation, especially in cases treated with laser surgery for TTTS.[18] The Society for Maternal and Fetal Medicine does not recommend MCA-PSV screening at all, due to the lack of evidence that routine screening improves perinatal outcome in TAPS.[19] This study showed that an advanced antenatal TAPS stage was a significant risk factor for perinatal mortality and severe neonatal morbidity. We can therefore speculate that a timely detection allowing antenatal intervention could improve outcome. Based on the mounting evidence of serious effects of TAPS[20], we suggest that to improve early detection and possibly outcome, routine MCA-PSV examination should be included in the standard bi-weekly work-up starting in the early second trimester.

Due to international collaboration, we were able to report on the largest group of spontaneous TAPS placentas. In line with previous studies, we found that the vast majority (94%) of TAPS placentas showed only minuscule anastomoses.[1] Our data also demonstrate that AA anastomoses do not prevent the development of TAPS, as they were observed in 19% of TAPS placentas. This rate is slightly higher than the 11% reported before.[21] Moreover, this study was the first to show

that VV anastomoses are rare, but not absent in TAPS placentas.[22] Interestingly, there were three TAPS placentas that showed only one minuscule AA or VV anastomosis. It is postulated that, these bidirectional anastomoses act like an AV anastomosis (allowing unidirectional flow) under certain circumstances. Of note, there were seven placentas from TAPS cases showing no anastomoses after color dye injection. In three cases, TAPS resolved during pregnancy, likely as a result of spontaneous thrombosis in an AV anastomosis.[23] The other four placentas belonged to severe postnatal TAPS cases, which also presented with high reticulocyte ratios, suggestive of a true chronic unbalanced feto-fetal transfusion. Possibly, deep-hidden anastomoses were responsible for the unbalanced blood flow.[24] Alternatively, minuscule anastomoses may not have been seen due to suboptimal color-dye injection, which is known to be technically challenging in TAPS placentas.[25]

Studies investigating perinatal outcome in TAPS are scarce, and the majority combines outcome of spontaneous and post-laser TAPS twins. In a recent long-term outcome, study fetal demise occurred in 3% and neonatal mortality in 2% of spontaneous TAPS twins, which is roughly comparable to the 5% and 4% in this study, respectively.[20] The long-term follow-up study also showed that spontaneous TAPS donors have a four-fold higher odd of neurodevelopmental impairment than recipients, and show high rates of cognitive impairment and deafness. The current study demonstrated that TAPS donors do not only have a more detrimental outcome on the long-term, but are also at increased risk for mortality antenatally. Additionally, almost half of the donors in our cohort were severely growth-restricted, in contrast to 12% of recipients. Growth restriction in TAPS is not related to unequal placental sharing, but is likely a result of chronic anemia and hypoalbuminemia.[26] In this cohort, GA at birth was a strong predictor for both perinatal mortality and severe neonatal morbidity, showing that prolonging pregnancy is crucial to improve outcome in spontaneous TAPS twins.

This study shows that perinatal mortality is lower in spontaneous TAPS than in post-laser TAPS, 15% vs. 25%, respectively.[7] Aside from the fact that spontaneous TAPS did not experience TTTS, a possible alternative explanation for this difference can be found in the type of placental anastomoses. Most spontaneous TAPS placentas demonstrated AV anastomoses in both directions, allowing compensating blood flow from recipient to donor. In post-laser TAPS,

most placentas showed AV anastomoses in one direction.[7] Alternatively, antenatal treatment might have been of influence. Although management in spontaneous TAPS is diverse, a significant proportion of TAPS twins was treated with laser surgery, an intervention aimed at permanently blocking unbalanced inter-twin blood transfusion, thereby preventing further deterioration of the disease. A detailed comparison of differences in perinatal outcome between various treatment strategies is presented in a separate study.[27]

Caution is needed when interpreting the findings of our study, due to the limitations associated with registry investigations. Notably, this study depended on local registrations of tertiary fetal therapy centers. Therefore, our outcome could be biased towards severe cases of TAPS, as they are more likely to be referred by peripheral clinics. Furthermore, this study did not compare the outcome of spontaneous TAPS twins to a cohort of uncomplicated monochorionic twins. Nonetheless, this large international study presents new important information which has potential implications for the future care of monochorionic twins.

To conclude, spontaneous TAPS can occur across a wide gestational-age range, is managed heterogeneously, and is associated with high rates of adverse perinatal outcome, particularly in donor twins. Since perinatal outcome is greatly dependent on TAPS stage, timely detection allowing consideration of antenatal treatment is of utmost importance. To adequately investigate the best treatment for TAPS, an international randomized controlled trial is needed.[28]

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