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

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

Short title: Treatment and Outcome in 370 TAPS twins

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CONTRIBUTION

What does this work add to what is already known?

Antenatal treatment for TAPS differs considerably amongst fetal therapy centers. Perinatal mortality is comparable for all treatment groups. Severe neonatal morbidity was significantly higher in cases treated with IUT (± PET) or delivery. Prolonging pregnancy was best achieved in expectant management, laser surgery and selective feticide.

What are the clinical implications of this work?

There is no international consensus on the best treatment for TAPS. Treatment groups differed greatly at baseline, hampering reliability and generalizability of results. To improve outcome for TAPS, a randomized controlled trial investigating the best treatment option is urgently needed.

KEYWORDS

Monochorionic twins, twin anemia polycythemia sequence, TAPS, treatment, intrauterine transfusion, laser surgery, selective feticide, expectant management

DECLARATION OF INTEREST

The authors report to have no financial nor commercial conflict of interest.

*Missing values of the results presented in this paper are reported in the corresponding tables

Abstract

Objective: to investigate antenatal management and outcome in a large international cohort of spontaneous and post-laser twin anemia polycythemia sequence (TAPS).

Methods: Data of monochorionic twins diagnosed antenatally with TAPS collected in the TAPS Registry between 2014-2019 were included in this study. Antenatal diagnosis of TAPS was based on middle cerebral artery peak systolic velocity (MCA-PSV) > 1.5 Multiples of the Median (MoM) in the TAPS donor and < 1.0 MoM in the TAPS recipient. Cases were assigned to the management groups based on the first treatment that was received. The primary outcome included perinatal mortality and severe neonatal morbidity. The secondary outcome was diagnosis-to-birth interval.

Results: In total, 370 TAPS cases were antenatally diagnosed and managed either with expectant management in 31% (113/370), laser surgery in 30% (110/370), intrauterine transfusion (IUT) (with or without partial exchange transfusion (PET)) in 19% (70/370), delivery in 12% (43/370), selective feticide in 8% (30/370) or termination of pregnancy in 1% (4/370). Perinatal mortality occurred in 17% (37/225) of the expectant group, in 18% (38/215) of the laser group, in 18% (25/140) in the IUT (± PET) group, in 11% (9/86) in the delivery group and in 7% (2/30) of the co-twins in the selective-feticide group (p = 0.177). Severe neonatal morbidity was 49% (41/84) in delivery, 46% (56/122) in IUT (± PET), 31% (60/193) in expectant management, 31% (57/182) in laser surgery and 25% (7/28) in selective feticide (p = 0.027). Median diagnosis-to-birth interval was longest after selective feticide (10.5 weeks; IQR: 4.2-14.9), followed by laser surgery (9.7 weeks, IQR: 6.6-12.7), expectant management (7.8 weeks; IQR: 3.8-14.4), IUT (± PET) (4.0 weeks, IQR: 2.0-6.9 weeks) and delivery (0.3 weeks, IQR: 0.0-0.5), p < 0.001. Treatment 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. Prolonging pregnancy was best achieved in expectant management, laser surgery and selective feticide.

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Introduction

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

TAPS is a relatively new disease, with its first description originating from 2006[4]. Since then, knowledge of TAPS has greatly increased and insights into pathophysiology, diagnosis and outcome have gradually been established[5]. However, the best antenatal management option 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 outcome, it is crucial to investigate which management strategy provides TAPS twins the best outcome[6-8]. Unfortunately, due to the low incidence of the condition, studies are limited to small numbers, hampering generalizability of results and demanding extreme caution when comparing the outcomes. To generate more substantiated knowledge on the effects of management strategies for TAPS twins, we set up the TAPS Registry, an international collaboration aimed at collecting data on diagnosis, management and outcome in TAPS.

The aim of the current study is to investigate perinatal outcome of different antenatal management strategies and to report the antenatal management choices for TAPS in various fetal therapy centers across the world.

Methods

Registry

The TAPS Registry (www.tapsregistry.org) was established in 2014 as a web-based registry for anonymous data collection. 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 (see list in Appendix 1).

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 MCA-PSV discrepancy, with

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an increased MCA-PSV value (>1.5 Multiples of the Median (MoM)) in the TAPS donor combined with a decreased MCA-PSV value (<1.0 MoM) in the TAPS recipient, in absence of TOPS[9]. Cases were excluded if they only had a postnatal diagnosis of TAPS (and were missed antentally) and/or if they were diagnosed with post-laser TAPS within one week after laser for TTTS, unless TAPS was ongoing after one week and/or if they were first diagnosed with TAPS at stage 5. Of note, the outcome from postnatally diagnosed cases are presented in two other studies investigating outcome in spontaneous and post-laser TAPS separately[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, moment of diagnosis (ante- or postnatal), gestational age (GA) at diagnosis and TAPS stage at diagnosis. For antenatal management for TAPS, the type of management was recorded: 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 previously published staging system by Slaghekke et al.[12]. For delivery, the following parameters were retrieved: type of delivery (spontaneous or planned), mode of delivery (vaginal or cesarean) and type of cesarean (elective or emergency). Based on placental color dye examination, the type, size and number of placental anastomoses were recorded. Perinatal outcome included: donor/recipient status, hemoglobin and reticulocyte values, treatment with blood transfusion for anemia or partial exchange transfusion for polycythemia on day 1, the presence of severe neonatal morbidities and/or severe cerebral injury and the 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 TAPS cases can be managed according to different strategies in the same pregnancy, management-group allocation was based on the first treatment that was performed. The following rules were applied to management-group allocation: cases were assigned to the laser, IUT (± PET), or selective-feticide group if that was the first treatment they received within 14 days after diagnosis of TAPS (we allowed a one-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 group.

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When cases had an incomplete laser surgery and other interventions were needed to manage persisting or recurring TAPS, they were assigned to the laser group.

Characteristics for the population

The following parameters were studied for all management groups: type of TAPS (post-laser or spontaneous), location of the placenta, GA at diagnosis, TAPS stage at diagnosis, preterm premature rupture of the membranes (PPROM), GA at PPROM, type of delivery (spontaneous or planned), mode of delivery (vaginal or cesarean), GA at birth, the presence of TAPS postnatally, treatment for postnatal TAPS (defined as a blood transfusion for the donor and/or a partial exchange transfusion for the recipient at birth) and number of survivors per case. The postnatal diagnosis for TAPS was established on the presence of an inter-twin hemoglobin difference > 8.0 g/dL combined with least one of the following: a reticulocyte count ratio > 1.7 or the presence of only minuscule vascular anastomoses detected through color dye injection of the placenta[13, 14]. Furthermore, we studied specific management-related characteristics for each management group. For expectant management we investigated spontaneous resolution of TAPS (defined as the absence of TAPS postnatally). For IUT (±PET), the number of interventions, time interval between interventions (in days), and site(s) of transfusion were examined. In cases with multiple IUT (± PET) procedures, the median number of days between interventions was used. For laser surgery we examined recurrent/persistent TAPS, the presence of residual anastomoses, and delivery within 24 hours after the procedure. For selective feticide, donor/recipient status of the treated fetus and the reason 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 expectant management, delivery, IUT (± PET), laser surgery and selective feticide, for the total group, 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 only reported for the co-twin. 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 ≥ stage 2[15], retinopathy of prematurity ≥ stage 3[16], amniotic band syndrome, ischemic limb injury or severe cerebral injury. Severe cerebral injury was diagnosed in case of one of the following abnormalities was identified on cerebral imaging: intraventricular hemorrhage ≥ stage 3[17], ventricular dilatation (including post-hemorrhagic ventricular dilatation)[18], cystic

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periventricular leukomalacia ≥ grade 2[19], porencephalic or parenchymal cysts, arterial infarction or other severe cerebral lesions associated with adverse outcome.

Statistical analyses were carried out using SPSS version 25.0 (IBM, Armonk, NY, USA). Data are presented as medians and interquartile ranges (IQR) or range (minimum-maximum), or n/N (%), as appropriate. A p-value < 0.05 was considered statistically significant. To compare management groups, the outcome in the expectant-management group was set as the reference value. Continuous data on pregnancy level was compared using the one-way ANOVA with Tukey correction. A Chi-square test was used for categorical data on pregnancy-level. To account for the fact that observations between co-twins are not independent, outcomes on fetal or neonatal level were compared using the Generalized Estimated Equation (GEE) module. As a GEE cannot be carried out when an outcome event does not occur in one of the groups, an adjustment to the data was applied. With this adjustment, an unaffected child was changed into an affected child, for all groups. This correction generates more conservative p-values.

Results

Of the 422 TAPS cases that were entered in the TAPS Registry, 10% (43/422) was diagnosed postnatally and excluded from the study. From the remaining 379 cases, nine cases were excluded based on post-laser TAPS diagnosed within one week after laser for TTTS (n = 8) and antenatal TAPS stage 5 at diagnosis (n =1). A total of 370 cases were included in the study. Information on the cases contributed by each fetal therapy are detailed in Appendix 1. Antenatal management consisted of expectant management in 31% (113/370), laser surgery in 30% (110/370), IUT (± PET) in 19% (70/370), delivery in 12% (43/370), selective feticide in 8% (30/370) and termination of pregnancy in 1% (4/370). Table 1 shows diagnosis-, pregnancy- and delivery-related characteristics for expectant management, laser surgery, IUT (± PET), delivery and selective feticide.

Expectant management group

The median GA at diagnosis in the expectant management group was 22.6 weeks (IQR: 19.9-27.1, range: 15.1-35.1). The median antenatal TAPS stage at diagnosis was 2 (IQR: 1-2). Spontaneous resolution was seen in 16% (18/111)* of cases that were managed expectantly, and occurred after stage 1 in 17% (9/52), stage 2 in 13% (6/45), stage 3 in 20% (2/11) and in stage 4 in 20% (1/5). In 11% (13/113) of cases, an alternative management strategy was performed after 14 days of expectant management. An IUT (± PET) was elected in eight TAPS cases (after 15-97 days from diagnosis), based upon 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 five cases managed expectantly, laser surgery was

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performed for progression of TAPS (after 15-38 days from diagnosis). In two cases managed with laser surgery, a delivery took place within 24 hours after the procedure, resulting in miscarriage (23 weeks) and premature (28 weeks) birth, with double survival in the latter. In the other three cases, perinatal survival was seen in 5/6 neonates.

Laser surgery group

Laser surgery was performed at a median GA of 22.0 weeks (IQR: 19.5-24.3, range: 16.1-30.1). Spontaneous TAPS cases made up the majority of this treatment group (78%; 86/110). In total, 43% (47/110) of the TAPS cases 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 cases. In 4% (4/108) of cases treated with laser, a delivery took place within 24 hours after the procedure (at 21, 22, 24 and 28 weeks). Recurrent TAPS was seen in 15% (16/106) of the cases treated with laser surgery. Out of the 16 cases with recurrent TAPS, one was diagnosed with TAPS only postnatally. The remaining 15 were managed expectantly in 2% (3/110), with IUT (± PET) in 5% (5/110), laser reintervention in 2% (2/110) and selective feticide in 6% (5/110). In the cases managed expectantly, spontaneous resolution of TAPS was seen in one case. In the other two cases 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 out of the five twins after the first IUT. In both cases the co-twin survived. In the other three cases, two or three IUT (± PET) interventions were performed and all infants survived. Both laser reinterventions for recurrent TAPS were successful resulting in perinatal survival of the twins. Five recurrent TAPS cases were treated with selective feticide; four were performed in the donor twin, one in the recipient twin. In one case, fetal demise of the co-twin occurred. Aside from the recurrent-TAPS cases, a selective feticide was performed in two other cases treated with laser surgery, based on severe cerebral injury in the donor detected after laser intervention. In 9% (6/65) of liveborn twin pairs treated with laser surgery, postnatal TAPS was diagnosed. Placental injection information was available in 32% (36/110) of cases treated with laser surgery. Residual anastomoses, which were always minuscule, were detected in 19% (7/36). All cases with residual anastomoses (100%; 7/7) had recurrent TAPS.

IUT (± PET) group

An IUT (± PET) was performed at a median GA of 26.3 weeks (IQR: 23.6-28.8, range: 18.0-32.1). The median antenatal TAPS stage at diagnosis was 2 (IQR: 1-2). An IUT was combined with PET in the recipient in 21% (15/70). In total, 73% (51/70) of 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 with IUT (± PET). The median time between interventions was 13.0 days (IQR: 8.6-16.8; range: 6.5-21.0). The

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transfusion site was only intravenous in 70% (15/67), only intraperitoneal in 10% (7/67), and combined in 19% (13/67). 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 one week after the first IUT and based on progressive or recurrent TAPS. One laser procedure was complete, 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) took place at a median GA of 31.9 weeks (IQR: 29.1-34.1; range: 26.0-36.0). The median antenatal TAPS stage for cases treated with delivery was 1 (IQR: 1-2). In total, 88% (76/86) had a cesarean section.

Selective feticide group

Selective feticide was performed at a median GA of 22.1 weeks (IQR: 19.9-23.2, range: 17.1-24.6). Reasons for selective feticide included TAPS (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 case, selective feticide was performed on request of the parents (3%; 1/30). In 87% (26/30) of the group, selective feticide was performed in the TAPS donor.

Comparison of outcome between groups

Table 2a provides further information on the outcome for each management strategy. The rate of perinatal mortality was comparable for expectant management (17%; 39/225), laser surgery (18%; 38/215), IUT (± PET) (18%; 25/140), delivery (11%; 9/86), and selective feticide (7%; 2/30), p = 0.177. Severe neonatal morbidity was significantly higher in twins treated with delivery (49%; 41/84) and IUT (± PET) (46%; 56/122) than in twins managed expectantly (31%; 60/193), treated with laser surgery (31%; 57/182) or selective feticide (25%; 7/28), p = 0.027. Diagnosis-to-birth interval was 7.8 weeks (IQR: 3.8-14.4) in the expectant management group, 9.7 weeks (IQR: 6.6-12.7) after laser surgery and 10.5 weeks (IQR: 4.2-14.9) after selective feticide and was significantly shorter in twins treated with delivery (0.3 weeks, IQR: 0.0-0.5) and IUT (± PET) (4.0 weeks, IQR: 2.0-6.9), p < 0.001. The prevalence of postnatal TAPS was comparable for expectant management (74%; 66/89), IUT (± PET) (71%; 36/51), and delivery (84%; 36/43), and significantly lower in twins treated with laser surgery (9%; 6/65), p < 0.001. In table 2b and 2c, outcome for management strategies are presented for spontaneous TAPS and post-laser TAPS separately.

Management choices for 17 fetal therapy centers

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Figure 1 shows management choices for TAPS amongst 17 fetal therapy centers. Overall, management varied considerably. Some centers, like Leiden, Milan and Brisbane, adopt a more conservative attitude and manage a considerable number of cases expectantly. In contrast, London, Paris, and Houston treat TAPS cases more invasively, with laser treatment or selective feticide. Fetal therapy centers in Hamburg and Barcelona generally refrain from doing in-utero interventions and manage the majority of cases expectantly or with delivery. The remaining centers do not show a remarkable trend or preference in management and apply the different treatment options alternately.

Discussion

This is the first large international study investigating outcome after antenatal management for TAPS. We found that perinatal mortality and severe neonatal morbidity rates were high in all treatment groups. Management for TAPS varied considerably within and between fetal therapy centers, reflecting the lack of international consensus on the most optimal management strategy. With this study we present new information on treatment for TAPS, thereby providing a more detailed context to management decisions, leading to a more enhanced understanding of TAPS and the clinical implications of each treatment strategy.

Perinatal outcome

Confirming findings from previous smaller studies[20-22] , we found comparable perinatal mortality rates for all management strategies, for the total cohort as well as for spontaneous and post-laser TAPS separately. Notably, post-laser TAPS twins showed substantially higher rates of perinatal mortality than spontaneous TAPS twins 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. Notably, twins managed with IUT (± PET) were delivered at a significantly earlier gestation, which is known to have significant impact on short-term outcome[10, 11]. However, twins that had a delivery were born at a comparable gestation as twins treated with laser, which might suggest that other factors might also play a role. Our results show that expectant management, laser surgery and selective feticide generate a prolongation of pregnancy of 7-10 weeks after the diagnosis of TAPS. A prolonged pregnancy after laser surgery compared to expectant management and IUT (± PET) 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

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over continuous exposure of TAPS, as soon as an acceptable gestation was achieved. The shortest diagnosis-to-birth interval was seen in the delivery group, in accordance with the management-group definition.

Optimal treatment?

Determining the most optimal treatment option is crucial to improve outcome in TAPS. Laser surgery is the only management option that directly treats the cause of TAPS, and has shown to drastically improve outcome in TTTS[23]. However, laser 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 case 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 chances of PPROM and premature birth. However, we report PPROM in 37% and delivery within 24 hours after laser in 4%, which is comparable to laser for TTTS[3]. A second technical problem comes with the size of TAPS anastomoses, which are known to be minuscule and might therefore be harder to find during procedure. In line, 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 the 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 in TAPS was comparable to the rate of residual anastomoses in TTTS (both 19%),[3] and 43% of lasers were performed in cases with an anterior placenta, showing that, despite the practical limitations, laser for TAPS is technically feasible.

Although promising in approach, our data show that laser surgery does not seem to improve (nor deteriorate) perinatal outcome when compared to expectant management. However, laser surgery was associated with a high diagnosis-to birth interval, especially in contrast to treatment with IUT (± PET). As prematurity has a profound impact on short- and long-term health in TAPS twins, prolonging pregnancy is of 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 do not have a guarantee of healthy survival for the co-twin. Alternatively, in expectant management, prolonging of pregnancy likely results in continuous exposure to potential detrimental effects of TAPS, as only 16% showed spontaneous resolution. As risk for perinatal mortality and morbidity increases with incrementing antenatal TAPS stage, definitive treatment with laser might be the most optimal intervention to improve perinatal outcome for this condition[24, 25].

*Missing values of the results presented in this paper are reported in the corresponding tables

One should be extremely cautious with drawing conclusions based on the results of this registry. Due to the retrospective nature of this study, management groups are very likely to be subject to selection bias. As our data have indicated, management groups differed in terms of GA at diagnosis, severity of TAPS, and type of TAPS. Since higher TAPS stages and post-laser TAPS are associated with poorer prognosis, these factors could have significantly influenced perinatal outcome rates[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.

In conclusion, this registry shows that there is an extensive heterogeneity in management for TAPS, both within and amongst fetal therapy centers. To improve outcome in TAPS, and to generate an international consensus on optimal management, a randomized controlled trial (RCT) is urgently needed. Recently, the TAPS trial, an international multicenter open-label RCT comparing laser surgery to standard care (expectant management, IUT (± PET), preterm delivery) has started recruiting patients[26].

*Missing values of the results presented in this paper are reported in the corresponding tables

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*Missing values of the results presented in this paper are reported in the corresponding tables

Table 1. Diagnosis-, pregnancy-, and delivery-related characteristics for expectant management, laser surgery, IUT (±PET), delivery and selective feticide

	Expectant management (N = 113, 226 fetuses)	Laser surgery (N=110, 220 fetuses)	IUT (± PET) (N=70, 140 fetuses)	Delivery (N=43, 86 fetuses)	Selective feticide (N=30, 60 fetuses)
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)	52/70 (37)	34/43 (79)	18/30 (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)	2 (2-3)	2 (1-2)	1 (1-2)	2 (2-3)
1	52/113 (46)	25/110 (23)	18/70 (26)	23/43 (54)	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 (24)	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)
5	0/113 (0)	-	0/70 (0)		
Alternative treatment	13/113 (11)	16/110 (15)	9/70 (14)	-	-
Expectant		2/110 (2)	-		
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)†	17/69 (25)§	4/43 (9)	13/30 (45)
GA at PPROM (weeks)	29.0 (25.1-31.3; 21.0-36.4)	29.7 (25.9-32.1; 16.9-35.9)	29.0 (25.8-31.5; 17.7-34.0)	29.3 (26.6-33.4; 26.2-34.2)	27.9 (24.8-31.6; 20.2-33.3)
Spontaneous start of delivery	43/113 (38)	60/106 (57)‡	20/69 (29)§	3/43 (7)	24/29 (83)¶
Cesarean	138/226 (61)	160/212 (76)‡	100/138 (73)	76/86 (88)	26/58 (46)¶

Data are presented as median (IQR; range) or n/N (%). † 3 missing values , ‡ 4 missing values (same as '†' plus one case with missing delivery data) §1 missing value (one case with missing delivery and PPROM info), ¶ 1 case with missing delivery information

IUT, intrauterine transfusion; GA, gestational age; BT, blood transfusion; PET, partial exchange transfusion; TAPS, twin anemia polycythemia sequence; PPROM, preterm premature rupture of the membranes

*Missing values of the results presented in this paper are reported in the corresponding tables

Table 2a. Outcome of expectant management, laser surgery, IUT (± PET), delivery, and selective feticide for all TAPS twins

TOTAL GROUP	Expectant management (N = 113 pregnancies; 226 fetuses)	Laser surgery (N= 110 pregnancies; 220 fetuses)	IUT (± PET) (N=70 pregnancies; 140 fetuses)	Delivery (N=43 pregnancies; 86 fetuses)	Selective feticide (N=30 pregnancies; 30 co-twins)	p-value
GA at birth (weeks)	33.0 (30.1-34.9)	31.8 (29.1-34.1)	**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)†	38/215 (18)¶	25/140 (18)	9/86 (11)	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$^{\psi}$	15/201 (8)†	10/187 (5)¶	7/122 (6)	9/86 (11)*	0/28 (0)	0.280
Survivors						
None	5/112 (5)†	8/107 (8)*	3/70 (4)	1/43 (2)	2/30 (7)	0.359
One	27/112 (24)†	20/107 (19)	18/70 (26)	7/43 (16)	**28/30 (93)***	**<0.001**
Two$^{\psi}$	80/112 (71)†	78/107 (73)	49/70 (70)	35/43 (81)	**0/30 (0)***	**<0.001**
At least one	108/112 (95)†	99/107 (92)	67/70 (96)	42/44 (98)	27/30 (93)	0.304
Severe neonatal morbidity	60/193 (31)‡	57/182 (31)¥	**56/122 (46)**	**41/84 (49)***	7/28 (25)	**0.027**
Severe cerebral injury$^{\psi}$	10/193 (5)‡	6/182 (3)¥	13/122 (11)*	8/84 (10)	0/28 (0)	0.098
Postnatal TAPS	66/89 (74)	**6/65 (9)***	36/51 (71)	36/43 (84)	-	**<0.001**
BT/PET at birth for TAPS$^{\psi}$	81/188 (43)§	**13/171 (8)***£	60/118 (51)∫	48/84 (57)	0/23 (0)◊	**<0.001**

Data are presented as median (IQR) or n/N (%). To compare treatments, expectant management was set as a reference. Bold numbers represent significant p-values, an * indicates the smallest p-value that is presented in the p-value column.

† 1 missing value (1 infant with incomplete neonatal outcome) ‡ 8 missing values (same as '†' plus 3 cases that died shortly after birth, and 4 cases with unknown neonatal morbidity), § 13 missing values (same as '‡' plus 5 cases with unknown BT/PET information ¶ 5 missing values ¥ 10 missing values (as '¶' plus 5 cases with missing neonatal outcome) £ 21 missing values (same as '¥' plus 11 cases with missing data on BT/PET at birth), ∫ 4 missing values, ◊ 5 co-twin with missing data on BT/PET

$^{\psi}$ Statistical correction for non-occurring events is applied

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

*Missing values of the results presented in this paper are reported in the corresponding tables

Table 2b Outcome of expectant management, laser surgery, IUT (± PET), delivery and selective feticide for spontaneous TAPS twins

SPONTANEOUS TAPS	Expectant management (n = 51 pregnancies; 102 fetuses)	Laser surgery (n = 86 pregnancies; 172 fetuses)	IUT (± PET) (n = 26 pregnancies; 52 fetuses)	Delivery (n = 34 pregnancies; 68 fetuses)	Selective feticide (n= 19 pregnancies; 19 co-twins)	p-value
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)†	26/168 (16)¶	2/52 (4)*	5/68 (7)	2/19 (11)	0.118
Fetal demise$^{\psi}$	5/102 (5)	20/168 (12)¶	2/52 (4)	0/68 (0)	2/19 (11)*	0.104
Neonatal Mortality$^{\psi}$	7/96 (7)†	6/148 (4)¶	0/50 (0)*	5/68 (7)	0/17 (0)	0.165
Survivors						
None $^{\psi}$	1/50 (2)	5/84 (6)	0/26 (0)	0/34 (0)	2/19 (11)	0.178
One	8/50 (16)	16/84 (19)	2/26 (8)	5/34 (15)	**15/19 (89)***	**<0.001**
Two$^{\psi}$	41/50 (82)	62/84 (74)	24/26 (92)	29/34 (85)	**0/19 (0)***	**<0.001**
At least one	49/50 (98)	79/84 (94)	26/26 (100)	34/34 (100)	15/19 (89)	0.174
Severe neonatal morbidity	26/93 (28)‡	45/145 (31)¥	22/50 (44)	**32/67 (48)***∫	4/17(24)	**0.046**
Severe cerebral injury$^{\psi}$	2/93 (2)‡	3/145 (2)	4/50 (8)*	5/67 (8) ∫	0/17 (0)	0.099
Postnatal TAPS	31/46 (67)	4/51 (8)	17/24 (71)	28/34 (82)	-	**<0.001**
BT/PET at birth for TAPS$^{\psi}$	36/89 (40)§	**9/135(7)***£	27/50 (54)	**40/67 (60)**∫	0/13 (0) ◊	**<0.001**

Data are presented as median (IQR) or n/N (%). To compare treatments, expectant management was set as a reference. Bold numbers represent significant p-values, an * represents the smallest p-value that is presented in the p-value column

† 1 missing value (unknown neonatal outcome), ‡ 4 missing values (same as '†' plus 3 cases with unknown neonatal outcome). § 8 missing values (same as '‡' plus 4 cases with missing information on BT/PET at birth ¶ 4 missing values (2 pregnancies missing outcome), ¥ 7 missing values (same as '¶', plus 3 infants with unknown neonatal morbidity). £ 17 missing values (same as '¥' plus 10 infants without BT/PET information)), ∫ 1 missing value (one infant died directly after birth) ◊ 5 missing values

$^{\psi}$ Statistical correction for non-occurring events is applied

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

*Missing values of the results presented in this paper are reported in the corresponding tables

Table 2c Outcome of expectant management, laser surgery, IUT (± PET), delivery and selective feticide for post-laser TAPS twins

POST-LASER TAPS	Expectant management (n = 62 pregnancies; 124 fetuses)	Laser surgery (n = 24 pregnancies; 48 fetuses)	IUT (± PET) (n = 44 pregnancies; 88 fetuses)	Delivery (n = 9 pregnancies; 18 fetuses)	Selective feticide (n= 11 pregnancies; 22 fetuses)	p-value
GA at birth (wks)	32.6 (29.4-34.6)	31.7 (29.1-33.7) §	**29.9 (29.0-33.0)***	29.0 (27.7-31.8)	32.6 (31.13-34.0)	**0.027**
Diagnosis-to-birth interval (wks)	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$^{\psi}$	27/124 (22)	12/47 (26) §	23/88 (26)	4/18 (22)	0/11 (0)*	0.217
Fetal demise$^{\psi}$	19/124 (15)	8/47 (17) §	16/88 (18)	0/18 (0)*	0/11 (0)*	0.268
Neonatal Mortality$^{\psi}$	8/105 (8)	4/39 (10)	7/72 (10)	**4/18 (22)***	0/11 (0)	**0.040**
Survivors						
None$^{\psi}$	4/62 (7)	3/23 (13)	3/44 (7)	1/9 (11)	0/11 (0)	0.111
One	19/62 (31)	4/23 (17)	16/44 (36)	2/9 (22)	**11/11 (100)***	**<0.001**
Two$^{\psi}$	39/62 (63)	16/23 (70)	27/44 (57)	6/9 (67)	**0/11 (0)***	**<0.001**
At least one	58/62 (93)	20/23 (87)	41/44 (93)	8/9 (89)	11/11 (100)	0.111
Severe neonatal morbidity	34/100 (34)†	12/37 (32)¶	34/72 (47)	9/17 (53)* ∫	3/11 (27)	0.158
Severe cerebral injury$^{\psi}$	8/100 (8)	3/37 (8)¶	9/72 (13)	3/17 (18)* ∫	0/11 (0)	0.141
Postnatal TAPS	35/43 (81)	**2/14 (14)***	19/27 (70)	8/9 (89)	-	**<0.001**
BT/PET at birth for TAPS$^{\psi}$	45/99 (46)‡	**4/36 (11)*** ¥	33/68 (49)£	8/17 (47) ∫	0/10 (0) ◊	**0.011**

Data are presented as median (IQR) or n/N (%). To compare treatments, expectant management was set as a reference. Bold numbers represent significant p-values, an * represents the smallest p-value that is presented in the p-value column

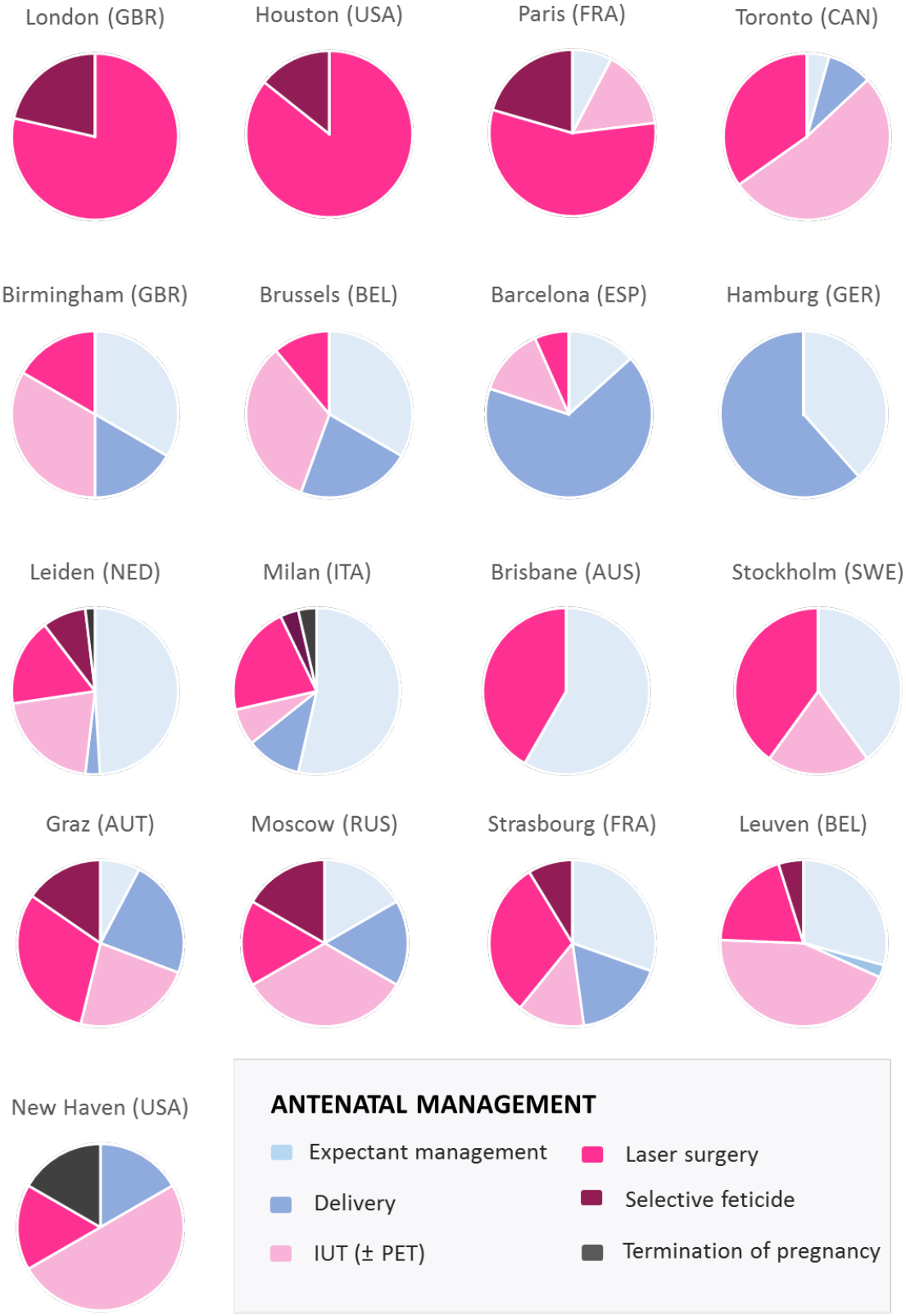
† 5 missing values (2 infants died directly after birth, 3 infants with missing outcomes) ‡ 6 missing values (same as '†', plus one case with missing BT/PET information) § 1 missing value (unknown outcome) ¶ 2 missing values, ¥ 3 missing values (same as '¶' plus one case with missing BT/PET information) £ 4 missing values (4 neonates unknown BT/PET information). ∫ 1 missing values (1 infant died directly after birth) , ◊ 1 missing value

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

$^{\psi}$ Statistical correction for non-occurring events is applied

*Missing values of the results presented in this paper are reported in the corresponding tables

Figure 1. Antenatal management for TAPS in 17 fetal therapy centers



*Missing values of the results presented in this paper are reported in the corresponding tables

Appendix 1.

Center	Country	Antenatally diagnosed TAPS Cases
Leiden University Medical Center	The Netherlands	105
Leuven University Hospital	Belgium	41
Necker-Enfants Malades Hospital Paris	France	39
Children's Hospital V. Buzzi Milan	Italy	28
Center Medico-Chirurgical Obstetrical Strasbourg	France	23
Mount Sinai Hospital Toronto	Canada	22
Hospital Universitari Vall d'Hebron Barcelona	Spain	15
Saint George's Hospital London	United Kingdom	14
University of Texas McGovern Medical School at Houston	United States of America	14
Medical University of Graz	Austria	13
University Medical Center Hamburg-Eppendorf	Germany	13
Mater Hospital Brisbane	Australia	12
Brugmann University Hospital	Belgium	8
Birmingham Women's and Children's NHS Foundation Trust	United Kingdom	6
V.I. Kulakov National Medical Research Center of Obstetrics, Gynecology and Perinatology Moscow	Russia	6
Yale New Haven Hospital	United States of America	6
Karolinska University Hospital Stockholm	Sweden	5

*Missing values of the results presented in this paper are reported in the corresponding tables

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