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Twin Anemia Polycythemia Sequence: Knowledge and Insights After 15 Years of Research

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Abstract

Twin anemia polycythemia sequence (TAPS) is a chronic form of unbalanced feto-fetal transfusion through minuscule placental anastomoses in monochorionic twin pregnancies, leading to anemia in the donor twin and polycythemia in the recipient twin. TAPS can occur spontaneously in up to 5% of monochorionic twins or can arise in 2%–16% of cases after incomplete laser surgery for twin-twin transfusion syndrome. TAPS can develop across the entire second and third trimester. Antenatal diagnosis for TAPS is reached via Doppler measurement of the fetal middle cerebral artery peak systolic velocity, showing an increased velocity in the donor, combined with a decreased velocity in the recipient. Treatment options for TAPS include expectant management, preterm delivery, intrauterine blood transfusion with or without a partial exchange transfusion, fetoscopic laser surgery and selective feticide. The best treatment option is unclear and is currently being investigated in an international multicenter randomized trial (the TAPS trial). Spontaneous fetal demise occurs in 5%–11% of TAPS twins, more often in donors (8%–18%) than in recipients (2%–5%). Severe long-term neurodevelopmental impairment is seen in 9% of TAPS twins, with donors having an increased risk for cognitive impairment and hearing problems (15%).

Keywords: Polycythemia; Anemia; Twin anemia polycythemia sequence; Monochorionic twins; Twin-twin transfusion syndrome; Placenta

Introduction

Monochorionic twins share one placenta and have their circulations connected to each other via placental vascular anastomoses. Under normal circumstances, feto-fetal blood transfusion through these anastomoses is balanced. However, in approximately 15% of monochorionic twins, blood flow between the fetuses is unequal, which may lead to severe complications including twin-twin transfusion syndrome (TTTS) or twin anemia polycythemia sequence (TAPS).¹ In TTTS, an imbalanced blood flow through relatively large placental anastomoses causes hypovolemia and oliguria in the TTTS donor and hypervolemia and polyuria in the TTTS recipient. This gradually leads to oligohydramnios in the donor twin and polyhydramnios in the recipient twin, a situation also referred to as twin oligohydramnios-polyhydramnios sequence (TOPS).

Whereas the diagnosis of TTTS has been widely established, TAPS is a relatively recently described form of chronically unbalanced feto-fetal transfusion, leading to anemia in the donor twin and polycythemia in the recipient twin, without signs of TOPS.² There are two types of TAPS: spontaneous and post-laser TAPS. Spontaneous TAPS occurs in up to 5% of monochorionic twin pregnancies.^{3,4} Post-laser TAPS can develop in 2%–16% of TTTS twins treated with laser surgery as the result of residual anastomoses.^{5,6} In 2006, Robyr *et al.* were the first to report that TAPS may occur in a subgroup of TTTS cases that had fetoscopic laser surgery of the vascular anastomoses.⁵ However, at that time the cause of the disease was still unknown, and no clear terminology was used to describe this phenomenon. At the same time, our research group reported three cases of spontaneous TAPS and proposed the pathophysiologic explanation for the onset of the disease based on the presence of minuscule placental anastomoses.² To clearly demarcate this new form of feto-fetal transfusion from the well-known TTTS, the term “twin anemia polycythemia sequence”, as well as its acronym TAPS, was introduced. Since then, multiple reports of TAPS cases across the world emerged, which gradually have led to acceptance of this diagnosis as a distinct, separate disease in monochorionic twins. This review presents the current insights regarding pathogenesis, diagnostics, treatment and outcomes in this condition, and provides a comprehensive overview of the results of 15 years of research into TAPS.

Pathogenesis

Placental characteristics

TAPS is caused by a slow and chronic unbalanced feto-fetal transfusion through minuscule placental anastomo-

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ses, gradually leading a large hemoglobin difference with anemia in the donor twin and polycythemia in the recipient twin.² The classical clinical picture of TAPS is a pale anemic donor and a plethoric polycythemic recipient (Fig. 1). TAPS placentas differ from placentas of uncomplicated monochorionic twins in various ways. Whereas the latter is characterized by multiple large anastomoses of various caliber (arterio-venous (AV), veno-arterial (VA), arterio-arterial (AA), and veno-venous (VV)) (Fig. 2), TAPS placentas demonstrate only one or a few very small anastomoses (diameter <1 mm) (Fig. 3). These are mostly only minuscule AV and VA anastomoses, which allow slow unidirectional fetofetal blood flow.^{7,8} AA anastomoses are less frequently seen in TAPS placentas (19%) than in placentas of uncomplicated monochorionic twins (91%).⁷⁻⁹ When AA anastomoses are present in TAPS, they are always minuscule. AA anastomoses are considered to protect against the development of TAPS or TTTS, because their bidirectional nature allows for intertwin equilibration of blood volumes. VV anastomoses are even more uncommon (7%) in TAPS placentas.^{7,8} Spontaneous TAPS and post-laser TAPS placentas differ from one another as well. Spontaneous TAPS placentas have more anastomoses, and they are located across the entire vascular equator.¹⁰ Post-laser TAPS placentas often only have one minuscule residual AV anastomosis that is likely to be located at the margin of the placenta, where it more easily missed during laser surgery (Fig. 4).

TAPS vs. TTTS

The absence of TOPS is an essential element in the diagnosis of TAPS. The presence of TOPS is only pathognomonic for TTTS. The mechanism that prevents the TAPS donor to develop oligohydramnios and the TAPS recipient to develop polyhydramnios is not entirely understood. The most probable hypothesis is that the slow transfusion in TAPS allows more time for a hemodynamic compensatory mechanism to take place. Another aspect that could explain the difference in clinical presentation, might be the hormonal dysregulation that

has been reported to take place in twins with TTTS.¹¹ TTTS donors show high renin levels, likely as results of renal hypoperfusion, and recipients have absent renin protein, due to down-regulation caused by hypervolemia. In TAPS, this hormonal discordance is not described.

Interestingly, in small subgroup of monochorionic twins TTTS and TAPS seem to co-exist. Approximately 8%–19% of TTTS twins show signs of fetal anemia in the TTTS donor and fetal polycythemia in the TTTS recipient twin before laser treatment.^{12–14} Similar to the placental angioarchitecture of TAPS, placentas of twins with TTTS and co-existing anemia-polycythemia showed fewer anastomoses than twins with isolated TTTS.

TAPS and fetal growth restriction (FGR)

Co-existing FGR commonly occurs in TAPS pregnancies, and usually affects the TAPS donor. Recent reports show that in spontaneous TAPS, around 50% of the donors is severely growth-restricted (birth weight <3rd centile) compared to 11% of recipients.⁸ In case of FGR in the recipient twin, the donor twin was usually also growth restricted but even more severe. In post-laser TAPS, this difference between donor and recipient is not observed, probably due to the fact that a large part of post-laser TAPS donors have previously been TTTS recipients, which in turn are often the larger twin.^{7,8} Although the donor usually is the smaller infant, it often has a paradoxically larger placental share compared to its recipient co-twin (Figs. 3A,3B).¹⁵ This finding is only reported in TAPS twins and not in twins with isolated selective FGR or TTTS.^{16,17} FGR in TAPS therefore appears to be determined by inter-twin blood transfusion rather than unequal placental sharing.

Unusual TAPS cases

Although TAPS generally occurs in monochorionic diamniotic (monozygotic) twin pregnancies, there are reports of the condition to develop in monochorionic monoamniotic twins and even in dichorionic diamniotic



Figure 1. Spontaneous TAPS twins at birth. On the left hand-side the plethoric polycythemic recipient and on the right-hand side the pale anemic donor. Parental consents were obtained for publication of the pictures of the children. TAPS: Twin anemia polycythemia sequence.



Figure 2. Placenta of an uncomplicated monochorionic twin showing multiple large anastomoses. AA: Arterio-arterial; AV: Arterio-venous; VA: Veno-arterial; VV: Veno-venous.

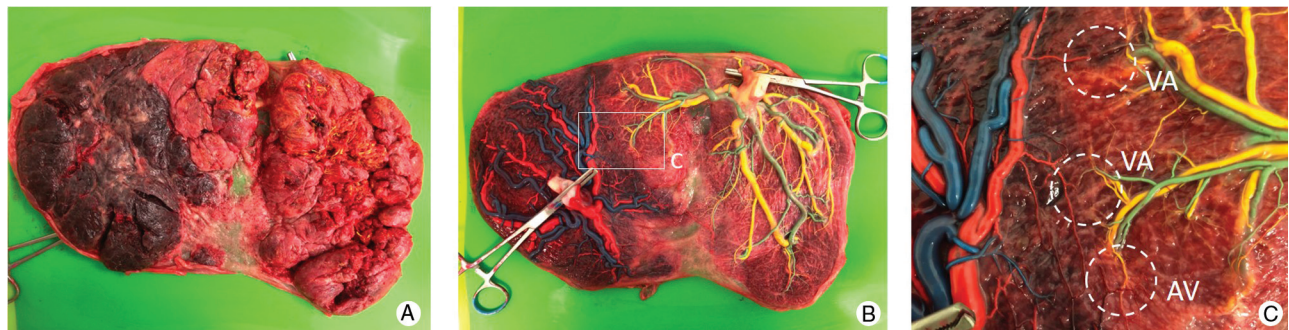


Figure 3. Placenta from a spontaneous TAPS twin born at a gestational age of 34⁺¹ weeks. Twin 1 is the recipient (1990 g, Hb 26.1 g/dL), twin 2 is the anemic donor (1730 g, Hb 8.2 g/dL). A The maternal side of the placenta, demonstrating a striking color difference between the plethoric placental share of the recipient and the pale share for the anemic donor. B Fetal side of the placenta injected with color dye. The placental share of the recipient is injected with blue (arteries) and red (veins), the placental share of the donor is injected with green (arteries) and yellow (veins), (C: refers to Fig. 3C). C Three minuscule anastomoses: two veno-arterial anastomoses (recipient ← donor) and one arterio-venous anastomoses (recipient → donor). AV: Arterio-venous; Hb: Hemoglobin; TAPS: Twin anemia polycythemia sequence; VA: Veno-arterial.

twins. Diehl *et al.* reported a monoamniotic twin that was diagnosed with TAPS at 26 weeks of gestation and was successfully treated with fetoscopic laser surgery.¹⁸ While monoamniotic twins are characterized by large placental anastomoses (with a large AA anastomosis between the proximately inserted umbilical cords), this case only showed minuscule placental anastomoses at fetoscopy, consistent with the pathophysiology of TAPS. Dichorionic twins are generally not at risk of developing TAPS, due to the separate placentas with no vascular connections between the two fetal circulations. However, Zilliox *et al.* described an atypical case of a dichorionic twin diagnosed with TAPS at 31 weeks, resulting in neonatal mortality in the severely anemic donor.¹⁹ Although the clinical picture was confirming TAPS, the typical minuscule anastomoses could not be found at placental color dye injection. Recently, our research group also reported on a dichorionic twin with TAPS which led to severe cerebral injury in the polycythemic infant (unpublished data). In our case, placental injection revealed a minuscule deep-

hidden VV anastomosis. Lastly, TAPS has also been reported in two cases of monochorionic dizygotic twins with opposite sexes.^{20,21}

Antenatal diagnosis

Time of onset

TAPS can develop across a wide range in pregnancy, from 15 to 35 weeks of gestation, and is, in contrast to TTTS, not restricted to a certain trimester.⁸ The cause for the variety in time of onset is not entirely clear, but might be related to the type of anastomoses. Possibly, TAPS placentas with AA anastomoses have a later time of onset of the condition. In post-laser TAPS, most cases develop within one month after the laser surgery for TTTS, but the condition can be detected up to 17 weeks post-surgery.²² In the majority of post-laser TAPS cases, the operator assumed that laser surgery for TTTS was complete, showing that this complication often develops unexpect-

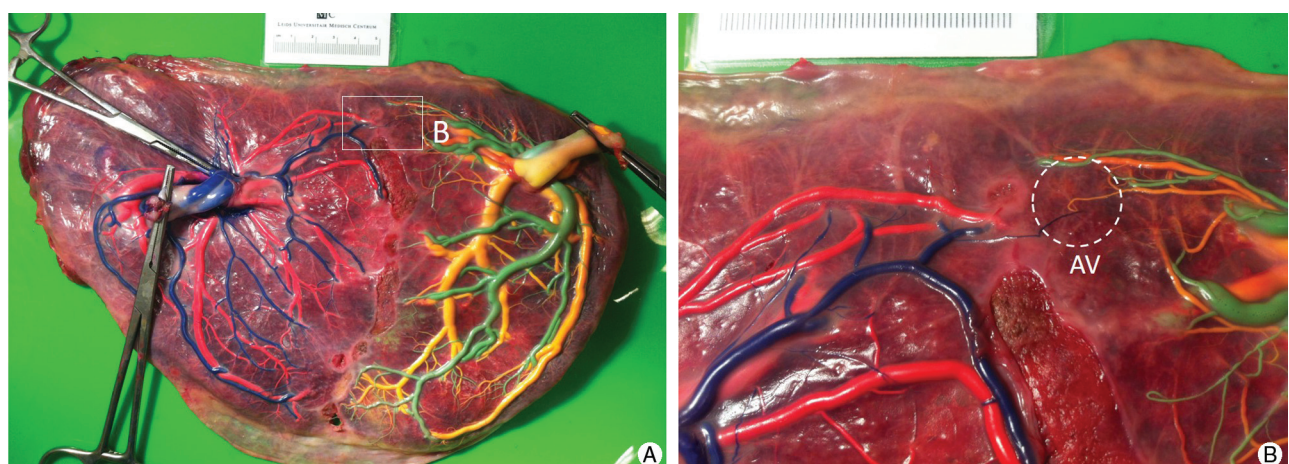


Figure 4. Placenta from a post-laser TAPS twin, born at a gestational age of 31⁺⁶ weeks. Twin 1 is the TAPS donor and former TTTS recipient (1445 g, Hb 9.3 g/dL), twin 2 is the TAPS recipient and former TTTS donor (1715 g, Hb 23.5 g/dL). A Fetal side of the placenta injected with color dye. The placental share of the donor is injected with blue (arteries) and red (veins), the placental share of the recipient is injected with green (arteries) and yellow (veins), (B: refers to Fig. 4B). B One minuscule anastomosis at the margin of the placenta (arterio-venous, donor → recipient). AV: Arterio-venous; Hb: Hemoglobin; TAPS: Twin anemia polycythemia sequence; TTTS: Twin-twin transfusion syndrome.

edly. The first studies on post-laser TAPS showed that it frequently was the former TTTS donor that became the polycythemic TAPS recipient, and the former TTTS recipient that became the anemic TAPS donor.^{5,23,24} However, a recent large international study demonstrated that reversal of donor-recipient role in post-laser TAPS occurred less frequently than previously thought.²² From a total of 164 post-laser TAPS cases, 55% changed donor-recipient role when post-laser TAPS developed.

Middle cerebral artery peak systolic velocity (MCA-PSV) Doppler measurements

The antenatal diagnosis of TAPS is based on discordant fetal MCA-PSV Doppler measurements, with an increased velocity for the TAPS donor, suggestive of anemia, combined with a decreased velocity in the recipient, suggestive of polycythemia. MCA-PSV criteria for TAPS have been changed over the years. First, MCA-PSV >1.5 multiples of the median (MoM) in the donor combined with MCA-PSV <0.8 MoM in the recipient were proposed for the antenatal detection of the condition.⁵ Thereafter, a more conservative approach was adopted with regard to the cut-off level for the recipient, and <1.0 MoM was introduced to detect fetal polycythemia in TAPS.²⁵ Three recent cohort studies show that an inter-twin difference (or delta) MCA-PSV >0.5 MoM might be more sensitive to detect TAPS than the use of strict cut-off levels, and the classification system for TAPS was subsequently updated with a delta MCA-PSV >0.5 MoM for stage 1 and >0.7 MoM for stage 2 (Table 1).^{26–28} In a recent Delphi investigation a group of maternal-fetal medicine specialists and neonatologists agreed on the use of ≥1.5 MoM for the donor a MCA-PSV ≤0.8 MoM for the recipient or a delta MCA-PSV >1.0 MoM to identify TAPS.²⁹ However, during the Delphi investigation, the results of the recent cohort studies investigating a delta MCA-PSV >0.5 MoM were not available to all participants. What is the best diagnostic criterion remains a subject of debate. Due to the low incidence of TAPS, studies investigating the diagnostic accuracy of MCA-PSV criteria are based on small numbers and generally retrospective, thereby limiting generalizabil-

Table 1 Antenatal classification system for TAPS.	
TAPS stage	Findings at Doppler ultrasound examination
Stage 1	A delta MCA-PSV > 0.5 MoM Without other signs of fetal compromise*
Stage 2	A delta MCA-PSV > 0.7 MoM Without other signs of fetal compromise*
Stage 3	As stage 1 or 2, with cardiac compromise of the donor, defined critically abnormal flow
Stage 4	Hydrops in the donor
Stage 5	Intra-uterine demise of one or both fetuses preceded by TAPS

MCA-PSV: Middle cerebral artery peak systolic velocity; MoM: Multiples of the median; TAPS: Twin anemia polycythemia sequence.
* Critically abnormal Doppler is defined as absent or reversed end-diastolic flow in the umbilical artery, pulsatile flow in the umbilical vein, increased pulsatility index or reversed flow in the ductus venosus.

ity and reliability of the proposed diagnostic criteria. Large prospective studies investigating MCA-PSV Doppler in the general monochorionic-twin population are needed to investigate which diagnostic criteria are most accurate to identify TAPS.

Additional ultrasound findings

Although MCA-PSV discordancy is the cornerstone of the diagnosis of TAPS, additional ultrasound markers associated with anemia and polycythemia have also been reported. The placenta in TAPS can appear dichotomous on sonographic examination with a hyperechogenic (enlarged) placental share for the donor and a hypoechogenic (flattened) placental share for the recipient (Fig. 5A).³⁰ Moreover, donors can present with cardiomegaly as a sign of cardiac remodeling to the chronic anemic environment.³¹ Lastly, a so-called “starry-sky” liver has been detected in recipients, an observation that is based on the hyperechogenic congested portal venules and diminished liver parenchyma, thereby mimicking a starry sky (Fig. 5B).³² A recent study shows that placental dichotomy is seen in 44% of TAPS twins, that 70% of

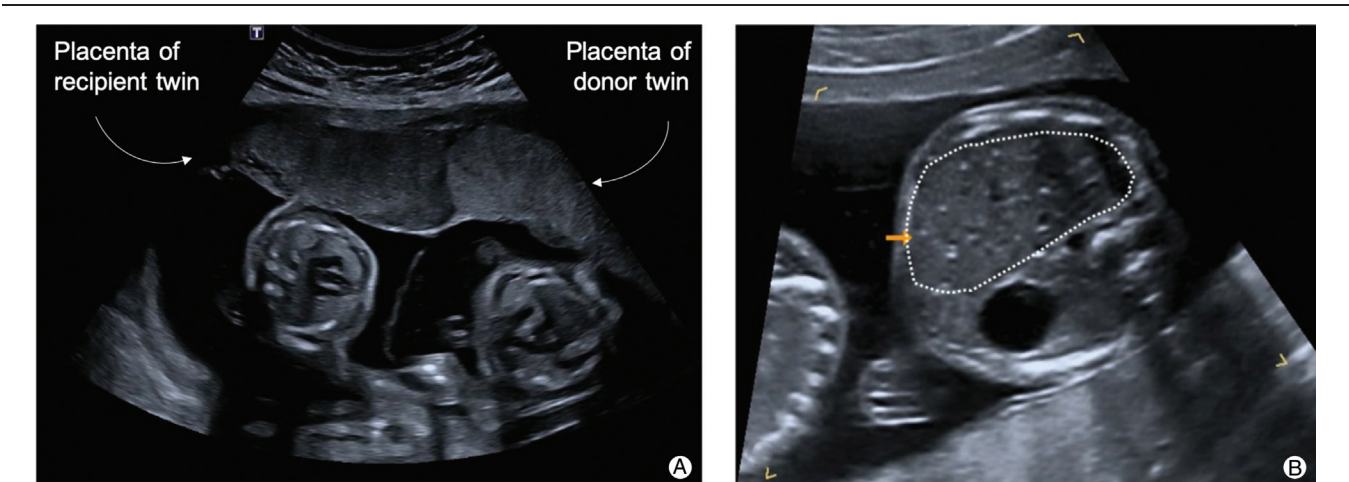


Figure 5. Sonographic image. A Sonographic image of placental dichotomy, with hyperechogenic placental share for the TAPS recipient with an hyperechogenic placental share for the TAPS donor. B Starry-sky liver in a TAPS recipient. TAPS: Twin anemia polycythemia sequence.

donors present with cardiomegaly, and that a starry-sky liver is observed in 66% of recipients.³¹ The vast majority (86%) of TAPS twins presented with at least one of these ultrasound markers. Whether the presence of these markers might indicate a poorer prognosis is unclear and is subject of future research.

Antenatal management

Treatment options for TAPS include expectant management, preterm delivery, intrauterine blood transfusion (IUT) in the donor with or without a partial exchange transfusion (PET) in the recipient, fetoscopic laser coagulation of the placental anastomoses and selective feticide.

Expectant management

Expectant management consists of close monitoring with MCA-PSV Doppler measurements. With expectant management, the pregnancy will not be exposed to iatrogenic risks of intrauterine treatment, while allowing the condition to resolve spontaneously. Spontaneous resolution has been reported before, and might occur after thrombosis of the responsible AV anastomosis, or due to reequilibration of blood flow through the small AV/VA (or in rare cases AA or VV) anastomoses.³³ Recently, data of 370 TAPS twins collected in an international registry (TAPS Registry) were published. In this large international cohort, spontaneous resolution occurred in 16% of TAPS twins managed expectantly.³⁴

Preterm delivery

In some cases of TAPS, it is more preferable to deliver the twins and treat anemia and polycythemia in the neonatal intensive care unit than continuing the pregnancy and extending exposure to chronic anemia and polycythemia. A preterm delivery is of course only feasible after viability is achieved, and preferably takes place after administration of steroids to promote fetal lung maturation, and magnesium sulfate for brain protection. TAPS twins treated with preterm delivery are generally diagnosed at a later gestational age and with a milder form of TAPS (mostly stage 1).³⁴

IUT (with or without PET)

In case of severe anemia in the donor, an IUT can be considered for symptomatic treatment. IUT can be performed either intravascularly into the umbilical cord insertion or in the intrahepatic portion of the umbilical vein, or intraperitoneally into the abdominal cavity. The techniques can also be combined. An (additional) intraperitoneal IUT might have benefits, as it facilitates a slower absorption of blood cells into the circulation of the anemic fetus. A possible side effect of IUT is further deterioration of the polycythemia-hyperviscosity syndrome in the TAPS recipient, which might result in skin necrosis or limb ischemia.⁵ Therefore, in cases with signs of severe fetal polycythemia in the recipient, an intrauterine PET can be considered. With a PET, the recipients' blood is partially replaced with saline, lowering the

hematocrit and thus its viscosity. Although the added value of PET has been supported by a computational model and several case reports, recent results show that a simultaneous PET was only performed in 21% of the cases treated with IUT.^{34–37} IUT ($\pm$ PET) is not a definitive treatment and only a temporary solution, and therefore reintervention might be required. Time between interventions is reported to be approximately two weeks, but varies between one to three weeks depending on the progressive-ness of TAPS.³⁷ In TAPS, IUT ($\pm$ PET) is mostly performed after viable gestation and the majority of cases receives only one intervention, followed by preterm delivery. However, reintervention up to four to six times has also been described.

As TAPS twins are identical and have the exact same blood type, it might be of additional value to transfuse the anemic twin with the recipient's whole blood as donor source instead of foreign blood. There is one report in the literature of a postnatally diagnosed TAPS case, in which the donor twin was successfully transfused with blood of the recipient that was obtained during a postnatal PET.³⁸ Whether this technique can also be safely used during an intrauterine procedure, and whether this leads to improved outcome is unclear and requires further investigation.

Laser surgery

The only causal treatment for TAPS, apart from delivery, is fetoscopic laser surgery of the vascular anastomoses at the placental surface. Laser surgery has shown to drastically decrease mortality and morbidity in TTTS,³⁹ however, in TAPS, the procedure is technically more challenging, due to the absence of TOPS, the enlarged donor placental share and size of the anastomoses, resulting in reduced accessibility and visibility of the vascular equator. These features might be especially limiting in TAPS cases with an anterior placenta. TOPS can be artificially created with amniodrainage of one sac and amnioinfusion in the other sac, but this requires more needle insertions and might increase the risk of preterm premature rupture of the membranes (PPROM). Confirming technical limitations, recurrence rate of TAPS after laser is 15%, which is higher than the recurrence rate of TTTS (1%), or the rate of post-laser TAPS after laser for TTTS (3%).^{34,40} Residual anastomoses are found in 19% of the color-dye injected TAPS placentas that were treated with laser surgery.³⁴ This rate is comparable with the residual anastomosis rate in TTTS (19%).⁶ However, in contrast to TTTS, residual anastomoses after laser for TAPS always result in recurrence of the disease.³⁸ To increase likelihood of coagulation of all minuscule anastomoses, even the ones that cannot be visualized, the Solomon technique might be of added value when performing a laser procedure in TAPS. The rate of PPRM in laser for TAPS is 37% and comparable with the PPRM rate in TTTS cases that have been treated with laser.^{34,40}

Selective feticide

Selective feticide can be an option in severe early-onset TAPS, or on request of the parents and is aimed at sacrificing one fetus to increase the chances of healthy survival in the co-twin. In TAPS, it is commonly (87%) the

donor twin who is sacrificed.³⁴ Selective feticide does not guarantee a complication-free survival for the co-twin, as perinatal mortality and severe neonatal morbidity occur in 7%–25% of co-twins, respectively.

Best treatment option

Currently, there is no consensus on the best treatment for TAPS.^{34,41} Results of the TAPS Registry show that treatment choices differ considerably within and amongst fetal therapy centers; some centers only perform laser surgery and selective feticide, others refrain from any in-utero intervention and treat their TAPS cases expectantly or with preterm delivery.³⁴ When outcome is compared between expectant management, preterm delivery, IUT ($\pm$ PET), laser surgery and selective feticide for 370 TAPS cases, there is no difference in perinatal mortality between treatment groups.³⁴ This finding confirms results from previous smaller studies.^{42,43} Severe neonatal morbidity was significantly higher in cases treated with IUT ($\pm$ PET) or with preterm delivery.³⁴ Pregnancy was most successfully prolonged in twins that were managed expectantly, treated with laser surgery or with selective feticide. As treatment groups were not comparable at baseline and differed considerably in terms of type of TAPS, gestational age at diagnosis, and antenatal TAPS stage, it is likely that outcome is heavily biased. 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. Recently, the TAPS trial (NL6879), an international multicenter open-label RCT comparing laser surgery to standard care (expectant management, IUT ($\pm$ PET), preterm delivery) has started recruiting patients.⁴⁴ From the 44 TAPS pregnancies that are needed for the study, 7 have been randomized since April 2019.

Prevention

In contrast to the spontaneous form of TAPS, post-laser TAPS is a complication after surgery for TTTS, and can, therefore, be prevented. In the first years of fetoscopic laser for TTTS, all vessels crossing the membranous equator were coagulated, including vessels that were not anastomoses. The technique was then refined by introduction of the Selective technique, in which only vessels that were

actual anastomoses were coagulated.⁴⁵ However, this sometimes resulted in the development of post-laser TAPS as tiny anastomoses could be missed.⁴⁶ The Solomon technique, an alternative approach aimed at coagulating the entire vascular equator, from one placental margin to the other, without coagulating vessels that were not anastomoses (but including the anastomoses that could not be visualized), was shown to reduce the incidence of residual anastomoses and post-laser TAPS.^{6,40} After implementation of this new technique in our center, the incidence of residual anastomoses has drastically dropped.⁴⁵ We therefore strongly recommend to perform the Solomon technique during laser procedure for TTTS to prevent TAPS.

Postnatal diagnosis

As approximately 40%–63% of the diagnosis TAPS is missed antenatally but only diagnosed after birth, postnatal diagnostic criteria for TAPS have also been proposed.^{10,25} The first criterion for TAPS is an inter-twin hemoglobin difference >8 g/dL.⁴⁷ However, TAPS is not the only condition that presents with discordant hemoglobin levels at birth. Acute peripartum TTTS, a rare form of the well-known TTTS that is believed to develop during labor, presents with a large hemoglobin discrepancy as well.⁴⁸ As the two conditions require a different therapeutic neonatal approach, distinction at birth is crucial. Donors with acute peripartum TTTS suffer from acute anemia and hypovolemia and may thus need an acute blood transfusion and fluid resuscitation in the first hours after birth. In contrast, TAPS donor would benefit from a more conservative therapeutic approach, with slower blood transfusion or, in case of sufficient erythropoiesis, even no blood transfusion at all. To differentiate between TAPS and acute peripartum TTTS, two additional criteria have been proposed (Table 2). The first is a reticulocyte count ratio ($\%$) >1.7 .⁴⁷ In TAPS, there is a high reticulocyte count ($\%$) in the donor twin, as a result of increased erythropoiesis due to chronic anemia. In acute peripartum TTTS, the rapid fetofetal blood flow has not allowed the donor to adapt, and, therefore, reticulocyte values will be normal. The second criterion for the postnatal diagnosis of TAPS is the presence of only minuscule placental anastomoses (diameter <1 mm), detected through color dye injection.² The pathogenesis of acute peripartum TTTS is based on a large AA or VV

Table 2

Postnatal criteria to distinguish between TAPS and peripartum TTTS based on hemoglobin and reticulocyte measures, and color dye injection of the placenta.

Key criteria	TAPS	Acute peripartum TTTS
Inter-twin hemoglobin difference	>8 g/dL	>8 g/dL
Reticulocyte count ratio ($\%$)	>1.7	<1.7
Anastomoses	Only a few minuscule anastomoses (diameter <1.0 mm)	Numerous large anastomoses (diameter >1.0 mm), with at least one AA or VV anastomosis
Placental observation	Additional placental observation that can support either of the diagnoses	
Maternal side of the placenta	Striking color difference between the pale anemic share of the donor and the plethoric polycythemic share of the recipient	No color difference

AA: Arterio-arterial; TAPS: Twin anemia polycythemia sequence; TTTS: Twin-twin transfusion syndrome; VV: Veno-venous.

anastomoses, allowing a large volume of blood to flow acutely and directly from donor to recipient.⁴⁸ TAPS can also simply be distinguished from acute peripartum TTTS by observation of the maternal side of the placenta. In TAPS, the placenta will show a striking color difference between the pale share of the donor twin and the plethoric share of the recipient twin (color difference ratio >1.5, measured with ImageJ) (Fig. 3A).⁴⁹ In acute peripartum TTTS, this difference is not observed.⁵⁰ To indicate the severity of TAPS postnatally, a postnatal classification system, based on magnitude of the inter-twin hemoglobin difference, has been published (Table 3).²⁵

Short- and long-term outcome

Perinatal mortality

Spontaneous perinatal mortality occurs in 9% of spontaneous TAPS twins and in 18% of post-laser TAPS twins, with donor twins having a 4-fold increased risk.^{7,8} In spontaneous TAPS, perinatal mortality occurs in 12% of donors, compared to 5% of recipients.⁸ In post-laser TAPS the difference is even more striking: more than a quarter (26%) of TAPS donors dies, much more than the 10% of TAPS recipients.⁷ This difference in mortality between donor and recipient is primarily seen antenatally.^{7,8} After birth, spontaneous TAPS twins show comparable risks for neonatal mortality. In post-laser TAPS, TAPS donor twins are more at risk for neonatal mortality compared to their recipient co-twins. Aside from donor-status, risk factors for perinatal mortality are high antenatal TAPS stage (risk increases with incrementing stage) and low gestational age at birth.

Neonatal morbidity

Neonatal outcome in TAPS may vary between isolated large inter-twin hemoglobin differences to severe neonatal morbidity, including severe cerebral injury.^{37,51} Hematological complications are frequently seen in TAPS, requiring one or multiple blood transfusions in the donor twin and a PET in the recipient twin.⁴⁷ Aside from a large hemoglobin discordancy, other hematological values in TAPS may also be abnormal. Donor twins may demonstrate low levels of albumin and total protein, which might partly explain the impaired fetal growth.⁵² Furthermore, donors are more frequently diagnosed with leukopenia at birth than the recipient co-twin and show an increased risk for early-onset neonatal sepsis.⁵³ These low albumin, protein and leukocyte values indicate that not only erythrocytes are transported through the minuscule anastomoses in TAPS, but also that other hematological

substances may be unequally distributed between the two fetuses. Alternatively, chronic anemia and erythropoiesis may result in a decreased production due to bone marrow suppression. Recipient twins may have thrombocytopenia at birth, likely also due to impaired bone marrow production secondary to tissue hypoxia and impaired spleen perfusion.^{47,54}

TAPS donors may experience short-term renal dysfunction probably resulting from chronic renal hypoperfusion.⁵⁵ TAPS recipients are at risk of developing polycythemia-hyperviscosity syndrome, which can lead to necrosis of the skin and (multiple) limb ischemia.⁵ Although this has been described in a few case reports, limb ischemia was not reported in a cohort of 413 TAPS cases in the TAPS Registry, and should therefore be considered a rare complication in TAPS.^{8,22} Chronic anemia or polycythemia can also result in severe cerebral injury, which is reported to occur in 4% of spontaneous TAPS twins and in 10% of post-laser TAPS twins and, with similar rates for donors and recipients for both types of TAPS.^{8,22} Overall, severe neonatal morbidity occurs 32%–39% of TAPS twins, with no differences between donors and recipients. Independent risk factors for neonatal morbidity are low gestational age at birth, and antenatal TAPS stage 4, with fetal hydrops in the TAPS donor.

Long-term outcome

Due to the low incidence of the condition, large long-term outcome studies in TAPS are scarce and data is mostly based on uncontrolled cohort studies. In post-laser TAPS, severe neurodevelopmental impairment (NDI) was observed in 9% and was comparable to the rate of impairment in TTTS twins treated with laser surgery.²⁴ The rate of NDI was comparable for post-laser-TAPS donors and recipients. Risk factors for NDI in post-laser TAPS survivors were low gestational age at birth, and treatment with IUT ($\pm$ PET).

In spontaneous TAPS, long-term outcome was investigated in two studies. A small study from South Korea reported a comparable incidence of cerebral palsy at two years of age between TAPS survivors (0/17, 0%) and a control group of uncomplicated monochorionic twins (1/109, 0.9%). Other long-term outcome parameters were not investigated. Notably, the diagnosis of TAPS in this group was only based on an inter-twin hemoglobin difference >8.0 g/dL, so a mix-up with acute peripartum TTTS cases cannot be precluded. A larger study from our group was published recently. In a cohort of 74 spontaneous TAPS survivors, severe NDI was detected in 9%, and was higher in donors (18%) than in recipient (3%).⁵⁶ Overall, donors showed higher rates of mild cognitive impairment (35% *vs.* 18%), and lower rates of NDI-free survival (45% *vs.* 80%) than recipients. Additionally, a surprisingly high rate of bilateral deafness (15%) was observed in TAPS donors, and in 0% of recipients. Deafness was in all donors based on auditory neuropathy spectrum disorder. The exact cause for the high rate of deafness in donor twins is not entirely clear, but it is not observed in TTTS twins or children that suffered from chronic fetal anemia based on erythrocyte alloimmunization.^{57,58} Possibly, chronic hypoxia in TAPS

Table 3
Postnatal classification system for TAPS.

TAPS stage	Inter-twin hemoglobin difference (g/dL)
Stage 1	>8.0–11.0
Stage 2	>11.0–14.0
Stage 3	>14.0–17.0
Stage 4	>17.0–20.0
Stage 5	>20.0

TAPS: Twin anemia polycythemia sequence.

donors might damage not only the developing brain but also the auditory nerve system. Notably, histologic examination of TAPS placentas showed a decreased level of oxygenation in the placental share of the donor twin.⁵⁹ Aside from donor status NDI was also strongly associated with a low gestational age at birth, once again stressing the profound impact of prematurity on lifelong health.⁵⁶

Conclusions

During the last 15 years, our knowledge on TAPS has expanded greatly. TAPS has now become a distinct entity in monochorionic twinning, with its own characteristic pathogenesis, time of onset, diagnostic criteria, classification systems and short- and long-term outcome. To further improve care for TAPS, the future holds some major challenges. One of the biggest challenges will be the implementation and uniformization of routine MCA-PSV measurements into the biweekly ultrasound exams for monochorionic twins to timely reach the diagnosis. Moreover, every center caring for TAPS pregnancies should perform a complete postnatal diagnostic work-up including hemoglobin, reticulocyte count and placental color dye injection, to be able to adequately diagnose TAPS and distinguish the condition from other monochorionic twin problems such as acute peripartum TTTS, and check whether laser therapy was successful. Moreover, a lot can be learned if all centers managing TAPS twins would register short- and long-term outcomes, to enable evaluation of the effects of their treatment choice. As the consequences of TAPS are not limited to the neonatal phase but also manifest later in life, routine long-term neurodevelopmental follow-up in this population is of paramount importance. Lastly, investigation of the best treatment option for TAPS pregnancies is vital to prevent severe adverse outcome. Results of the TAPS Trial, an international randomized controlled trial are eagerly awaited.

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Conflicts of Interest

None.

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