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Treatment and outcome of 370 cases with spontaneous or post-laser twin anemia–polycythemia sequence managed in 17 fetal therapy centers

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KEYWORDS: expectant management; intrauterine transfusion; laser surgery; monochorionic twins; selective feticide; TAPS; treatment; twin anemia–polycythemia sequence

CONTRIBUTION

What are the novel findings of this work?
Antenatal treatment for twin anemia–polycythemia sequence (TAPS) differs considerably between fetal therapy centers. The rate of perinatal mortality was comparable following treatment of TAPS with expectant management, laser surgery, intrauterine transfusion (IUT) (with or without partial exchange transfusion (PET)), delivery or selective feticide. Severe neonatal morbidity was significantly higher in cases treated with IUT (± PET) or delivery within 7 days after diagnosis. Prolongation of pregnancy was best achieved by expectant management, laser surgery and selective feticide.

What are the clinical implications of this work?
There is no international consensus on the optimal management for TAPS. Treatment groups differed significantly at baseline, hampering reliability and generalizability of our results. To improve the outcome of TAPS pregnancies, a randomized controlled trial investigating the best treatment option is urgently needed.

ABSTRACT

Objective *To investigate the antenatal management and outcome in a large international cohort of monochorionic twin pregnancies with spontaneous or post-laser twin anemia–polycythemia sequence (TAPS).*

Methods *This study analyzed data of monochorionic twin pregnancies diagnosed antenatally with spontaneous or post-laser TAPS in 17 fetal therapy centers, recorded in the TAPS Registry between 2014 and 2019. Antenatal diagnosis of TAPS was based on fetal middle cerebral*

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artery peak systolic velocity > 1.5 multiples of the median (MoM) in the TAPS donor and < 1.0 MoM in the TAPS recipient. The following antenatal management groups were defined: expectant management, delivery within 7 days after diagnosis, intrauterine transfusion (IUT) (with or without partial exchange transfusion (PET)), laser surgery and selective feticide. Cases were assigned to the management groups based on the first treatment that was received after diagnosis of TAPS. The primary outcomes were perinatal mortality and severe neonatal morbidity. The secondary outcome was diagnosis-to-birth interval.

Results *In total, 370 monochorionic twin pregnancies were diagnosed antenatally with TAPS during the study period and included in the study. Of these, 31% (n = 113) were managed expectantly, 30% (n = 110) with laser surgery, 19% (n = 70) with IUT (± PET), 12% (n = 43) with delivery, 8% (n = 30) with selective feticide and 1% (n = 4) underwent termination of pregnancy. Perinatal mortality occurred in 17% (39/225) of pregnancies in the expectant-management group, 18% (38/215) in the laser group, 18% (25/140) in the IUT (± PET) group, 10% (9/86) in the delivery group and in 7% (2/30) of the cotwins in the selective-feticide group. The incidence of severe neonatal morbidity was 49% (41/84) in the delivery group, 46% (56/122) in the IUT (± PET) group, 31% (60/193) in the expectant-management group, 31% (57/182) in the laser-surgery group and 25% (7/28) in the selective-feticide group. Median diagnosis-to-birth interval was longest after selective feticide (10.5 (interquartile range (IQR), 4.2–14.9) weeks), followed by laser surgery (9.7 (IQR, 6.6–12.7) weeks), expectant management (7.8 (IQR, 3.8–14.4) weeks), IUT (± PET) (4.0 (IQR, 2.0–6.9) weeks) and delivery (0.3 (IQR, 0.0–0.5) weeks). Treatment choice for TAPS varied greatly within and between the 17 fetal therapy centers.*

Conclusions *Antenatal treatment for TAPS differs considerably amongst fetal therapy centers. Perinatal mortality and morbidity were high in all management groups. Prolongation of pregnancy was best achieved by expectant management, treatment by laser surgery or selective feticide.* © *2020 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of the International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Twin anemia–polycythemia sequence (TAPS) occurs as a result of chronic unbalanced fetofetal transfusion through minuscule placental anastomoses in monochorionic twins, leading to anemia in the donor and polycythemia in the recipient[1]. Unlike twin-to-twin transfusion syndrome (TTTS), TAPS develops in the absence of twin oligohydramnios–polyhydramnios sequence (TOPS). TAPS occurs spontaneously in 3–5% of monochorionic twins and arises after incomplete laser surgery for TTTS in 2–16% of cases, due to the presence of minuscule residual anastomoses[2,3].

TAPS is a relatively newly recognized condition, first described in 2006[4]. Since then, our knowledge with respect to this condition has increased greatly and insights into the pathophysiology, diagnosis and outcome of TAPS have gradually been established[5]. However, the best antenatal management for TAPS is still unknown. Options include expectant management, preterm delivery, intrauterine transfusion (IUT) in the donor with or without partial exchange transfusion (PET) in the recipient, fetoscopic laser surgery of the placental vascular anastomoses and selective feticide. Since TAPS is associated with high rates of adverse short- and long-term outcomes, it is crucial to investigate which management strategy offers TAPS twins the best outcome[6–8]. Unfortunately, due to the low incidence of the condition, studies are limited to small sample sizes, thus hampering generalizability of the results and necessitating caution when comparing the outcomes. To generate more substantiated knowledge on the effects of different management strategies for TAPS twins, we set up the TAPS Registry, an international collaboration aimed at collecting data on diagnosis, management and outcome of pregnancies with TAPS.

The aim of the current study was to investigate the perinatal outcome associated with different antenatal management strategies in monochorionic twin pregnancies with spontaneous or post-laser TAPS and to report the antenatal management choices for TAPS in 17 fetal therapy centers across the world.

METHODS

The TAPS Registry was established in 2014 as a web-based registry for anonymous data collection on twin pregnancies complicated by TAPS. 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, a total of 17 centers contributed to data collection (Appendix S1).

Inclusion criteria

Women were eligible for the study if they were pregnant with monochorionic twins diagnosed with spontaneous or post-laser TAPS. The diagnosis for TAPS was based on a middle cerebral artery (MCA) peak systolic velocity (PSV) discrepancy between the twins, defined as MCA-PSV > 1.5 multiples of the median (MoM) in the TAPS donor combined with MCA-PSV < 1.0 MoM in the TAPS recipient, in the absence of TOPS[9]. Cases were excluded if TAPS was diagnosed for the first time postnatally (i.e. missed antenatally) and/or if they were diagnosed with post-laser TAPS within 1 week after laser for TTTS, unless TAPS persisted after 1 week, and/or if they were first diagnosed with TAPS at Stage 5. The outcomes of TAPS cases diagnosed postnatally are presented in two

other studies investigating perinatal outcome separately in spontaneous and post-laser TAPS[10,11].

Collected information

Data on maternal characteristics, diagnosis, management, delivery, placental injection studies and perinatal outcome were collected. The following information was retrieved from local medical records: gravidity, parity, location of the placenta, time of diagnosis (antenatal or postnatal), gestational age (GA) at diagnosis and TAPS stage at diagnosis. In addition, the type of antenatal management was recorded, including expectant management, preterm delivery, IUT (± PET), fetoscopic laser surgery, selective feticide or termination of pregnancy (TOP). For each management decision, the GA and TAPS stage were noted, as well as the indication. The severity of antenatal TAPS was determined according to the staging system by Slaghekke *et al.* published previously[12]. The following delivery data were retrieved: type of delivery (spontaneous or planned), mode of delivery (vaginal or Cesarean) and type of Cesarean delivery (elective or emergency). Based on placental color dye examination, the type, size and number of placental anastomoses were recorded. Perinatal outcome information collected included donor/recipient status, hemoglobin and reticulocyte values, treatment with blood transfusion for anemia or PET for polycythemia on day 1, presence of severe neonatal morbidity and/or severe cerebral injury, and occurrence of perinatal mortality.

Management group allocation

We defined the following antenatal management groups for TAPS: expectant management, delivery (defined as a delivery within 7 days after diagnosis), IUT (± PET), laser surgery and selective feticide. Since different management strategies may be used in the same TAPS pregnancy, management-group allocation was based on the first strategy followed. The following rules were applied for management-group allocation: cases were assigned to the laser-surgery, IUT (± PET) or selective-feticide group if that was the first treatment they received within 14 days after diagnosis of TAPS (we allowed a 1-week re-examination to confirm the diagnosis of TAPS). If this treatment was performed after 14 days, cases were included in the expectant-management group. If cases received laser surgery combined with an IUT during the same procedure, they were assigned to the laser-surgery group. Cases with laser surgery in which other interventions were needed to manage persisting or recurrent TAPS, were assigned to the laser-surgery group.

Population characteristics

For all management groups, the following parameters were studied: type of TAPS (post-laser or spontaneous), location of the placenta, GA at diagnosis, TAPS stage at diagnosis, incidence of preterm prelabor rupture of the membranes (PPROM), GA at PPROM, type of delivery (spontaneous or planned), mode of delivery (vaginal or Cesarean), GA at birth, presence of TAPS postnatally, treatment for postnatal TAPS (defined as blood transfusion in the donor and/or PET in the recipient at birth) and number of survivors per pregnancy. The postnatal diagnosis of TAPS was established in the presence of intertwin hemoglobin difference > 8.0 g/dL combined with at least one of the following: a reticulocyte count ratio > 1.7 or presence of only minuscule vascular anastomoses detected through color dye injection of the placenta[13,14]. Furthermore, specific management-related characteristics were evaluated for each management group. For expectant management we investigated spontaneous resolution of TAPS, defined as absence of TAPS postnatally. In pregnancies managed with IUT (± PET), the number of interventions, time interval between interventions (in days) and site(s) of transfusion were examined. In cases that underwent multiple IUT (± PET) procedures, the median number of days between interventions was used. In cases that underwent laser surgery, we assessed recurrent/persistent TAPS, presence of residual anastomoses (evaluated after birth using color dye injection of the placental vessels) and delivery within 24 h after the procedure. In pregnancies treated with selective feticide, donor/recipient status of the treated fetus and the indication for selective feticide were evaluated. For expectant management, IUT (± PET) and laser surgery, any additional treatment after the initial intervention was recorded.

Primary and secondary outcomes

The primary outcomes of this study were perinatal mortality and severe neonatal morbidity. Secondary outcome was diagnosis-to-birth interval. Outcomes were compared between the different management groups (expectant management, delivery, IUT (± PET), laser surgery and selective feticide) in the total cohort and for spontaneous and post-laser TAPS separately. Perinatal mortality was defined as fetal demise or neonatal death within 28 days after birth. In the selective-feticide group, perinatal mortality was reported only for the cotwin. Severe neonatal morbidity was defined as the presence of at least one of the following, diagnosed 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 $\geq$ Stage 2[15], retinopathy of prematurity $\geq$ Stage 3[16], amniotic band syndrome, ischemic limb injury or severe cerebral injury. Severe cerebral injury was diagnosed in the presence of one of the following abnormalities on cerebral imaging: intraventricular hemorrhage $\geq$ Stage 3[17], ventricular dilatation (including post-hemorrhagic ventricular dilatation)[18], cystic periventricular leukomalacia $\geq$ Grade 2[19], porencephalic or parenchymal cysts, arterial infarction or other severe cerebral lesions associated with adverse outcome.

Statistical analysis

Statistical analyses were carried out using SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Data are presented as median and interquartile range (IQR) with or without range (minimum–maximum), or *n*/*N* (%), as appropriate. A *P*-value < 0.05 was considered statistically significant. For comparison between treatment groups of outcomes analyzed per pregnancy, one-way analysis of variance (ANOVA) with Tukey correction was used for comparison of continuous variables and a chi-square test was used for comparison of categorical variables. Comparison between groups of outcomes analyzed per fetus or neonate was performed using the generalized estimated equation (GEE) module to account for the fact that observations between cotwins are not independent. As a GEE cannot be used when an outcome event does not occur in one of the groups, an adjustment to the data was applied in such cases, according to which, an unaffected child was changed into an affected child in all groups. This correction generates more conservative *P*-values. For the one-way ANOVA and GEE, the outcome in the expectant-management group was set as the reference value. When using the chi-square test, *P*-values are reported for the comparison between all treatment groups.

RESULTS

Of the 422 TAPS cases that were entered in the TAPS Registry between 2014 and 2019, 10% ($n = 43$) were diagnosed postnatally and excluded from the present study. Of the remaining 379 cases, eight were excluded because post-laser TAPS was diagnosed within 1 week after laser for TTTS but did not persist beyond the first week, and one further case was excluded as it was TAPS Stage 5 at antenatal diagnosis. Therefore, a total of 370 cases were included in the study. The number of cases contributed by each fetal therapy center is presented in Appendix S1. Antenatal management consisted of expectant management in 31% ($n = 113$) of pregnancies, laser surgery in 30% ($n = 110$), IUT (± PET) in 19% ($n = 70$), delivery within 7 days after diagnosis in 12% ($n = 43$), selective feticide in 8% ($n = 30$) and TOP in 1% ($n = 4$). Pregnancies that underwent TOP are not considered further. Pregnancy and delivery characteristics for each management group are presented in Table 1.

Expectant-management group

The median GA at diagnosis in the expectant management group was 22.6 (IQR, 19.9–27.1; range, 15.1–35.0) weeks. The median antenatal TAPS stage at diagnosis was 2 (IQR, 1–2). The presence of TAPS at birth could be evaluated in 98% (111/113) of the cases managed expectantly. Spontaneous resolution was seen in 16% (18/111) of cases and occurred in 17% (9/52) with TAPS Stage 1, 13% (6/45) with Stage 2, 18% (2/11) with Stage 3 and 20% (1/5) with Stage 4. In 12% (13/113) of cases, an alternative management strategy was performed after 14 days of expectant management. IUT (± PET) was elected in eight TAPS cases (after 15–97 days from diagnosis), based on progression of TAPS stage ($n = 5$), ongoing Stage-1 TAPS ($n = 2$) and initial recovery followed by recurrence of TAPS after 13 weeks ($n = 1$). In the other five cases, laser surgery was performed for progression of TAPS stage (after 15–38 days from diagnosis). In two of the cases managed with laser surgery, delivery took place within 24 h after the procedure, resulting in miscarriage (23 weeks) in one case and premature (28 weeks) birth in the other with double infant survival. In the other three cases that underwent laser surgery, perinatal survival was seen in 5/6 neonates.

Laser-surgery group

Initial management by laser surgery was performed in 110 pregnancies at a median GA of 22.0 (IQR, 19.5–24.3; range, 16.7–30.1) weeks. Spontaneous TAPS cases comprised the majority of this treatment group (78%; 86/110). In total, 43% (47/110) of the TAPS pregnancies treated with laser surgery had an anterior placenta. Laser surgery was combined with an IUT in the same procedure in 11% (12/110) of the pregnancies. In 4% (4/108) of cases treated with laser surgery, delivery took place within 24 h after the procedure (at 21, 22, 24 and 28 weeks, respectively).

Recurrent TAPS was seen in 15% (16/106) of the cases that underwent laser surgery. In one of these cases, recurrent TAPS was diagnosed only postnatally. Of the remaining 15 pregnancies, 20% ($n = 3$) were managed expectantly, 33% ($n = 5$) with IUT (± PET), 13% ($n = 2$) with laser reintervention and 33% ($n = 5$) with selective feticide. Of the three cases managed expectantly, spontaneous resolution of TAPS was seen in one, and in the other two, neonatal mortality occurred in three of four liveborn infants. In the recurrent-TAPS cases that were managed with IUT (± PET), fetal demise of the donor occurred in two of the five twin pairs after the first IUT. In both cases the cotwin survived. In the other three cases, two or three IUT (± PET) interventions were performed and all infants survived. In both pregnancies with recurrent TAPS that had laser reintervention, the procedure was successful resulting in perinatal survival of the twins. Of the five recurrent-TAPS cases treated with selective feticide, this was performed in the donor twin in four and in the recipient twin in one. In one case, fetal demise of the cotwin occurred. Aside from the recurrent-TAPS cases, selective feticide was performed in two additional cases treated with laser surgery, based on severe cerebral injury in the donor detected after laser intervention.

Postnatal TAPS was diagnosed in 9% (6/65) of liveborn twin pairs treated with laser surgery. Placental injection information was available in 33% (36/110) of pregnancies treated with laser surgery. Residual anastomoses were detected in 19% (7/36) of these and were minuscule in all instances. All cases with residual anastomoses (7/7) had recurrent TAPS.

Table 1 Pregnancy and delivery characteristics of 366 monochorionic twin pregnancies diagnosed prenatally with twin anemia–polycythemia sequence (TAPS), according to initial management strategy after diagnosis

Characteristic	*Expectant management (n = 113)*	*Laser surgery (n = 110)*	*IUT (± PET) (n = 70)*	*Delivery (n = 43)*	*Selective feticide (n = 30)*
GA at diagnosis (weeks)	22.6 (19.9–27.1; 15.1–35.0)	21.7 (19.3–23.9; 16.1–28.9)	25.8 (23.3–28.0; 17.0–32.1)	31.3 (28.6–34.0; 26.0–35.0)	21.4 (19.1–22.9; 15.1–24.0)
GA at intervention (weeks)	—	22.0 (19.5–24.3; 16.7–30.1)	26.3 (23.6–28.8; 18.0–32.1)	31.9 (29.1–34.1; 26.0–36.0)	22.1 (19.9–23.2; 17.1–24.6)
Spontaneous TAPS	51/113 (45)	86/110 (78)	26/70 (37)	34/43 (79)	19/30 (63)
Anterior placenta	55/113 (49)	47/110 (43)	42/70 (60)	22/43 (51)	19/30 (63)
TAPS stage at diagnosis	2 (1–2; 1–4)	2 (2–3; 1–4)	2 (1–2; 1–4)	1 (1–2; 1–4)	2 (2–3; 1–4)
1	52/113 (46)	25/110 (23)	18/70 (26)	23/43 (53)	5/30 (17)
2	45/113 (40)	51/110 (46)	37/70 (53)	13/43 (30)	12/30 (40)
3	11/113 (10)	27/110 (25)	10/70 (14)	5/43 (12)	11/30 (37)
4	5/113 (4)	7/110 (6)	5/70 (7)	2/43 (5)	2/30 (7)
Subsequent treatment	13/113 (12)	17/110 (16)	10/70 (14)	—	—
Expectant	—	3/110 (3)	—	—	—
IUT (± PET)	8/113 (7)	5/110 (5)	—	—	—
Laser (reintervention)	5/113 (4)	2/110 (2)	3/70 (4)	—	—
Selective feticide	—	7/110 (6)	7/70 (10)	—	—
PPROM	29/113 (26)	40/107 (37)[a]	17/69 (25)[c]	4/43 (9)	13/29 (45)[c]
GA at PPROM (weeks)	29.0 (25.1–31.3; 21.0–36.4)	29.7 (25.9–32.1; 16.9–35.9)[a]	29.0 (25.8–31.5; 17.7–34.0)[c]	29.3 (26.6–33.4; 26.2–34.2)	27.9 (24.8–31.6; 20.2–33.3)[c]
Spontaneous onset of delivery	43/113 (38)	60/106 (57)[b]	20/69 (29)[c]	3/43 (7)	24/29 (83)[c]
Cesarean delivery	69/113 (61)	80/106 (75)[b]	50/69 (72)[c]	38/43 (88)	13/29 (45)[c]

Data are presented as median (interquartile range; range) or *n*/*N* (%). Data missing for: [a]three pregnancies; [b]four pregnancies (including three with missing PPROM data); [c]one pregnancy missing PPROM and delivery data. GA, gestational age; IUT, intrauterine transfusion; PET, partial exchange transfusion; PPROM, preterm prelabor rupture of membranes.

Intrauterine transfusion (with or without partial exchange transfusion) group

Initial management by IUT with or without PET was performed in 70 pregnancies at a median GA of 26.3 (IQR, 23.6–28.8; range, 18.0–32.1) weeks. The median antenatal TAPS stage at diagnosis was 2 (IQR, 1–2). IUT was combined with PET in the recipient in 21% (15/70) of pregnancies. In total, 73% (51/70) of the cases in the IUT (± PET) group had one intervention, 13% (9/70) had two, 7% (5/70) had three, 6% (4/70) had four, and 1% (1/70) had six interventions. The median time between interventions was 13.0 (IQR, 8.6–16.8; range, 6.5–21.0) days. The transfusion site was intravenous only in 70% (47/67), intraperitoneal only in 10% (7/67) and combined in 19% (13/67) of cases. An alternative management strategy was decided in 14% (10/70) of the cases treated with IUT (± PET). Three cases were treated with laser surgery, all within 1 week after the first IUT and based on progressive or recurrent TAPS. Of these, one laser procedure was complete and the other two were incomplete and both had recurrent TAPS. In seven cases treated with IUT (± PET), a selective feticide in the TAPS donor was performed based on recurrent or progressive TAPS ($n = 5$) or severe cerebral injury ($n = 2$).

Delivery group

Delivery within 7 days after diagnosis of TAPS was the management choice in 43 pregnancies and took place at a median GA of 31.9 (IQR, 29.1–34.1; range, 26.0–36.0) weeks. The median antenatal TAPS stage for cases treated with delivery was 1 (IQR, 1–2). In total, 88% (38/43) of these pregnancies had a Cesarean section.

Selective-feticide group

Selective feticide was the first management choice in 30 TAPS pregnancies and was performed at a median GA of 22.1 (IQR: 19.9–23.2, range: 17.1–24.6) weeks. Indications for selective feticide were TAPS alone (67%; 20/30) or TAPS with co-existing severe growth restriction (10%; 3/30), severe cerebral injury (10%; 3/30) or congenital anomalies (10%; 3/30). In one further case, selective feticide was performed at request of the parents (3%; 1/30). Selective feticide was performed in the TAPS donor in 87% (26/30) of pregnancies in this group.

Comparison of outcome between management groups

Outcome data for the whole study population according to management strategy are presented in Table 2. The incidence of perinatal mortality was similar following expectant management (17%; 39/225), laser surgery (18%; 38/215), IUT (± PET) (18%; 25/140), delivery (10%; 9/86), and selective feticide (7%; 2/30) (smallest *P*-value = 0.177 (selective feticide *vs* expectant management)). Severe neonatal morbidity was significantly higher in TAPS twins that underwent delivery within 7 days after diagnosis (49%; 41/84) and IUT

Table 2 Outcome of 366 monochorionic twin pregnancies diagnosed prenatally with twin anemia–polycythemia sequence (TAPS), according to initial management strategy after diagnosis

Outcome	*Expectant management (n = 113 pregnancies; n = 226 fetuses)*	*Laser surgery (n = 110 pregnancies; n = 220 fetuses)*	*IUT (± PET) (n = 70 pregnancies; n = 140 fetuses)*	*Delivery (n = 43 pregnancies; n = 86 fetuses)*	*Selective feticide (n = 30 pregnancies; n = 30 cotwins)*	P
GA at birth (weeks)	33.0 (30.1–34.9)	31.8 (29.1–34.1)[d]	31.1 (28.3–33.0)†‡	31.9 (29.1–34.1)	32.1 (27.7–34.8)	< 0.001
Diagnosis-to-birth interval (weeks)	7.8 (3.8–14.4)	9.7 (6.6–12.7)	4.0 (2.0–6.9)‡	0.3 (0–0.5)†‡	10.5 (4.2–14.9)	< 0.001
Perinatal mortality	39/225 (17)[a]	38/215 (18)[d]	25/140 (18)	9/86 (10)	2/30 (7)†	0.177
Fetal demise*	24/226 (11)	28/215 (13)	18/140 (13)	0/86 (0)†‡	2/30 (7)	0.024
Neonatal mortality*	15/201 (7)[a]	10/187 (5)[d]	7/122 (6)	9/86 (10)†	0/28 (0)	0.280
Survivors						
None	5/112 (4)[a]	8/107 (7)[d]	3/70 (4)	1/43 (2)	2/30 (7)	0.700
One	27/112 (24)[a]	20/107 (19)[d]	18/70 (26)	7/43 (16)	28/30 (93)	< 0.001
Two*	80/112 (71)[a]	79/107 (74)[d]	49/70 (70)	35/43 (81)	0/30 (0)	< 0.001
At least one	107/112 (96)[a]	99/107 (93)[d]	67/70 (96)	42/43 (98)	28/30 (93)	0.696
Severe neonatal morbidity	60/193 (31)[b]	57/182 (31)[e]	56/122 (46)‡	41/84 (49)[h]†‡	7/28 (25)	0.027
Severe cerebral injury*	10/193 (5)[b]	6/182 (3)[e]	13/122 (11)†	8/84 (10)[h]	0/28 (0)	0.098
Postnatal TAPS	66/89 (74)	6/65 (9)	36/51 (71)	36/43 (84)	—	< 0.001
BT or PET at birth for TAPS*	81/188 (43)[c]	13/171 (8)[f]†	60/118 (51)[g]	48/84 (57)[h]	0/23 (0)[i]	< 0.001

Data are presented as median (interquartile range) or *n/N* (%). Data missing for: [a]one infant with unknown neonatal outcome; [b]nine infants (one with unknown neonatal outcome, three that died shortly after birth and five with unknown neonatal morbidity); [c]14 infants (same as 'b' plus five cases with missing BT/PET data); [d]five infants (three pregnancies) with missing outcome; [e]10 fetuses (same as 'd' plus five with missing neonatal outcome); [f]21 infants (same as 'e' plus 11 with unknown BT/PET data); [g]four infants with missing BT/PET data; [h]two infants that died shortly after birth; [i]five cotwins with missing BT/PET data. For comparisons using one-way analysis of variance and generalized estimated equation (all outcomes per fetus/neonate and continuous outcomes per pregnancy), expectant management was set as reference. For comparisons using chi-square test (categorical outcomes per pregnancy), *P*-values are for comparison between all treatment groups. *Statistical correction for non-occurring events was applied. †Smallest *P*-value, which is presented in *P*-value column. ‡Statistically significant *P*-value. BT, blood transfusion; GA, gestational age; IUT, intrauterine transfusion; PET, partial exchange transfusion.

(± PET) (46%; 56/122) compared with those managed expectantly (31%; 60/193), treated with laser surgery (31%; 57/182) or selective feticide (25%; 7/28) (smallest *P*-value = 0.027 (delivery *vs* expectant management)). Diagnosis-to-birth interval was 7.8 (IQR, 3.8–14.4) weeks in the expectant-management group, 9.7 (IQR, 6.6–12.7) weeks after laser surgery and 10.5 (IQR, 4.2–14.9) weeks after selective feticide, and was significantly shorter in twins treated with delivery (0.3 (IQR, 0.0–0.5) weeks) and IUT (± PET) (4.0 (IQR, 2.0–6.9) weeks) (smallest *P*-value < 0.001 (delivery *vs* expectant management). The prevalence of postnatal TAPS was similar following expectant management (74%; 66/89), IUT (± PET) (71%; 36/51) and delivery (84%; 36/43), and it was significantly lower in twins treated with laser surgery (9%; 6/65) ($P < 0.001$, chi-square test). Outcome data according to management strategy followed are presented separately for spontaneous TAPS and post-laser TAPS in Tables 3 and 4, respectively.

Management choice in 17 fetal therapy centers

Figure S1 shows the management choices for TAPS pregnancies amongst the 17 fetal therapy centers. Overall, management varied considerably between the centers. Some centers, such as Leiden University Medical Center, Vittore Buzzi Children's Hospital in Milan and Mater Mothers' Hospital in Brisbane, adopted a more conservative approach and managed a considerable number of cases expectantly. In contrast, St George's University Hospital in London, Necker-Enfants Malades Hospital in Paris and Children's Memorial Hermann Hospital in Houston, opted for more invasive treatment of TAPS cases, using laser treatment or selective feticide. The University Medical Center Hamburg-Eppendorf in Hamburg and Vall d'Hebron University Hospital in Barcelona in general refrained from performing *in-utero* interventions and managed the majority of cases expectantly or with delivery. The remaining centers did not show a remarkable trend or preference in management of TAPS pregnancies and applied the different treatment options alternately.

DISCUSSION

This is the first large international study investigating the outcome of TAPS pregnancies following different antenatal management strategies. We found that the incidence of perinatal mortality and severe neonatal morbidity was high in all treatment groups. Management of TAPS varied considerably within and between fetal therapy centers, reflecting the lack of international consensus on the optimal management strategy for this condition. This study presents new information on treatment for TAPS, thereby providing a more detailed context for management decisions and an enhanced understanding of TAPS and the clinical implications of each treatment strategy.

Table 3 Outcome of 216 monochorionic twin pregnancies diagnosed prenatally with spontaneous twin anemia–polycythemia sequence (TAPS), according to initial management strategy after diagnosis

Variable	*Expectant management (n = 51 pregnancies; n = 102 fetuses)*	*Laser surgery (n = 86 pregnancies; n = 172 fetuses)*	*IUT (± PET) (n = 26 pregnancies; n = 52 fetuses)*	*Delivery (n = 34 pregnancies; n = 68 fetuses)*	*Selective feticide (n = 19 pregnancies; n = 19 cotwins)*	P
GA at birth (weeks)	33.6 (31.3–35.4)	31.9 (29.1–34.4) ‡	31.3 (30.1–33.1)	32.2 (31.1–34.3)	30.6 (27.2–35.5)†‡	0.024
Diagnosis-to-birth interval (weeks)	7.7 (2.5–15.4)	10.3 (6.7–14.0)	2.4 (1.3–5.3) ‡	0.3 (0.0–0.8)†‡	11.1 (3.6–16.3)	< 0.001
Perinatal mortality	12/101 (12)[a]	26/168 (15)[d]	2/52 (4)†	5/68 (7)	2/19 (11)	0.118
Fetal demise*	5/102 (5)	20/168 (12)[d]	2/52 (4)	0/68 (0)	2/19 (11)†	0.104
Neonatal mortality*	7/96 (7)[a]	6/148 (4)[d]	0/50 (0)†	5/68 (7)	0/17 (0)	0.165
Survivors						
None*	1/50 (2)[a]	5/84 (6)[d]	0/26 (0)	0/34 (0)	2/19 (11)	0.178
One	8/50 (16)[a]	16/84 (19)[d]	2/26 (8)	5/34 (15)	17/19 (89)	< 0.001
Two*	41/50 (82)[a]	63/84 (75)[d]	24/26 (92)	29/34 (85)	0/19 (0)	< 0.001
At least one	49/50 (98)[a]	79/84 (94)[d]	26/26 (100)	34/34 (100)	17/19 (89)	0.174
Severe neonatal morbidity	26/93 (28)[b]	45/145 (31)[e]	22/50 (44)	32/67 (48)[g]†‡	4/17(24)	0.046
Severe cerebral injury*	2/93 (2)[b]	3/145 (2)[e]	4/50 (8)†	5/67 (7)[g]	0/17 (0)	0.099
Postnatal TAPS	31/46 (67)	4/51 (8)	17/24 (71)	28/34 (82)	—	< 0.001
BT or PET at birth for TAPS*	36/89 (40)[c]	9/135(7)[f]†‡	27/50 (54)	40/67 (60)[g]‡	0/13 (0)[h]	< 0.001

Data are presented as median (interquartile range) or *n*/*N* (%). Data missing for: [a]one infant with unknown neonatal outcome; [b]four infants (one with unknown neonatal outcome, one that died shortly after birth and two with unknown neonatal morbidity); [c]eight infants (same as 'b' plus four with missing BT/PET data); [d]four infants (two pregnancies) with unknown outcome; [e]seven infants (same as 'd' plus three with unknown neonatal morbidity); [f]17 infants (same as 'e' plus 10 without BT/PET data); [g]one infant that died shortly after birth; [h]four cotwins with missing BT/PET data. For comparisons using one-way analysis of variance and generalized estimated equation (all outcomes per fetus/neonate and continuous outcomes per pregnancy), expectant management was set as reference. For comparisons using chi-square test (categorical outcomes per pregnancy), *P*-values are for comparison between all treatment groups. *Statistical correction for non-occurring events was applied. †Smallest *P*-value, which is presented in *P*-value column. ‡Statistically significant *P*-value. BT, blood transfusion; GA, gestational age; IUT, intrauterine transfusion; PET, partial exchange transfusion.

Table 4 Outcome of 150 monochorionic twin pregnancies diagnosed prenatally with post-laser twin anemia–polycythemia sequence (TAPS), according to initial management strategy after diagnosis

Variable	*Expectant management (n = 62 pregnancies; n = 124 fetuses)*	*Laser surgery (n = 24 pregnancies; n = 48 fetuses)*	*IUT (± PET) (n = 44 pregnancies; n = 88 fetuses)*	*Delivery (n = 9 pregnancies; n = 18 fetuses)*	*Selective feticide (n = 11 pregnancies; n = 22 cotwins)*	P
GA at birth (weeks)	32.6 (29.4–34.6)	31.7 (29.1–33.7)[c]	29.9 (29.0–33.0)†‡	29.0 (27.7–31.8)	32.6 (31.13–34.0)	0.027
Diagnosis-to-birth interval (weeks)	8.0 (4.7–14.3)	8.1 (5.9–11.4)	4.8 (2.5–8.9)‡	0.3 (0.2–0.4)†‡	10.4 (9.2–14.4)	< 0.001
Perinatal mortality*	27/124 (22)	12/47 (26)[c]	23/88 (26)	4/18 (22)	0/11 (0)†	0.217
Fetal demise*	19/124 (15)	8/47 (17)[c]	16/88 (18)	0/18 (0)†	0/11 (0)†	0.268
Neonatal mortality*	8/105 (8)	4/39 (10)[c]	7/72 (10)	4/18 (22)†‡	0/11 (0)	0.040
Survivors						
None*	4/62 (6)	3/23 (13)[c]	3/44 (7)	1/9 (11)	0/11 (0)	0.692
One	19/62 (31)	4/23 (17)[c]	16/44 (36)	2/9 (22)	11/11 (100)	< 0.001
Two*	39/62 (63)	16/23 (70)[c]	25/44 (57)	6/9 (67)	0/11 (0)	0.002
At least one	58/62 (94)	20/23 (87)[c]	41/44 (93)	8/9 (89)	11/11 (100)	0.692
Severe neonatal morbidity	34/100 (34)[a]	12/37 (32)[d]	34/72 (47)	9/17 (53)[g]†	3/11 (27)	0.158
Severe cerebral injury*	8/100 (8)[a]	3/37 (8)[d]	9/72 (13)	3/17 (18)[g]†	0/11 (0)	0.141
Postnatal TAPS	35/43 (81)	2/14 (14)	19/27 (70)	8/9 (89)	—	< 0.001
BT or PET at birth for TAPS*	45/99 (45)[b]	4/36 (11)[e]†‡	33/68 (49)[f]	8/17 (47)[g]	0/10 (0)[h]	0.011

Data are presented as median (interquartile range) or *n*/*N* (%). Data missing for: [a]five infants (two that died shortly after birth and three with unknown outcome); [b]six infants (same as 'a' plus one with missing BT/PET data); [c]one infant with unknown outcome; [d]three infants (one with unknown outcome and two with unknown neonatal morbidity); [e]four infants (same as 'd' plus one with missing BT/PET data); [f]four neonates with unknown BT/PET data; [g]one infant that died shortly after birth; [h]one cotwin with missing BT/PET data. For comparisons using one-way analysis of variance and generalized estimated equation (all outcomes per fetus/neonate and continuous outcomes per pregnancy), expectant management was set as reference. For comparisons using chi-square test (categorical outcomes per pregnancy), *P*-values are for comparison between all treatment groups. *Statistical correction for non-occurring events was applied. †Smallest *P*-value, which is presented in *P*-value column. ‡Statistically significant *P*-value. BT, blood transfusion; GA, gestational age; IUT, intrauterine transfusion; PET, partial exchange transfusion.

Perinatal outcome

Confirming findings from previous smaller studies[20–22], we found comparable perinatal mortality rates between the different management strategies, in the total cohort as well as for spontaneous and post-laser TAPS pregnancies separately. Notably, perinatal mortality was substantially higher in pregnancies with post-laser TAPS compared with those with spontaneous TAPS in all management groups, illustrating the impact of preceding TTTS on the outcome of twins with post-laser TAPS. Severe perinatal morbidity rates were high in all groups, but were significantly increased in cases treated with IUT (± PET) or delivery within 7 days after diagnosis. Notably, TAPS twins managed with IUT (± PET) were delivered at a significantly earlier gestation compared with all other management groups, which is known to have significant impact on short-term outcome[10,11]. However, twins managed with delivery were born at a comparable gestational age to that of twins treated with laser surgery, which suggests that other factors might play a role. Our results show that expectant management, laser surgery and selective feticide are associated with a prolongation of the pregnancy for 7–10 weeks after the diagnosis of TAPS. Significant prolongation of TAPS pregnancy after laser surgery was previously reported by Slaghekke *et al.*[20]. Our study shows that TAPS cases treated with IUT (± PET) had a significantly shorter diagnosis-to-birth interval. Although gestation can be prolonged by reintervention with IUT (± PET), the majority of TAPS cases had only one intervention. A possible explanation could be that, due to the relatively high GA at diagnosis, caregivers preferred delivery with subsequent postnatal treatment over continuous exposure to TAPS, as soon as an acceptable gestation was achieved.

What is the optimal treatment for twin anemia–polycythemia sequence?

Determining the optimal treatment option is crucial in order to improve the outcome of TAPS pregnancies. Laser surgery is the only management option that treats the cause of TAPS and has been shown to drastically improve outcome in TTTS[23]. However, laser treatment in TAPS is technically more challenging than in TTTS, due to the absence of TOPS, which may lead to reduced accessibility and visibility of the placental surface. This can be especially problematic in cases of an anterior placenta. To optimize technical conditions, TOPS can be artificially created with amnioinfusion in one sac and amniodrainage of the other, but this requires more needle insertions and might increase the risk of PPROM and premature birth. In our cohort, PPROM occurred in 37% and delivery within 24 h after the procedure in 4% of pregnancies treated with laser surgery, which is comparable to findings following laser for TTTS[3]. A second technical problem is the minuscule size of TAPS anastomoses, which makes harder their detection during the procedure. Indeed, our data showed that TAPS recurred in 15% of cases treated with laser surgery, which is more than twice as high as the recurrence rate of TTTS after laser[3]. Moreover, we have shown that residual anastomoses after laser for TAPS always lead to recurrence of the disease. To prevent residual anastomoses and to ensure coagulation of anastomoses that cannot be visualized, the Solomon technique might be of added value[3]. Nevertheless, the rate of residual anastomoses following laser in our TAPS cohort was comparable to the rate of residual anastomoses in TTTS (both 19%)[3], and 43% of cases treated with laser had an anterior placenta, which shows that, despite the practical limitations, laser surgery for TAPS is technically feasible.

Our data show that, although a promising approach, laser surgery does not seem to improve (nor deteriorate) perinatal outcome when compared with expectant management. However, laser surgery was associated with a high diagnosis-to-birth interval, especially in comparison to treatment with IUT (± PET). As prematurity has a profound impact on short- and long-term health in TAPS twins, prolongation of pregnancy is of the utmost importance to improve outcome[6,7,10,11]. Notably, a comparable prolongation of pregnancy was achieved with selective feticide and expectant management. However, selective feticide comes with a high price, as parents lose at least one baby and healthy survival of the cotwin is not guaranteed. On the other hand, in expectant management, prolongation of pregnancy likely results in continuous exposure to the potential detrimental effects of TAPS, as only 16% of cases showed spontaneous resolution. As risk for perinatal mortality and morbidity increases with increasing antenatal TAPS stage, definitive treatment with laser might be the optimal intervention to improve perinatal outcome for this condition[11,24].

Strengths and limitations

This large, international multicenter study is the first to evaluate treatment choices for TAPS across the world, and provides valuable information for clinicians on both treatment and subsequent fetal and neonatal outcomes. Nevertheless, caution should be exercised when drawing conclusions based on the results we obtained. Due to the retrospective nature of this study, management groups are very likely to be subject to selection bias. The management groups differed in terms of GA at diagnosis, severity of TAPS and type of TAPS. Since higher TAPS stage and post-laser TAPS are associated with poorer prognosis, these factors could have influenced significantly the perinatal outcome[10,11]. Moreover, long-term outcome was not investigated in this study. Previous studies have shown that the detrimental effects of TAPS are not limited to the perinatal period, but also manifest later in life[6,7]. Therefore, the true effect of management for TAPS can only be properly investigated when TAPS cases are randomized between treatment groups, when stratification for risk factors is applied, and when long-term consequences are taken into account.

Conclusions

This study shows that there is extensive heterogeneity in the management choice for TAPS, both within and amongst fetal therapy centers. To improve outcome of TAPS pregnancies and to generate an international consensus on optimal management, a randomized controlled trial is urgently needed. Recently, the TAPS trial, an international multicenter open-label randomized controlled trial comparing laser surgery with standard care (expectant management, IUT (± PET), preterm delivery) has started recruiting patients[25].

COLLABORATORS

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Appendix S1 Details of 17 centers that contributed to data collection and number of cases from each center

Figure S1 Antenatal management of pregnancies with TAPS in 17 fetal therapy centers. IUT (± PET), intrauterine transfusion (with or without partial exchange transfusion).