

Twin Anemia-Polycythemia Sequence: What do we know about it?

Sequência Anemia-Policitemia em Gêmeos: O que sabemos sobre isto?

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Abstract

Twin anemia-polycythemia sequence (TAPS) is a pathology of monochorionic twin pregnancy that results from slow unequal blood distribution that causes the discrepancy of hemoglobin values between the anemic fetus (the donor) and the polycythemic one (the recipient). Unlike twin-to-twin transfusion syndrome (TTTS), twin oligohydramnios-polyhydramnios sequence (TOPS) is not present in TAPS. TAPS might occur spontaneously or after laser treatment for TTTS. Prenatal diagnosis relies on twin discrepant values of middle-cerebral-artery (MCA) peak-systolic-velocity (PSV). Management options include laser surgery, expectant management, intrauterine transfusions, and delivery. This review aims to summarize the research made on the last 7 years on TAPS.

Keywords: Twin; Anemia; Polycythemia; Placenta, Laser.

INTRODUCTION

On monochorionic twin pregnancy a single placenta is shared and vascular anastomoses on the fetal surface connect the blood circulation of both twins.¹ One of the unique pathologies of monochorionic twins is twin-to-twin transfusion syndrome (TTTS), where an unequal distribution of blood between the two fetuses is significant enough for twin oligohydramnios-polyhydramnios sequence (TOPS) to happen.^{2,3} Another recently described pathology, twin anemia-polycythemia sequence (TAPS), also results from unequal blood distribution caused by slow blood transfusion between them.⁴ Occurring spontaneously or after laser treatment for TTTS, TAPS brings us clinical challenges on diagnosis and management. This review aims to summarize the research made on the last 7 years on TAPS, raising awareness and enlightenment on this under-recognized pathology.

MATERIAL AND METHODS

A search in Pubmed using the terms “Twin anemia-polycythemia” restricted to the last five years was conducted in spring summer 2018 (concerning articles between august 2013 and august 2018) and newly updated in march 2020 for a total span of seven years of literature, with a total of 135 articles found within the languages spoken by the authors (Portuguese, English, Spanish, German or French). 6 articles were excluded because they did not contain specific information on TAPS, thus remaining 129 articles. After careful reading, sections of 58 articles were selected to be quoted in this narrative literature review.

THE MONOCHORIONIC PLACENTA

Almost all the monochorionic (MC) twins have vascular anastomoses between the two fetal circulations^{5,6}, while dichorionic twins share no anastomosis.⁶ There are three types of anastomosis – artery-to-vein (AV), artery-to-artery (AA), and, less commonly⁶, vein-to-vein (VV).

AV anastomoses are by definition unidirectional, with the blood flowing, deeply⁷, from the artery of one

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twin to the vein of the other.^{1,8} Almost all of monochorionic placentas have multiple AV anastomoses.⁹

AA and VV anastomoses are superficial⁸ and the blood flow can be bidirectional⁵. AA anastomoses are considered protective against the development of TTTS and TAPS as they counterbalance the flow of the unidirectional AV anastomoses, but the presence of an AA anastomosis does not exclude the possibility of TAPS or TTTS.⁹ A disproportion in the ratio¹⁰ or diameter⁹ between the AV and the AA anastomoses is thought to be a key component in the hemodynamic imbalance that ultimately causes these pathologies. The role of VV anastomoses is unclear.⁵

TWIN-TO-TWIN TRANSFUSION SYNDROME (TTTS)

TTTS is a syndrome that happens in about 10-15%^{3,10} of monochorionic pregnancies.¹ The diagnosis of TTTS is based on the presence of twin oligohydramnios-polyhydramnios sequence (TOPS). To diagnose TTTS, two ultrasound criteria are required: the pregnancy is diagnosed as monochorionic twin pregnancy (ideally with a scan carried out in the first trimester showing a T-sign, a monochorionic characteristic sign of the 2 opposing amnions at the base of the separating membrane)^{2,11}, and a combination of oligohydramnios in one twin's amniotic cavity (the "donor") with polyhydramnios in the other twin's amniotic cavity (the "recipient") – the so called TOPS.^{1,11} Oligohydramnios is defined as a deepest vertical pocket (DVP) <2 cm in the donor twin. Polyhydramnios is defined as a DVP of >8 cm, although in Europe a cut-off of DVP of >10 cm is traditionally used after 20 weeks.^{1,11}

TWIN ANEMIA-POLYCYTHEMIA SEQUENCE (TAPS)

Twin anemia-polycythemia sequence (TAPS) was only first described, as its post-laser form, in 2006, while the spontaneous form of TAPS was first described in 2007.⁴ Its major feature is the discrepancy of the hemoglobin values between the anemic fetus (the donor) and the polycythemic one (the recipient) caused by slow blood transfusion – estimated to be around 5 ml to 15 ml per day⁴ – due to AV anastomoses not counterbalanced by a large enough AA anastomosis.

Spontaneous TAPS has been said to occur in bet-

ween 3-5% of monochorionic diamniotic pregnancies^{4,11,12}, though one single-center study recently reported a smaller incidence of 1,6%.¹³ It has also been reported twice in very unusual dichorionic pregnancies.^{14,15}

However, TAPS is more frequent after laser-treated TTTS, with an incidence of 2-16%^{4,16}. Even with optimal surgical technique, some patent intertwin-anastomoses might remain present after laser ablation.⁸ Its reported frequency varies widely⁸; most of the residual anastomoses are small and peripherally located.^{8,9,17} It is important to notice that not all residual anastomoses after TTTS laser surgery cause pathology.¹⁸ This post-laser TAPS usually occurs acutely within one or two weeks after the surgery³, but much later cases have been reported.¹⁹

DIAGNOSIS

Prenatal

Prenatal recognition of TAPS is essential for the management of these pregnancies. The absence of TOPS is an essential element in the diagnosis of TAPS, as TOPS is only an hallmark for TTTS.^{4,20} Besides that, prenatal diagnosis is based on the Doppler ultrasound middle cerebral artery-peak systolic velocity (MCA-PSV).⁴ During the past decade, different MCA-PSV values for the diagnosis of TAPS have been proposed.⁴ An increased MCA-PSV has been well established for the diagnosis of fetal anemia, with a MCA-PSV >1.5 multiples of the median (MoM) being reported as very sensitive²¹, but the evidence supporting a decrease of MCA-PSV on fetal polycythemia, however, is much more scarce.²¹

A study²² concluded that, although there was a correlation between MCA-PSV and anemia, MCA-PSV was similar among polycythemic and normal fetuses and that even severely polycythemic fetuses might have a normal MCA-PSV, and suggested that the difference in intertwin MCA-PSV (delta MCA-PSV) might serve as a reliable tool for a prenatal diagnosis of TAPS, as it was positively correlated with the intertwin hematocrit difference. Another recent studies^{23,24}, corroborated these findings, helping establishing delta MCA-PSV >0.5 MoM as having higher diagnostic accuracy for TAPS.

Another proposed clue for the prenatal suspicion and diagnosis of TAPS is placental dichotomy, it is, one part of the placenta, usually the one from the anemic twin, being reported as hyperechogenic and the other portion as hypoechogenic.^{25,26}

Postnatal

The postnatal criteria is mainly based on hematological criteria at birth.²⁷ Currently an inter-twin hemoglobin difference >8 g/dL is the base of the postnatal diagnosis.^{11,12,27} As a large Hb difference (>8 g/dL) at birth is also detected in case of acute peripartum TTTS at least one of two additional criteria must be fulfilled:^{4,27} An inter-twin reticulocyte count ratio (measured by dividing the reticulocyte count of the donor by the reticulocyte count of the recipient).⁴ over 1.7 is pathognomonic for TAPS (as a result of increased erythropoiesis in the donor due to chronic anemia).⁴; the other established postnatal criterion is the presence of small residual anastomoses, of less than 1 mm of diameter⁴ (as acute peripartum TTTS, in contrast to TAPS, is thought to be based on large placental AA or VV, allowing a large amount of blood to flow during the birth).⁴

The common find of pale parenchyma on the maternal side of the placenta portion of the anemic twin and dark red parenchyma on the polycythemic twin portion might become an additional criterion for postnatal diagnosis in the future.^{28,29}

TAPS VS TTTS

TTTS and TAPS have been described as mutually exclusive diagnoses³⁰, as a diagnosis of TTTS is given to any monochorionic pregnancy with TOPS¹¹, and TAPS diagnosis implies the absence of TOPS.^{4,20}

However, this point of view has not been unanimous in our literature review, with some studies mentioning “TAPS combined with TTTS”³¹ or “TTTS cases with secondary TAPS”¹⁰, “coexisting TAPS”³² or “presence of TAPS with TTTS”³³. On the other hand, it is clear that there are some cases in the cross between TAPS and TTTS, and that there is a continuum between these conditions²⁰. A study aimed to survey cases of TTTS with superimposed twin anemia-polycythemia (AP)³⁰ and found that 2.4% (9/369) of TTTS patients had TTTS+AP (based on discordance MCA-PSV values). Such a small fraction of TTTS patients having MCA-PSV suggestive of anemia/polycythemia supports the hypothesis that the mechanisms responsible for the amniotic fluid discordances seen in TTTS may be different than the mechanisms responsible for the large fetal hemoglobin differences seen in TAPS.³⁰

It is interesting to note that amniotic fluid discordance (AFD) >3 cm (and that does not fulfil the TTTS criteria) has been shown to increase the risk for TAPS.³⁴

TAPS VS ACUTE TTTS

Acute peripartum TTTS is a rare form of twin-to-twin transfusion – estimated to occur in about 1.2%¹² to 2.5% of all MC twins³⁵ – thought to be due to acute shifts of blood between the two fetuses during delivery.²⁷

The physiopathology is not clear and based mainly on case reports and small series, but it is thought that acute peripartum TTTS may be due to acute shifts of relatively large volumes of blood from one twin to the other due to blood pressure differences following uterine contractions or changes in fetal positions,^{27,35} which is likely only possible through large AA or VV superficial anastomoses²⁷

To reach the diagnosis of acute peripartum TTTS in a twin pair with large hemoglobin difference at birth, the presence of chronic TTTS and TAPS must be ruled out.³⁵ A key factor is that in acute TTTS, unlike in TAPS, the reticulocyte counts are not elevated.²⁷ Colour difference between the two portions of the placenta also seems to be notably stronger in TAPS.³⁶ The distinction between acute peripartum TTTS and TAPS is important as acute TTTS donors suffer from acute blood loss (resulting in severe anemia and hypovolemic shock)^{27,36} and may therefore need acute blood transfusions (and volume expanders) within the first few hours after birth^{27,36}, while TAPS donors (as TAPS is a chronic process) would benefit from a more conservative therapeutic approach with slower blood transfusion (or even no blood transfusion at all) to prevent hemodynamic complications.³⁶ Therefore, a quick distinction between acute peripartum TTTS and TAPS within one hour of birth could be helpful.³⁶

The differences between these three entities are summed up on Table I.

STAGING OF TTTS AND TAPS

TTTS has established staging, the so-called “Quintero Stages”, which divides the severity of TTTS into five stages.⁵ The stages are described on Table II.

Staging the progression of TAPS is important for better research and clinical applicability concerning decision (and means) of treatments.

A prenatal and postnatal classification system of TAPS has been proposed⁴ and thus updated due to new prenatal diagnostic criteria based on delta MCA-PSV.²³ In these new prenatal classifications, stage 1

TABLE I. DIFFERENCES BETWEEN TTTS, TAPS AND ACUTE TTTS. Adapted from “Hematological disorders at birth in complicated monochorionic twins” by L.Verbeek *et al.*

	Pathogenesis	Diagnosis criteria	Hematological disorders at birth
TTTS	Chronic inter-twin transfusion through anastomoses, usually during the second trimester of pregnancy	Antenatal: TOPS on ultrasound	Inter-twin Hb discordance might occur
TAPS	Chronic inter-twin transfusion through small anastomoses	Antenatal: discordant MCA-PSV values on Doppler ultrasound or postnatal; inter-twin discordance + large inter-twin reticulocyte count ratio or small AV-anastomoses on placental examination)	Large inter-twin Hb difference (>8 g/dl) Reticulocytosis in the donor and inter-twin reticulocyte count ratio >1.7 Anemia in the donor Polycythemia and increased risk of thrombocytopenia in the recipient
Acute TTTS	Acute inter-twin transfusion through anastomoses during delivery	Postnatal: inter-twin Hb discordance without inter-twin difference in reticulocyte count	Large inter-twin Hb difference >8g/dl No reticulocytosis in donor Reticulocyte count ratio <1.7

Hb – hemoglobin; TAPS – twin anemia-polycythemia sequence; TOPS – twin oligo-polyhydramnios sequence; TTTS – twin-to-twin transfusion syndrome.

consists on a delta MCA-PSV >0.5 MoM, without further signs of fetal compromise. Stage 2 implies a delta MCA-PSV >0.7 MoM (new criteria), without further signs of fetal compromise. Stage 3 consists on the criteria from stage 1 or 2 with cardiac compromise of the donor, shown by critically abnormal Doppler: absent or reverse end-diastolic velocity in the umbilical artery, reverse flow in the ductus venosus, pulsatile flow in the umbilical vein or increased pulsatility index. Stage 4 is defined by the presence of hydrops on a TAPS donor. Stage 5 implies the demise of one or both fetuses, in a pregnancy previously known to be affected by TAPS. The postnatal staging of TAPS is based on the difference of hemoglobin values between the two fetuses (assuming that another criterion, such as the reticulocyte count ratio, is met for the diagnosis of TAPS to be made): an inter-twin hemoglobin difference >8 g/dL is the inferior limit for stage 1, >11 g/dL for stage 2, >14 g/dl for stage 3, 17 g/dl for stage 4 and 20 g/dl for stage 5. Whether these classifications offer an additional value to adequately stage and treat TAPS requires further investigation.⁴

Table II summarizes staging of TTTS using the Quintero Stages, and prenatal (old and new criteria) and postnatal staging of TAPS.

COMPLICATIONS

Perinatal outcomes of TAPS vary from mild hematological complications to severe cerebral injury and perinatal death.¹²

Cardiac decompensation of the donor, hydrops of donor and demise of any of the twins are complications stated in the staging classification of TAPS.⁴

Neonates with TAPS have mainly short-term hematological complications.^{27,37} A blood transfusion is needed for most donors.²⁷ Recipients of TAPS may be severely polycythemic and require partial exchange transfusion (PET) often.²⁷

Thrombocytopenia is also common in TAPS.²⁷ Postnatal short-term renal dysfunction was also described³⁸, and it was found to be more common in donors.

A study³⁹ concerning fetal brain imaging following laser surgery for TTTS found out that the development of post-laser TAPS (as well as recurrence of TTTS) was a risk factor for prenatal brain damage. There is also a case report of a prenatal brain lesion in a spontaneous TAPS recipient, thought to be caused by hyperviscosity/polycythemia⁴⁰. Bilateral deafness and spastic paralysis have also been reported.⁴¹ The recipient of TAPS seems to be at greater risk for brain damage.⁴²

TABLE II. STAGING FROM TTTS AND TAPS (PRENATAL – BOTH OLD AND NEW CRITERIA – AND POSTNATAL)
Adapted from “Twin–twin transfusion syndrome – What we have learned from clinical trials” by F.Djaafari *et al*, “Improved antenatal prediction of twin anemia-polycythemia sequence by *delta* middle cerebral artery peak systolic velocity: a new antenatal classification system” by L.Tollenaar *et al*, and “Twin Anemia Polycythemia Sequence: Current Views on Pathogenesis, Diagnostic Criteria, Perinatal Management, and Outcome.” by L.Tollenaar *et al*.

	Quintero Staging (TTTS)	Prenatal TAPS Staging (Old Criteria)	Prenatal TAPS Staging (New Criteria)	Postnatal TAPS Staging
Stage 1	Association of twin oligohydramnios and polyhydramnios (TOPS); donor's bladder remains visible	MCA-PSV donor >1.5 MoM and MCA-PSV recipient <1.0 MoM without signs of fetal compromise	Delta MCA-PSV > 0.5 MoM without signs of fetal compromise	Inter-twin Hb difference >8 g/dL
Stage 2	TOPS and absence of a visible bladder in the donor	MCA-PSV donor >1.7 MoM and MCAPSV recipient <0.8 MoM without signs for fetal compromise	Delta MCA-PSV > 0.7 MoM without signs of fetal compromise	Inter-twin Hb difference >11 g/dL
Stage 3	Critically abnormal Doppler in either of the twins with absent/reverse end-diastolic velocity in the umbilical artery, reverse flow in the ductus venosus, or pulsatile flow in the umbilical vein or umbilical vein increased pulsatility index	As stage 1 or 2, with cardiac compromise of the donor, defined by critically abnormal Doppler: absent/reverse end-diastolic velocity in the umbilical artery, reverse flow in the ductus venosus, pulsatile flow in the umbilical vein or umbilical vein increased pulsatility index	As stage 1 or 2, with cardiac compromise of the donor, defined by critically abnormal Doppler: absent/reverse end-diastolic velocity in the umbilical artery, reverse flow in the ductus venosus, pulsatile flow in the umbilical vein or umbilical vein increased pulsatility index	Inter-twin Hb difference >14 g/dL
Stage 4	Presence of hydrops in either twin	Presence of hydrops on donor	Presence of hydrops on donor	Inter-twin Hb difference >17 g/dL
Stage 5	Intra-uterine demise of one or both fetuses preceded by TTTS	Intra-uterine demise of one or both fetuses preceded by TAPS	Intra-uterine demise of one or both fetuses preceded by TAPS	Inter-twin Hb difference >20 g/dL

Hb – hemoglobin; MCA-PSV – middle cerebral artery peak systolic velocity; TAPS – twin anemia-polycythemia sequence; TOPS – oligohydramnios-polyhydramnios sequence; TTTS – twin-to-twin transfusion syndrome.

Prenatally acquired limb ischemia, including multiple limb ischemia, not explained by other factors has been reported in recipients of TAPS.⁴³

PRENATAL MANAGEMENT

There is no clear evidence on the optimal management of these pregnancies, and therefore it is suggested that management decisions should be made after careful individual analysis, including TAPS stage, gestational age,

the feasibility and availability of the different types of intra-uterine intervention.⁴

Laser surgery

Laser coagulation of the vascular anastomoses is the only curative treatment for TAPS.^{4,17} Moreover, laser therapy in TAPS can be technically more challenging than in TTTS^{17,44} because of the possible absence of polyhydramnios and of a ‘stuck twin’, and difficult visualization of the very small communicating anastomoses.²⁰ When considering laser therapy for TAPS, preo-

perative amnioinfusion is thus advisable⁴⁵. Laser surgery is also generally technically more difficult in anterior and centrally located placentas, due to limited access and visualization of the placental vascular bed^{10,46} and in obesity⁴⁶. Laser surgery is contraindicated with active labour, preterm premature rupture of membranes (PPROM), chorioamnion separation (CAS), active vaginal bleeding, or with subchorionic hematoma; short cervix and discordance for fetal malformations with TTTS are relative contraindications in certain centres.¹⁰

A study¹⁷ evaluated the effectiveness of laser treatment on antenatally detected TAPS cases, compared to treatment by intrauterine transfusion or expectant management, and found no severe postnatal hematological complications and more time between diagnosis and birth.¹⁷

The traditional technique for laser treatment is known as selective fetoscopic laser photocoagulation and consists of, during fetoscopy, tracing vessels from each fetus and visualizing where they end: vessels that leave the cord root as an artery (identified as so as the artery always crosses over the vein), disappear deeply into a cotyledon, and then exit returning to the same fetus as a vein are considered functional and not pathologic.⁴⁷ In contrast, a vessel that travels from one fetus, inserts into a cotyledon, and then appears to exit into the cord root of the other fetus is considered nonfunctional and pathologic, and are therefore photocoagulated.⁴⁷

Residual anastomoses after laser treatment are common.⁴⁸ Analysis of post-laser TAPS placentas typically show small diameter unidirectional AV anastomoses found within 2 cm of placental edge, and, due to the laser surgery, there are no remaining compensatory anastomoses that could alleviate the unbalanced blood transfer.⁴⁴

When performing the laser treatment it is thus also advisable to use the Solomon technique^{4,44}, developed to minimize these residual anastomoses⁴⁹ and therefore the incidence of recurrent/persistent TTTS or post-laser TAPS.⁴⁷ Solomon technique consists in, after closing all the visible anastomoses with the selective technique⁴⁷, coagulating a thin line of tissue at the placental surface from one edge of the placenta to the other^{47,48} to close tiny anastomoses that might had not been visualised during the procedure.^{48,49}

The Solomon trial reported less cases of TAPS and recurrent TTTS in the Solomon group compared to the control group, and it did not seem to be associated with an increase in any identifiable adverse effect or complications.⁴⁸ A systematic review⁵⁰ including the Solomon trial and two other retrospective studies^{49,51} concluded

that the Solomon technique is certainly equivalent to the standard selective technique, has some advantages over it, with no increase in other adverse events, and is thus recommendable. Another review study⁵² also supported the use of the Solomon technique.

It is important to state that, based on these results, the Solomon procedure does not guarantee that recurrence of TTTS or TAPS do not occur, and therefore careful follow-up evaluation with serial MCA-PSV measurements, as well as measurements of amniotic fluid volumes, still remains crucial.^{10,48,52}

Moreover, if there was any previous laser treatment (as in, by definition, all cases of post-laser TAPS), careful consideration should be made before attempting a new laser procedure: if the anastomoses were not visualized in the first laser treatment for TTTS, it is unlikely that they will be identified any better during a second procedure.⁴⁵ However, changing the access route may be helpful.⁴⁵

Complications after placental laser surgery are common, with PPRM being the most frequent; post-laser CAS is a major risk factor for its occurrence.¹⁰ Disruption of the amnion can result in pseudoamniotic constrictions on the distal extremities of one fetus, which is estimated to occur in 2% of post-laser pregnancies.¹⁰ When laser treatment is not possible, other management options include expectant management, intrauterine blood transfusion (IUT) in the donor, with or without in-utero partial exchange transfusion (iPET) in the recipient, fetoscopic laser surgery, induction of labour/termination of pregnancy, and selective feticide.⁴

Expectant management

Expectant management consists of close monitoring with ultrasound, including Doppler measurements of MCA-PSV. It can be considered in less severe cases of TAPS, such as stage 1-2.⁴ This is also a valuable treatment option in presentations after 30 weeks' gestation with a stable fetal condition.¹⁷

Only one spontaneous regression of twin anemia-polycythemia sequence presenting in the first trimester was reported⁵³. Some studies^{4,54} mention another case in 2008 of an apparent spontaneous resolution of TAPS, probably due to thrombosis of the residual AV-anastomosis. The odds of spontaneous recovery are therefore low.¹⁷

Intrauterine blood transfusion (IUT) with or without in-utero partial exchange transfusion (iPET)

Treatment with in-utero transfusions can be performed

in the donor either intravascularly (in the umbilical vein of the anemic twin) or intraperitoneally.^{4,55} Intraperitoneal IUT is generally preferred, since it may allow slower absorption of red blood cells into the fetal circulation, preventing rapid loss of transfused blood in the circulation of the recipient twin.^{4,44,46} This is especially important as a potential side effect of IUT treatment is worsening of the polycythemia hyperviscosity syndrome in the recipient.^{4,56}

To reduce the risk of increasing polycythemia hyperviscosity, combining an IUT in the donor and iPET in the recipient can be useful.⁴ iPET consists of, after taking a sample for the determination of hematocrit, taking some fetal blood from the umbilical vein of the recipient twin and then replace with 0.9% NaCl.⁵⁵ iPET for the recipient and IUT for donor are performed during the same procedural session, starting with the iPET⁵⁵, and can also be done several times during the course of a pregnancy.^{45,55}

However, it is important to state that IUT (with or without iPET) is only a symptomatic treatment for TAPS as it does not solve the underlying problem of small (residual) anastomoses⁴. IUT might be especially useful as a management option when laser treatment is not feasible, especially in cases of very early onset of TAPS (as a bridge management until laser surgery), placenta covering the whole anterior uterine wall, or obese patients.⁴⁶

Pregnancy termination/delivery

If the above management strategies are unsuccessful, further clinical progression then necessitates preterm delivery.⁴⁴ Indications towards delivery, taking into account the gestational age, include worrisome Doppler³⁷, nonreassuring fetal heart rate^{19,37}, severe intrauterine growth restriction⁵⁷, fetal hydrops^{41,57}, fetal cardiac failure⁴¹ or active labour.⁵⁸ In a literature review of 29 cases of TAPS, 23 of them were delivered by cesarean section.¹⁹

Timing of cord clamping has importance on hemoglobin values at birth.²⁷ Delayed cord clamping could be beneficial to reduce the risk in anemia in donors, and early cord clamping advantageous to reduce the risks of hyperviscosity in recipients.²⁷ More research is needed on this topic.

Selective feticide

Selective feticide, through umbilical cord occlusion, might be an option in severe cases of TAPS^{10,45}, such as prenatally diagnosed brain lesions.^{17,39}

MANAGEMENT PROTOCOL

In the absence of a clear, evidence-based, antenatal management protocol, in a review study from the Leiden group (the most noticeable group on TAPS research), one proposal was made. According to this proposal, TAPS stage 1, and eventually stage 2, can be observed only with close monitoring by frequent ultrasound (including measurement of the MCA-PSV); if TAPS progresses quickly to stage 2 or in case of stage ≥ 3 , active intervention should be considered.⁴ Gestational age should be taken into account: below 28 weeks and laser treatment is feasible, laser treatment should be considered, as it is the only causal treatment for TAPS and it likely prolongs the pregnancy.^{4,17} When laser treatment is not feasible and gestational age is below 30-32 weeks of pregnancy, IUT should be considered as a management option; when repeated IUT transfusions are expected or in case of severe polycythemia in the recipient, PET of the recipient should also be made.⁴ After 32 weeks, delivery is an acceptable management for case ≥ 3 or progressive stage 2 cases.⁴

A simplified flowchart of this management protocol is shown on Table III.

DISCUSSION AND CONCLUSIONS

TAPS is a pathology exclusive to monochorionic pregnancies, characterised by a striking difference of hemoglobin values between two fetuses: the anemic one (the donor) and the polycythemic (the recipient). TAPS happens due to chronic slow blood transfusion through the placenta from the donor to the recipient twin, probably due to small AV-anastomosis not enough compensated by the bidirectional AA anastomoses. This might happen spontaneously on the course of a monochorionic pregnancy, or after laser surgery for twin-to-twin transfusion syndrome.

TAPS is a newly described pathology, and that is reflected on the lack of consensual diagnostic parameters and the absence of a clear evidence-based management protocol. However, it is clear today that prenatal diagnosis of this condition relies on discrepant values of MCA-PSV between the fetuses. A delta >0.5 MoM between the twins' MCA-PSV seems now to be the best prenatal diagnosis criterion. Absence of TOPS is an essential criterion for the prenatal diagnosis of TAPS. Postnatally, a hemoglobin difference >8 g/dl between the two newborns is essential for the diagnosis.

TABLE III. SIMPLIFIED TAPS PROPOSED MANAGEMENT PROTOCOL. Adapted from “Twin Anemia Polycythemia Sequence: Current Views on Pathogenesis, Diagnostic Criteria, Perinatal Management, and Outcome.” by L.Tollenaar *et al.*

Gestational Age	TAPS Staging	Management Options
<28 weeks	1	Expectant management
	≥2	Delivery
28-32 weeks	1	Expectant management
	2	Quick progression? No → Expectant management Yes → Laser treatment
	≥3	Laser treatment
>32 weeks	1	Expectant management
	2	Quick progression? No → Expectant management Yes → Delivery
	≥3	Delivery

Moreover, to differentiate TAPS from acute TTTS, other criteria should be met: a reticulocyte count ratio >1.7 or placental examinations revealing the presence of small AV anastomoses.

Screening of TAPS with MCA-PSV should be routine after laser surgery for TTTS. Screening for spontaneous TAPS in otherwise uncomplicated monochorionic twins is not so consensual, but growly recommended.

Prenatal and postnatal staging of TAPS has been proposed. Prenatal complications include prenatal brain

injury, prenatal limb occlusion, fetal hydrops, cardiac decompensation and fetal death. Postnatal complications include persistence of prenatal existing injuries, complications related to prematurity and, specially, hematological complications caused by the anemia and polycythemia.

There is no clear evidence-based management algorithm for TAPS. Laser surgery is the only causal treatment for this condition, but it is not always possible, and it is technically more challenging in TAPS cases

than in TTTS. The Solomon technique is recommended. Other prenatal management options include expectant management, intrauterine transfusion with or without further partial exchange transfusion, termination of pregnancy/delivery or selective feticide. Expectant management is common in less advanced cases of TAPS.

As a rare and newly described pathology, further research on TAPS is essential. To help this a web-based registry of TAPS cases (<https://www.tapsregistry.org>) was recently created.

REFERENCES

- Couck I, Lewi L. The Placenta in Twin-to-Twin Transfusion Syndrome and Twin Anemia Polycythemia Sequence. *Twin Res Hum Genet.* 2016 Jun;19(03):184-90.
- Simpson LL. What You Need to Know When Managing Twins: 10 Key Facts [Internet]. Vol. 42, *Obstetrics and Gynecology Clinics of North America.* 2015
- Djaafari F, Stirnemann J, Mediouni I, Colmant C, Ville Y. Twin-twin transfusion syndrome – What we have learned from clinical trials Vol. 22, *Seminars in Fetal and Neonatal Medicine.* 2017. p. 367-75.
- Tollenaar LSA, Slaghekke F, Middeldorp JM, Klumper FJ, Haak MC, Oepkes D, Lopriore E. Twin Anemia Polycythemia Sequence: Current Views on Pathogenesis, Diagnostic Criteria, Perinatal Management, and Outcome. *Twin Res Hum Genet.* 2016;19(3):222-33.
- Slaghekke F, Zhao DP, Middeldorp JM, Klumper FJ, Haak MC, Oepkes D, Lopriore E. Antenatal management of twin-twin transfusion syndrome and twin anemia-polycythemia sequence. *Expert Rev Hematol.* 2016 Aug;9(8):815-20.
- Zhao D, Lipa M, Wielgos M, Cohen D, Middeldorp JM, Oepkes D, Lopriore E. Comparison Between Monochorionic and Dichorionic Placentas With Special Attention to Vascular Anastomoses and Placental Share. *Twin Res Hum Genet.* 2016 Jun;19(03):191-6.
- Zhao DP, de Villiers SF, Slaghekke F, Walther FJ, Middeldorp JM, Oepkes D, Lopriore E. Prevalence, size, number and localization of vascular anastomoses in monochorionic placentas. *Placenta.* 2013 Jul;34(7):589-93.
- Paeppe ME De. Examination of the twin placenta. *Semin Perinatol.* 2015 Feb;39(1):27-35.
- Atallah A, Bolze P-A, Buenerd A, Marino S, Massardier J, Gaucherand P, Massoud M. Injection des anastomoses vasculaires pour la compréhension des complications propres aux grossesses monochoriales. *Gynécologie Obs Fertil Sénologie.* 2017 May;45(5):269-75.
- Johnson A. Diagnosis and Management of Twin-Twin Transfusion Syndrome. *Clin Obstet Gynecol.* 2015 Sep;58(3):611-31.
- Sueters M, Oepkes D, Therapy F. Diagnosis of twin-to-twin transfusion syndrome, selective fetal growth restriction, twin anaemia-polycythaemia sequence, and twin reversed arterial perfusion sequence *Best Pract Res Clin Obstet Gynaecol.* 2014;28:215-26.
- Mabuchi A, Ishii K, Yamamoto R, Taguchi T, Murata M, Hayashi S, Mitsuda N. Clinical characteristics of monochorionic twins with large hemoglobin level discordance at birth. *Ultrasound Obstet Gynecol.* 2014 Sep;44(3):311-5.
- Yokouchi T, Murakoshi T, Mishima T, Yano H, Ohashi M, Suzuki T, Shinno T, Matsushita M, Nakayama S, Torii Y. Incidence of spontaneous twin anemia-polycythemia sequence in monochorionic-diamniotic twin pregnancies: Single-center prospective study. *J Obstet Gynaecol Res.* 2015 Jun;41(6):857-60.
- Zilliox M, Koch A, Favre R, Sananes N. Unusual twin anemia-polycythemia sequence in a dichorionic diamniotic pregnancy. *J Gynecol Obstet Hum Reprod.* 2019;48(5):359-61.
- Suzuki T, Kagami K, Mitani Y, Yamazaki R, Ono M. Twin anemia-polycythemia sequence with blood chimerism in monochorionic dizygotic opposite-sex twins. 2019;1-4.
- Persico N, Fabiatti I, D'Ambrosi F, Riccardi M, Boito S, Fedele L. Postnatal survival after endoscopic equatorial laser for the treatment of twin-to-twin transfusion syndrome. *Am J Obstet Gynecol.* 2016 Apr;214(4):533.e1-533.e7.
- Slaghekke F, Favre R, Peeters SHP, Middeldorp JM, Weingertner AS, van Zwet EW, Klumper FJ, Oepkes D, Lopriore E. Laser surgery as a management option for twin anemia-polycythemia sequence. *Ultrasound Obstet Gynecol.* 2014 Sep;44(3):304-10.
- Favre R, Koch A, Weingertner A-S, Sananes N, Trieu NT, Kohler M, Guerra F, Nisand I. Vascular pattern in monochorionic placentas with spontaneous TAPS and TTTS with residual anastomoses after laser: a case-control study. *Prenat Diagn.* 2013 Aug;33(10):1-4.
- Moaddab A, Nassr AA, Espinoza J, Ruano R, Bateni ZH, Shamshirsaz AA, Mandy GT, Welty SE, Erfani H, Popek EJ, Belfort MA, Shamshirsaz AA. Twin anemia polycythemia sequence: a single center experience and literature review. *Eur J Obstet Gynecol Reprod Biol.* 2016 Oct;205:158-64.
- Abdel-Sattar M, Platt LD, DeVore G, Porto M, Benirschke K, Chmait RH. Treatment of Complicated Spontaneous Twin Anemia-Polycythemia Sequence via Fetoscopic Laser Ablation of the Vascular Communications. *Fetal Diagn Ther.* 2015;38(3):233-7.
- Lucewicz A, Fisher K, Henry A, Welsh AW. Review of the correlation between blood flow velocity and polycythemia in the fetus, neonate and adult: appropriate diagnostic levels need to be determined for twin anemia-polycythemia sequence. *Ultrasound Obstet Gynecol.* 2016 Feb;47(2):152-7.
- Fishel-Bartal M, Weisz B, Mazaki-Tovi S, Ashwal E, Chayen B, Lipitz S, Yinon Y. Can middle cerebral artery peak systolic velocity predict polycythemia in monochorionic-diamniotic twins? Evidence from a prospective cohort study. *Ultrasound Obstet Gynecol.* 2016 Oct;48(4):470-5.
- Tollenaar LSA, Lopriore E, Middeldorp JM, Haak MC, Klumper FJ, Oepkes D, Slaghekke F. Improved antenatal prediction of twin anemia-polycythemia sequence by delta middle cerebral artery peak systolic velocity: a new antenatal classification system. *Ultrasound Obstet Gynecol.* 2018 Aug;
- Tavares de Sousa M, Fonseca A, Hecher K. Role of fetal inter-twin middle cerebral artery peak systolic velocity differences in predicting neonatal twin anemia-polycythemia sequence (TAPS). *Ultrasound Obstet Gynecol.* 2018;
- Stritzke A, Thomas S, Somerset D. Placental dichotomy: a hint in twin anemia polycythemia sequence. *J Obstet Gynaecol Can.* 2014 Dec;36(12):1097-100.
- Movva VC, Rijhsinghani A. Discrepancy in placental echo-

genicity: a sign of twin anemia polycythemia sequence. *Prenat Diagn.* 2014 Aug;34(8):809–11.

27. Verbeek L, Slaghekke F, Sueters M, Middeldorp JM, Klumper FJ, Haak MC, Oepkes D, Lopriore E. Hematological disorders at birth in complicated monochorionic twins. Vol. 10, Expert Review of Hematology. 2017. p. 525–32.

28. Tollenaar LSA, Zhao DP, Middeldorp JM, Slaghekke F, Oepkes D, Lopriore E. Color Difference in Placentas with Twin Anemia-Polycythemia Sequence: An Additional Diagnostic Criterion? *Fetal Diagn Ther.* 2016;40(2):123–7.

29. De Paepe ME, Gündo an F, Mao Q, Chu S, Shapiro S. Redness discordance in monochorionic twin placentas: Correlation with clinical and placental findings. *Placenta.* 2017 Dec;60:54–60.

30. Van Winden KR, Quintero RA, Kontopoulos E V, Korst LM, Llanes A, Chmait RH. Pre-operative twin anemia/polycythemia in the setting of twin-twin transfusion syndrome (TTTS). *Fetal Diagn Ther.* 2015;37(4):274–80.

31. Bamberg C, Diemert A, Glosemeyer P, Hecher K. Quantified discordant placental echogenicity in twin anemia-polycythemia sequence (TAPS) and middle cerebral artery peak systolic velocity. *Ultrasound Obstet Gynecol.* 2018 Jul;

32. Simpson LL. Ultrasound in twins: dichorionic and monochorionic. *Semin Perinatol.* 2013 Oct;37(5):348–58.

33. Donepudi R, Papanna R, Snowise S, Johnson A, Bebbington M, Moise KJ. Does anemia-polycythemia complicating twin-twin transfusion syndrome affect outcome after fetoscopic laser surgery? *Ultrasound Obstet Gynecol.* 2016 Mar;47(3):340–4.

34. Hirsch L, Eitan M, Ashwal E, Weisz B, Chayen B, Lipitz S, Yinon Y. Amniotic fluid discordance in monochorionic diamniotic twin pregnancies is associated with increased risk for twin anemia-polycythemia sequence. *Prenat Diagn.* 2016 Dec;36(12):1099–103.

35. Lopriore E, Holtkamp N, Sueters M, Middeldorp JM, Walther FJ, Oepkes D. Acute peripartum twin-twin transfusion syndrome: Incidence, risk factors, placental characteristics and neonatal outcome. *J Obstet Gynaecol Res.* 2014 Jan;40(1):18–24.

36. Tollenaar LSA, Zhao DP, Middeldorp JM, Oepkes D, Slaghekke F, Lopriore E. Can color difference on the maternal side of the placenta distinguish between acute peripartum twin-twin transfusion syndrome and twin anemia-polycythemia sequence? *Placenta.* 2017 Sep;57:189–93.

37. Ashwal E, Yinon Y, Fishel-Bartal M, Tsur A, Chayen B, Weisz B, Lipitz S. Twin Anemia-Polycythemia Sequence: Perinatal Management and Outcome. *Fetal Diagn Ther.* 2016;40(1):28–34.

38. Verbeek L, Slaghekke F, Favre R, Vieujoz M, Caviglioli F, Lista G, Oepkes D, Lopriore E. Short-Term Postnatal Renal Function in Twin Anemia-Polycythemia Sequence. *Fetal Diagn Ther.* 2016;39(3):192–7.

39. Stirnemann J, Chalouhi G, Essaoui M, Bahi-Buisson N, Sonigo P, Millischer A-E, Lapillonne A, Guigue V, Salomon L, Ville Y. Fetal brain imaging following laser surgery in twin-to-twin surgery. *BJOG An Int J Obstet Gynaecol.* 2018 Aug;125(9):1186–91.

40. Luminoso D, Figueira CO, Marins M, Peralta CFA. Fetal brain lesion associated with spontaneous twin anemia-polycythemia sequence. *Ultrasound Obstet Gynecol.* 2013 Dec;42(6):721–2.

41. Taniguchi K, Sumie M, Sugibayashi R, Wada S, Matsuoka K, Sago H. Twin Anemia-Polycythemia Sequence after Laser Surgery for Twin-Twin Transfusion Syndrome and Maternal Morbidity. *Fetal Diagn Ther.* 2015;37(2):148–53.

42. Kirkham FJ, Zafeiriou D, Howe D, Czarpran P, Harris A, Gunny R, Vollmer B. Fetal stroke and cerebrovascular disease: Advances in understanding from lenticulostriate and venous imaging, alloimmune thrombocytopaenia and monochorionic twins. *Eur J Paediatr Neurol.* 2018 Nov;22(6):989–1005.

43. Stránák Z, Kor ek P, Hympanová L, Kyn I M, Krofta L. Prenatally Acquired Multiple Limb Ischemia in a Very Low Birth Weight Monochorionic Twin. *Fetal Diagn Ther.* 2017;41(3):237–8.

44. Baschat A, Oepkes D. Twin Anemia-Polycythemia Sequence in Monochorionic Twins: Implications for Diagnosis and Treatment. *Am J Perinatol.* 2014 May;31(S 01):S25–30.

45. Sananès N, Veujoz M, Severac F, Barthoulot M, Meyer N, Weingertner A-S, Kohler M, Guerra F, Gaudineau A, Nisand I, Favre R. Evaluation of the Utility of in utero Treatment of Twin Anemia-Polycythemia Sequence. *Fetal Diagn Ther.* 2015;38(3):170–8.

46. Guenot C, Robyr R, Jastrow N, Vial Y, Raio L, Baud D. Fetal Intra-Peritoneal Transfusion for the Management of Very Early Spontaneous Twin Anemia-Polycythemia Sequence in an Obese Patient With a Whole Anterior Placenta. *Twin Res Hum Genet.* 2016 Apr;19(02):154–7.

47. Behrendt N, Galan HL. Twin-twin transfusion and laser therapy. *Curr Opin Obstet Gynecol.* 2016 Apr;28(2):79–85.

48. Slaghekke F, Lewi L, Middeldorp JM, Weingertner AS, Klumper FJ, Dekoninck P, Devlieger R, Lanna MM, Deprest J, Favre R, Oepkes D, Lopriore E. Residual anastomoses in twin-twin transfusion syndrome after laser: the Solomon randomized trial. *Am J Obstet Gynecol.* 2014 Sep;211(3):285.e1–7.

49. Ruano R, Rodo C, Peiro JL, Shamshirsaz AA, Haeri S, Nomura ML, Salustiano EMA, de Andrade KK, Sangi-Haghpeykar H, Carreras E, Belfort MA. Fetoscopic laser ablation of placental anastomoses in twin-twin transfusion syndrome using ‘Solomon technique.’ *Ultrasound Obstet Gynecol.* 2013 Sep;42(4):n/a–n/a.

50. Dhillon RK, Hillman SC, Pounds R, Morris RK, Kilby MD. Comparison of Solomon technique with selective laser ablation for twin-twin transfusion syndrome: a systematic review. *Ultrasound Obstet Gynecol.* 2015 Nov;46(5):526–33.

51. Baschat AA, Barber J, Pedersen N, Turan OM, Harman CR. Outcome after fetoscopic selective laser ablation of placental anastomoses vs equatorial laser dichorionization for the treatment of twin-to-twin transfusion syndrome. *Am J Obstet Gynecol.* 2013 Sep;209(3):234.e1–234.e8.

52. Slaghekke F, Oepkes D. Solomon Technique Versus Selective Coagulation for Twin–Twin Transfusion Syndrome. *Twin Res Hum Genet.* 2016 Jun;19(03):217–21.

53. Couck I, Valenzuela I, Russo F, Lewi L. Spontaneous regression of twin anemia-polycythemia sequence presenting in the first trimester. *Ultrasound Obstet Gynecol.* 2019;1–6.

54. Yarci E, Dizdar EA, Oncel MY, Cetinkaya AK, Derme T, Canpolat FE, Oguz SS, Dilmen U. Successful management of Twin anemia/polycythemia sequence by syngeneic partial exchange transfusion. *Fetal Diagn Ther.* 2014;36(3):251–4.

55. Bahtiyar MO, Ekmekci E, Demirel E, Irani RA, Copel JA. In utero Partial Exchange Transfusion Combined with in utero Blood Transfusion for Prenatal Management of Twin Anemia-Polycythemia Sequence. *Fetal Diagn Ther.* 2018 Mar;

56. Slaghekke F, Van Den Wijngaard JPHM, Akkermans J, Van Gemert MJC, Middeldorp JM, Klumper FJ, Oepkes D, Lopriore E. Intrauterine transfusion combined with partial exchange transfu-

sion for twin anemia polycythemia sequence: Modeling a novel technique. *Placenta*. 2015;36(5):599–602.

57. Casanova J, Paiva C, Carvalho C, Cunha AC. Twin anemia polycythemia sequence: a report of three cases. *J Reprod Med*. 2014;59(11–12):596–8.

58. Griersmith TH, Fung AM, Walker SP. Dichorionic Triamniotic Triplet Pregnancy Complicated by Twin Anemia Polycythemia Sequence: The Place of Fetal Therapy. *Twin Res Hum Genet*. 2014 Dec;17(06):589–93.

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