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

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Review Article

Obstetrics

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Abstract

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

Introduction: Monochorionic twins share a single placenta, and as vascular anastomoses connect the blood circulation of both fetuses, unequal blood distribution between the twins might occur. The most known unbalanced flow distribution pathology is twin-to-twin transfusion syndrome (TTTS), where twin oligohydramnios-polyhydramnios sequence (TOPS) is present. Another recently described pathology, twin anemia-polycythemia sequence (TAPS), also results from unequal blood distribution, but its marked characteristic, instead of TOPS, is the discrepancy of haemoglobin values between the anemic foetus (the donor) and the polycythemic one (the recipient) caused by slow blood transfusion between them. TAPS might occur spontaneously or after laser treatment for TTTS.

Objectives: This review aims to summarize the research made on the last 5 years on TAPS, raising awareness and enlightenment on this under-recognized pathology.

Materials and Methods: A search on Pubmed using the terms “Twin anemia-polycythemia” and “Twin anemia-polycythemia sequence” was conducted in the summer of 2018, and restricted for the last 5 years. New articles were added up to and including December 2018.

Results and Discussion: TAPS happens due to chronic slow blood transfusion through the placenta because of small artery-to-vein(AV)-anastomoses. Prenatal diagnosis relies on twin discrepant values of middle cerebral artery (MCA) peak systolic velocity (PSV). Postnatally a >8g/dl hemoglobin difference is needed, and at least one of the following: reticulocyte count ratio>1,7 or placental examination with presence of small AV-anastomoses. Colour difference on the placenta maternal side between the anemic twin part (pale) and the polycythemic part (dark red) might be used in the future.

Conclusion: TAPS etiology, diagnosis and management are still unclear, so more quality research is needed. Prenatal complications include fetal death, and postnatal haematological complications are very common. There is no clear management protocol and options include laser surgery (potential curative therapy), expectant management, intrauterine transfusion with/without partial exchange transfusion, delivery or selective feticide. Prognosis and outcome are especially difficult to measure.

Keywords: Twin pregnancy, Twin Anemia-Polycythemia Sequence, Twin-to-twin transfusion syndrome, Monochorionic pregnancy, TAPS

List of abbreviations and acronyms

AA - artery-to-artery

AFD - amniotic fluid discordance

AV - artery-to-vein

CAS - chorioamnion separation

CDR - colour discordance ratio

CI - confidence interval

DVP - deepest vertical pool

Hb - hemoglobin

iPET - in-utero partial exchange transfusion

IUT - intrauterine blood transfusion

MC - monochorionic

MCA-PSV - middle cerebral artery peak systolic velocity

MoM - multiples of the median

MRI - magnetic resonance imaging

PPROM - prelabour premature rupture of membranes

TAPS - twin anemia-polycythemia sequence

TOPS - twin oligohydramnios-polyhydramnios sequence

TTTS - twin-to-twin transfusion syndrome

VV - vein-to-vein

Introduction

Twin pregnancies offer us a glimpse into the complex pathophysiology of pregnancy, due to the unique clinical challenges they bring us. This is even more notable on monochorionic twins, where a single placenta 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 one twin to be hypervolemic and polyuric and other to be hypovolemic and oliguric, therefore with the finding of low fluid in one amniotic sac and high fluid in the other sac, which is known as the twin oligohydramnios-polyhydramnios sequence (TOPS).[2,3] Another recently described pathology, twin anemia-polycythemia sequence (TAPS), also results from unequal blood distribution, but its marked characteristic, instead of TOPS, is the discrepancy of the hemoglobin values between the anemic fetus (the donor) and the polycythemic one (the recipient) 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 5 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” was conducted on the 9th of august 2018, with 183 results. Restraining the results to the ones published in the last 5 years, 95 articles were found, of which 6 were excluded due to being in a foreign language not spoken by the author (Danish, Bulgarian, Hebrew, Czech and 2 in Chinese). Another 13 articles were excluded because they did not contain specific information on TAPS or useful unique information for the background of this paper, thus remaining 76 articles. Another search in Pubmed using the terms “Twin anemia-polycythemia sequence” was conducted on the 6th of september 2018, with 139 results. Restraining the results to the ones published in the last 5 years, 91 articles were found, of which 88 were already found with the previous search and thus rejected. The other 3 articles were actually newly published, of which one of them was excluded because it was in Hebrew, thus leaving us with 78 articles. Both the searches were repeated once a month up until the end of December 2018 in order to include the most recent papers. Using this method, 2 new relevant articles were found, making it a total of 80 articles used in this literature review. After careful reading, sections of the articles were selected to be quoted in this literature review.

The monochorionic placenta

Twins can be categorized according to zygosity and chorionicity. Zygosity refers to the type of conception: dizygotic twins, the most common type, result from fertilization of two oocytes (due to multiple ovulation) by two sperm cells; monozygotic twins ("identical" twins) result from division of a zygote originating from the fertilization of one oocyte by one sperm cell. Dizygotic twins are supposed to have two placentas, and therefore be dichorionic.[5] When it comes to monozygotic twin pregnancies, the type of placentation depends primarily on the timing of division of the zygote: a division within the first three days post-fertilization (70% of monozygotic twins), will usually result in dichorionic placentation; three to nine days post-fertilization (25%) will result in monochorionic-diamniotic placentation. Late division (8–12 days post-fertilization; 2%) leads to monochorionic-monoamniotic placentation, whereas even later zygotic splitting (13–16 days; 1:100.000) results in conjoined twins.[5]

It is important to establish the type of chorionicity (and amniocity) because monochorionic pregnancies are at increased risk of pathology, including monochorionic unique complications such as twin-to-twin transfusion, selective fetal growth restriction, twin-reversed arterial perfusion or conjoined twins[6], but also higher rates of non-specific anomalies such as malformations.[5] The optimal period to establish chorionicity is between 10 to 14 weeks.[7,8]

Almost all the monochorionic (MC) twins have vascular anastomoses between the two fetal circulations[9,10], while dichorionic twins share no anastomosis.[10] There are three types of anastomosis – artery-to-vein (AV), artery-to-artery (AA), and vein-to-vein (VV). In a study of 134 monochorionic placentas, the frequency of AV anastomoses, AA anastomoses, and VV anastomoses was, respectively, 99%, 85%, and 28%.[10]

AV anastomoses are by definition unidirectional, with the blood flowing from the artery of one twin to the vein of the other.[1,5] They are deep, occurring on a capillary level in a shared cotyledon (and therefore invisible to the naked eye examination of the chorionic plate). A study claimed that about 95% of monochorionic placentas have AV anastomoses, in a mean number of 7 AV anastomoses.[11] AV anastomoses are the ultimate cause of TTTS and TAPS, as they allow the imbalance of flow between the donor and the recipient fetus to occur.[9,11]

AA and VV anastomoses are superficial, as they do not penetrate the chorionic plate[5] and the blood flow can be bidirectional[9], depending on the pressure in each fetal circulation[12]. 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.[11] A disproportion in the ratio

between the AV and the AA anastomoses is thought to be a key component in the hemodynamic imbalance that ultimately causes these pathologies.[8] The role of VV anastomoses is not so clear.[9]

It is recommended for all twin pregnancies placentas to have a pathology examination after the birth, but there is no universal protocol for a standardized examination of the monochorionic twin placenta.[5] Studies of the vascular distribution of vessels on TAPS placenta have offered us some information on the pathology. One way to study the vascular pattern of a placenta is injection studies: first, the membranes of the monochorionic-diamniotic placenta are removed, and the cords sectioned 5–10 cm above the placenta level; the chorionical vessels are then "milked" to remove intravascular blood; then, the umbilical artery of one twin is cannulated, and dye is injected using manual pressure.[5] Normally, because there are AA anastomoses, the injection of one umbilical artery is enough to fill the co-twins arterial bed, but injection of the umbilical arteries of the fetus with two different colours might also be used.[11] Then, the process of injection is repeated with a different colour in the umbilical vein of one twin.[5] Chorionic arteries are identified by their near-universal tendency to course superficial to the accompanying veins.[5] This method, and others similar, allows for identification and counting of the three types of anastomoses.

Two different studies[11,13] regarding the number of anastomoses in TAPS reached the same ground conclusions: the number of AV, AA and VV anastomoses in spontaneous TAPS placentas was lower than in the control group of non-complicated MC pregnancies.

Contrary to the established belief that pathophysiology of spontaneous TAPS relies primarily on AV anastomosis, one study[14] describes a case where postnatal placenta examination revealed six AV anastomoses and one AA anastomosis, but where colored dye did not pass throughout the three AV anastomoses and passed with multiple forced injection in the remaining three AV anastomoses, whilst passing the AA anastomosis easily and without resistance, which led the researchers to suggest that the AA anastomosis (flowing from donor to recipient) caused TAPS development in spite of the presence of AV anastomoses.

However, one has to take into account that the number of anastomoses counted after injection may not be the same as the patent vessels *in vivo*, because the injection is made with an artificial level of high pressure.[13] Moreover, spontaneous infarction or thrombosis might have occurred.[15]

Besides the number, the diameter of the anastomoses also seems to play a role on spontaneous TAPS: one of the above studies[13] claims that the mean diameter of the artery-to-vein anastomoses in TAPS (2,26 mm) is smaller than the mean diameter of AV diameter

in normal monochorionic pregnancies (4,17 mm) matched for gestacional age, while the diameter discrepancy in artery-to-artery anastomosis is even more significant: 0,2 mm in spontaneous TAPS and 2,0 mm in normal pregnancies, It has been suggested that this small diameter of the AA anastomosis might be the reason why the presence of the AA anastomosis is not sufficient enough to prevent TAPS to happen.[11] VV anastomoses on TAPS pregnancies are also smaller [0,10 mm (0-1,8)] versus 1,6 mm (0-12) in the control group.[13] It is important to note that the Leiden group, the biggest research group on TAPS, considers the presence of a few very small AV anastomoses, with a diameter <1 mm, an essential characteristic of TAPS placentas[4], based on a single study of 2013.

A redness discordance from the two portions of the placenta, seen directly at the placental basal plate of the monochorionic placenta, has also been suggested as a marker of TAPS.[16] Though not extensively studied, the placental villi of the donor twin have been described as immature, and this might thus help explain why do TAPS placentas show colour discordance while acute peripartum transfusions generally do not, even with similar hemoglobin differences.[12] It will be discussed as a possible postnatal diagnosis criterion further ahead on this paper.

An unequal sharing of placenta weight was more frequent in TAPS as compared with monochorionic normal pregnancies (75% versus 29%, p=0,03).[13] In MC twins, a larger placental share usually leads to a a larger birth weight and vice-versa[17], but TAPS reports have been contradictory. The donor twin in TAPS cases is most often the smaller twin (90%) but it seems to have a larger placental territory (65% of cases) compared to its recipient co-twin.[17] This might suggest that in TAPS placental share might not be the decisive factor to fetal growth, but, instead, that the main factor is the net intertwin blood flow.[17] There are some explanations for this: one theory is that the chronic blood loss of the donor might lead to chronic hypoxia and depleted nutrition in the placenta share of the TAPS donor, and thus stimulate compensatory relative larger placental expansion and growth in order to deliver more oxygen and nutrition to the donor fetus[17]; another simpler explanation might be the selection bias on scientific papers – this study[17] only included placentas with two living infants, and the authors therefore speculate that TAPS donors with a relatively smaller placental share might be at increased risk of fetal death.[17]

It is also important to study placentas that have been subjected to laser photocoagulation during pregnancy due to TTTS or TAPS but in which TAPS appeared or persisted after the laser treatment, as injection studies will help us understand why the laser photocoagulation failed.[12] If the birth occurred within one month from the laser coagulation, the sites of laser impact are usually identifiable as hemorrhagic clotted vessels where the dye filling abruptly

stops.[5] After longer time intervals, usually there is regional or complete absence of intertwin anastomoses, often with deposition of subchorionic fibrin.[5] Findings following selective laser ablation may be quite subtle; in contrast, placentas treated with the more aggressive Solomon procedure (described further ahead) display extensive, occasionally even full-thickness, placental necrosis.[5] Even with optimal surgical technique, some residual anastomoses might remain.[5] Most of those anastomoses are small and are located in the periphery of the placenta.[5] Their frequency is not well established, varying from 5 to 32%[5] and only a portion of them will develop subsequent TAPS or other complications.[13]

Twin-to-twin transfusion syndrome (TTTS)

TTTS is a syndrome that happens in about 10-15%[3,8] of monochorionic pregnancies and presents typically between 16 and 26 weeks.[1] It was already described in the 19th century.[4]

The diagnosis of TTTS is based on the presence of polyhydramnios in the recipient twin, with a distended bladder and oliguric oligohydramnios in the donor twin. Oligohydramnios is defined as a deepest vertical pool (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 to adjust for the increase in amniotic fluid with gestation.[1,18] This is known as the twin oligohydramnios-polyhydramnios sequence (TOPS). Some controversy still arouses to this classification, as normal amniotic values of DVP vary throughout the pregnancy.[19] In addition, as fetal urine only provides a small portion of amniotic fluid volume before 14 weeks of gestation, TOPS can rarely be seen in the first or early second trimester.[8] Moreover, estimated birth weight discrepancy should not be used as diagnostic criterion for TTTS.[18]

There is an unbalanced transfusion of blood that is mediated, at least in part, by artery-to-vein (AV) anastomoses within the MC placenta.[3] This shift of blood is significant enough for the donor twin to become hypovolemic while the recipient twin becomes hypervolemic.[3] In the renal system of the donor twin, in response to the decreased circulating volume, the renine-angiotensin system is activated, increasing tubular reabsorption and the production of angiotensin II, which mediates vasoconstriction to maintain circulating volume and makes the donor fetus oliguric; this may also have the paradoxical effect of decreasing renal and placental perfusion, further worsening oliguria and resulting in growth restriction.[3]

As for the recipient twin, a variety of mediators may be involved in response to the increased blood volume. The increased atrial pressure mediates an increase in cardiac atrial natriuretic peptide synthesis, which increases glomerular filtration rate and decreases kidney tubular

reabsorption.[3] Suppression of antidiuretic hormone is also thought to increase the recipient's production of urine.[3] This oligury of the donor twin and poliury of the recipient twin causes the twins oligohidramnios-polihidramnios[8] sequence that is pathognomonic of TTTS.[4]

It has also been hypothesized that the high level of renine-angiotensin activation is transferred from the donor to the recipient through the placental anastomoses, causing further cardiovascular complications on the recipient twin not attributable to the increased blood volume alone.[3,8]

The understanding of abnormal vascular anastomoses as the etiological cause of TTTS (and TAPS, as described in the previous chapter of the review) led to the development of laser photocoagulation as a method to definitively treat the underlying vascular pathology in TTTS around 30 years ago, with the technique being refined ever since.[20] A newly described technique, the so-called "Solomon technique", consists on, after coagulation of all the identifiable anastomoses, making a coagulation line with the laser from one edge of the placenta to the other[21], and has been suggested to reduce the incidence of recurrent TTTS or TAPS[21], which will be discussed further ahead on this paper.

Expectant management in severe TTTS cases is not an option because of a perinatal mortality of 80 to 100% and a neurological morbidity in 15 to 50% of survivors.[3] Treatment options include serial amnioreduction, septostomy, elective premature delivery, selective feticide of one twin by cord coagulation, or fetoscopic laser coagulation.[3] Apart from laser coagulation, the other treatments focus on abating the secondary clinical symptoms of TTTS, but not do actually halt the disease process.

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 (as well as the acronym itself) 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 day[4] – due to AV anastomoses not counterbalanced by a large enough AA anastomosis (see section "The monochorionic placenta"). This pathological placental blood flow net might happen spontaneously in a monochorionic pregnancy[22], without any risk factor having been described so far.

Spontaneous TAPS has been said to occur in between 3-5% of monochorionic diamniotic pregnancies[4,18,23], though one single-center study recently reported a smaller incidence of

1,6%.[24] This possible overestimation might be due to different diagnosis criteria on TAPS and incorrect differentiation between TAPS and acute feto-fetal hemorrhage.[24] Spontaneous TAPS has been described in triplet pregnancies, whether it is a monochorionic-triamniotic pregnancy[15] or dichorionic-triamniotic pregnancy[25] and once in a monochorionic-monoamniotic pregnancy.[15] It is also important to take into account that a pregnancy can be falsely reported as dichorionic; if the clinic suggests TAPS (or another MC related pathology), it might be important to review the idea of dichorionicity.[26]

However, TAPS is more frequent after laser-treated TTTS, with an incidence of 2-16%[4,27]. The wide range of incidence rate in post-laser TTTS can be explained by the use of different laser surgical techniques, small sample sizes, or by the existence of different definitions and criteria for TAPS.[4]

Even with optimal surgical technique, some patent intertwin-anastomoses might remain present after laser ablation.[5] Its reported frequency varies widely (5-32%)[5]. While anastomoses in spontaneous cases of TAPS were more equally spread along the vascular equator, most residual anastomoses after the surgery are small and peripherally located.[5,11,28] 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.[29] However, it is important to notice that not all residual anastomoses after TTTS laser surgery cause pathology.[13]

There are several explanations for residual anastomoses: anastomoses might have been missed during the procedure, or they might have been too big to be coagulated in the procedure; the coagulation might have been incomplete, or have reopened after the surgery.[30] Some anastomoses might have been too small to be noted during the procedure because they were collapsed or too narrow to be seen with the fetoscospe, but they might have dilated after occlusion of the primary anastomoses.[30] Another possibility is that new vessels could have grown across intact unlasered placental procedures.[30].

This post-laser TAPS usually occurs acutely within one or two weeks after the surgery[3], but a literature review found that TAPS may occur at any time after laser surgery, with reported interval ranging from 1,2 to 11,2 weeks.[15]

Interestingly, in post-laser TAPS, it is usually the former recipient who becomes anemic, whereas the former donor becomes polycythemic[3,4]; this supports the hypothesis that the remaining anastomoses vessels are being used unidirectionally from the twin with the highest systemic pressure into the one with the lowest pressure and volemia[3]; moreover, the

amnioredution performed concomitantly with the laser surgery shortly increases the colloid osmotic pressure of the ex-recipient of TTTS, which attract excess fluid from the maternal blood to the TTTS ex-recipient's fetal blood, helping the anemia by hematocrit dilution.[4] However, one must be aware that not all the complications after TTTS laser surgery are TAPS: there is a case report[31] of a iatrogenic hematoma after TTTS surgery that caused one of the fetuses to become anemic.

In post-laser TAPS, the mean hemoglobin level of the anemic twin was higher than in the spontaneous TAPS anemic twin (p=0,029), but similar between spontaneous and post-laser polycythemic twins (p=0,135).[19] It might be then speculated that post-laser TAPS is in general less severe than spontaneous TAPS and that, eventually, they might have a different natural history.[19]

There is also a case report of anemia-polycythemia following amnioredution for TTTS, which was suggested to be due to sudden changes in intrauterine pressure and blood flow through anastomoses.[32] Unfortunately, reticulocyte levels on the newborn twins were not collected, although other data in the report (the presence of small residual anastomoses and colour difference in the maternal side of the placenta) suggest that it was indeed a case of TAPS following amnioredution – to our knowledge, the first and only reported.

Diagnosis

○ Prenatal

Prenatal recognition of TAPS is essential for the management of these pregnancies. The absence of oligohydramnios and polyhydramnios (absence of TOPS) is an essential element in the diagnosis of TAPS, as the presence of TOPS is only pathognomonic for TTTS.[4,33] Besides exclusion of TOPS, prenatal diagnosis is based on the Doppler ultrasound middle cerebral artery-peak systolic velocity (MCA-PSV), a non-invasive test.[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 having a sensitivity of 100% (95% confidence interval, 86–100%) for the detection of fetal anemia[34], but the evidence supporting a decrease of MCA-PSV on fetal polycythemia, however, is much more scarce.[34] This makes sense due to the fact that fetal anemia occurs in different scenarios, such as alloimmunization, parvovirus infection, fetomaternal hemorrhage and the anemic twin of a TAPS pair, while polycythemia is a problem only in the setting of TAPS[35] and in some cases of intrauterine growth restriction.[36] The first cut-off proposed for polycythemia, <0,8 MoM,

was suggested based on an observation of 13 twin pairs with TAPS.[34] Then, because research showed that a MCA-PSV between 0,8 and 1,0 MoM in the recipient was also frequently found in postnatally diagnosed TAPS cases, the cut-off of MCA-PSV <1,0 MoM in the polycythemic fetus was thus suggested.[4,34] A cut-off of <1,0 MoM, by definition, states that potentially half of normal fetuses could be identified as polycythemic.[34] A comprehensive literature review of ultrasound made in June 2014[34] found 9 studies defining fetal polycythemia as an MCA-PSV of <0,8 MoM, while five studies used an MCA-PSV cut-off of <1,0 MoM, and one study defined the cut-off as 0.8–1.0 MoM. A study[37] compared the prenatal cut-offs of >1,5 MoM and <1 MoM with the correspondent postnatal diagnosis of TAPS (though including postnatally some cases that did not meet all the formal diagnosis criteria but had a "strong clinical impression" of TAPS) and determined that the sensitivity and specificity of the prenatal diagnosis were 71% and 50%, respectively, regarding the correspondence with postnatal diagnosis. A study made by the Leiden group[38], calculated the sensibility of MCA-PSV >1,5 MoM as 94% and a specificity of 74% to predict severe anemia, and a sensibility of 97% and specificity of 96% of MCA-PSV <1,0 MoM as a marker of polycythemia. Another study by Fishel-Bartal et al.[39] about this question concluded that, although there was a correlation between MCA-PSV and anemia, MCA-PSV was similar among polycythemic and normal fetuses (0,95 MoM vs 1,02 MoM, respectively; p=0,47) 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. Unfortunately, all the above mentioned studies used different definitions of anemia-polycythemia, contributing to this wide discrepancy of results. Another recent study[40] also found that fetal inter-twin MCA-PSV MoM differences correlated positively with the neonatal inter-twin hemoglobin differences. In this study, for a postnatal hemoglobin difference of ≥ 7,25 g/dl at birth (cut-off used because it was the 90th percentile of postnatal hemoglobin difference in the MC pregnancies included), the optimal cut off for MCA-PSV MoM difference was 0,373 with a sensitivity of 93,3% (95%CI, 68,1-99,8) and a specificity of 95,7% (95%CI, 90,8-98,4), a positive predictive value was 70% (95%CI, 45,7-88,1) and a negative predictive value was 99,3% (95%CI, 95,9-100).

Based on this suggestion of delta MCA-PSV as a possible better diagnose tool for TAPS, the Leiden group has recently (August 2018) made a retrospective study on their own data[41], stating that the cut-off MCA-PSV values of >1,5 MoM and <1,0 MoM had a sensitivity of 46% and a specificity 100% to predict postnatal TAPS, while delta MCA-PSV >0,5 MoM showed a sensitivity of 83% and a specificity of 100%, thereby claiming the delta MCA-PSV to have a 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.[42,43] A study attempted to quantify the discordance of placental echogenicity in TAPS using the ImageJ software[44], and found that the echogenicity of donors twins was significantly higher than that of recipients (138,7±22,8 vs 77,9±37,0; p<0,0001), and that placental echogenicity was also correlated with MCA-PSV MoM. The mean placental thickness of donor twins was also higher than that of recipients. Unfortunately, this study used a broad definition of TAPS that allowed for many cases of TTTS overlapping with anemia-polycythemia to be included as TAPS, which may have biased the results.

A 'starry-sky' liver pattern in the recipient twin, characterized by clearly identified portal venules (stars) and diminished parenchymal echogenicity (sky) that accentuates the portal venule walls, has also been described[45] as an early sign of TAPS (as well as of TTTS). The most common cause of a starry sky pattern is acute hepatitis, but it has also been reported in other conditions such as right heart failure.[45] Both hypervolemia and ventricular hypertrophy from increased afterload in TAPS can lead to hepatic congestion and may explain the starry sky appearance of the recipient's liver.[45]

Other ultrasound findings such as discordant crown–rump length determined at mid-first trimester were found not to be a risk factor for TAPS (or TTTS).[46] Although nuchal translucency intertwin discrepancy in the first trimester has been associated with a higher chance of developing TTTS[8,47], to our knowledge there is no study regarding nuchal translucency and TAPS.

Screening of TAPS with MCA-PSV should be routine after laser surgery for TTTS.[47] It is controversial to screen for spontaneous TAPS in otherwise uncomplicated monochorionic twins, as some feel the data on natural history of TAPS and the impact of treatment is not sufficiently strong yet[48], but it should be considered when minor variances in amniotic fluid are detected during serial ultrasounds.[47] In a more recent ultrasound screening review (as of 2018), MCA-PSV measurement is recommended in all MC pregnancies from 20 weeks onward.[49] This serial monitoring should be made at least every two weeks.[4,14]

It is also important to take into account that TAPS, as well as TTTS, can appear late on in a, until then, uncomplicated pregnancy. In fact, a study, although with a sample of only 88 uncomplicated pregnancies at 28 weeks of gestation, found that 5,7% pregnancies (5 cases) with no significant abnormal findings until the second trimester had serious complications associated with placental circulatory imbalance (2 cases of TAPS, 2 TTTS and 1 acute TTTS) during the third trimester of pregnancy.[50]

○ Postnatal

It has been estimated than around half of the cases of TAPS are not diagnosed antenatally, but only at birth.[4] The postnatal criteria is mainly based on hematological criteria at birth.[51] Some classifications have been proposed, such as a hemoglobin level <11 g/dL in the anemic twin and >20 g/dL in the polycythemic twin, but absolute hemoglobin levels do not take into account that hemoglobin is known to increase linearly with gestation[51]; gestational-age-dependent cut-off levels to define anemia in the donor (Hb <5th percentile) and polycythemia in the recipient (haematocrit >65%) were also suggested, but had practical disadvantages since they required the use of normograms related to gestational age, and there were several available with many small differences between them.[4] Currently an inter-twin hemoglobin difference >8.0 g/dL is the base of the postnatal diagnosis.[18,23,51] As a large Hb difference (>8 g/dL) at birth is also detected in case of acute peripartum TTTS[4] (whose distinction will be discussed further ahead) another two criteria have been added, and at least one of these criteria must be fulfilled.[4,51] The first criterion is an increased reticulocyte count measured in the TAPS donor (as a result of increased erythropoiesis due to chronic anemia); an inter-twin reticulocyte count ratio (measured by dividing the reticulocyte count of the donor by the reticulocyte count of the recipient) over 1,7 is pathognomonic for TAPS.[4] This is based on the fact that, in acute peripartum TTTS, blood transfusion from the donor twin to the recipients occurs rapidly and reticulocyte count in the donor is typically still low at birth, though the acute anemia will later lead to an increased erythropoiesis.[4] The other established postnatal criterion is the presence of small residual anastomoses, of less than 1 mm of diameter[4], at the placental surface, which can only be accurately assessed by careful placental injections studies using colour dye.[51] This is because the pathogenesis of acute peripartum TTTS, in contrast to TAPS, is thought to be based on large placental AA or VV anastomoses with low resistance, allowing a large amount of blood to flow directly from the donor to the recipient during the birth.[4]

However, there are some problems with these criteria. First, reticulocyte count is not routinely performed unless there is awareness and suspicion of this condition.[52] Secondly, in the literature there is no consensus about units or values; in fact, the reticulocyte count is sometimes reported as a percentage in some articles, an absolute value in others, or is sometimes just unreported.[19] Thirdly, one study by Veujoz et al.[37] claims that both of these additional two postnatal criteria for TAPS are perhaps too restrictive. Lastly, placental examination with injection studies is too slow to help deciding on the clinical management of neonates.[53]

Taking these difficulties into account, a new additional criterion for postnatal diagnosis of TAPS has been proposed, based on the common find of pale parenchyma on the maternal side of the placenta portion of the anemic twin and dark red parenchyma on the portion of the polycythemic twin.[16,52] In one study, the intensity of the red placenta colour was digitally measured using the software ImageJ and colour discordance ratio (CDR) was thus calculated, and found to be higher in TAPS.[52] In that above-mentioned study, all of the TAPS placentas had a CDR value >1,5, whereas none of the CDR values of the control group of monochorionic pregnancies was >1,5. Moreover, they found a positive correlation between CDR and inter-twin Hb difference, suggesting a strong association between larger inter-twin Hb difference and higher CDR, but only in the TAPS group (and not in the control group of monochorionic twins).[52] Another study[16] supported the claim of intertwin CDR being correlated with intertwin hemoglobin difference and chorionic angioarchitecture. A CDR value ≥2,0 has high specificity (96%), but relatively low positive predictive value (60%) as indicator of TAPS, as currently defined.[16] A third study[53] investigated the CDR in acute peripartum TTTS, and found out that the median CDR in acute peripartum TTTS (1,20) was significantly lower compared to TAPS placentas (2,50), and that this low CDR was comparable to the control group. If more studies support these findings, a quick examination of the maternal side of the placenta could help perinatologists to make a quick distinction between acute peripartum TTTS and TAPS.[52] Another future possibility could be the creation of a postnatal TAPS risk scoring system that incorporates weighed hematologic and placental-choriovascular data.[16]

TAPS vs acute TTTS

Acute peripartum TTTS is a rare form of twin-to-twin transfusion – estimated to occur in about 1,2%[23] to 2.5% of all MC twins[54] – thought to be due to acute shifts of blood between the two fetuses during delivery.[51]

The physiopathology is not clear and is 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.[51,54] This is likely only possible through large AA or VV superficial anastomoses[51] (unlike the small anastomoses of TAPS), and placental examination therefore provides an important diagnostic tool through demonstration of the appropriately sized anastomoses.[12]

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.[54]

As mentioned in the postnatal diagnosis section of this paper the reticulocyte counts in acute pathology are not elevated, unlike in TAPS.[51]

As described previously, colour difference between the two portions of the placenta also seems to be notably stronger in TAPS.[53]

It has been suggested that acute TTTS is most likely through vaginal delivery, and that the first twin to be delivered is most likely to be the donor.[54] Hypothetically, after clamping the firstborn twin's cord, uterine contractions may allow placental blood from the first twin's low-pressure placental blood net to be transfused through the low-resistance superficial vascular anastomoses into the higher pressure circulation of the second twin.[54] However, another study does not support this hypothesis, claiming their 5 cases of acute TTTS all happened in caesareans, 4 of them without labour, and that order of birth on caesarean did not seem to play a role on the occurrence of acute TTTS.[23]

In TAPS donors, acute blood transfusion is contra-indicated, as it may cause hemodynamic complications because these neonates are not hypovolemic.[53] Therefore, a quick distinction between acute peripartum TTTS and TAPS within one hour of birth could be helpful.[53]

Clinical characteristics of concomitant TAPS and acute TTTS are yet to be described.[23] It is also worth noting that a lot of research on acute TAPS is incomplete (not including reticulocyte count or placental examination) and thus, specially older studies (due to limited knowledge on TAPS), might report cases of acute TTTS that are, in fact, TAPS cases.[51]

TAPS vs TTTS

TTTS and TAPS have been described as mutually exclusive diagnoses.[55] This means that a diagnosis of TTTS is given to any patient meeting TTTS criteria of oligohydramnios (DVP <2 cm in the donor twin) and polyhydramnios (DVP of >8 cm, or >10 cm after 20 weeks[18]), regardless of whether ultrasound suggestion of hemoglobin discordance exists[55]. Moreover, this means that a TAPS diagnosis implies the absence of TOPS.[4,33]

However, this point of view has not been unanimous in our literature review, with some studies mentioning "TAPS combined with TTTS"[44] or "TTTS cases with secondary TAPS"[8], "coexisting TAPS"[47] or "presence of TAPS with TTTS"[56]. 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 conditions[33]. A study aimed to survey cases of TTTS with superimposed twin anemia-polycythemia (AP)[55] and found that 2,4% (9/369) of TTTS patients had TTTS+AP (based on discordance MCA-PSV values). Of these 9 cases, in the fetoscopy 5 had placental and fetal colour discrepancy findings typically reported with isolated TAPS, it is, a lower mean number of AV anastomoses and an anemic twin visibly paler than the polycythemic.[55] The other 4 cases of TTTS+AP were considered "atypical", as they had large or numerous anastomoses and did not have any visible fetal color discordance. The fact that only a small fraction of TTTS patients have MCA-PSV suggestive of anemia/polycythemia is supportive of 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.[55] Postnatal values or complications were not provided because all the cases were subjected to laser photocoagulation.[55] Another study[56], although unfortunately not using such precise terminology, observed 8,3% (11/133) cases of TTTS+AP on the TTTS population, with a significantly lower number of anastomoses in the TTTS+AP cases than the "TTTS only" and similar outcomes. This might be useful for the surgeons to know during laser photocoagulation.[56] A different study[57] chose the blurry expression "atypical TAPS" for all the varying presentations of twin-to-twin transfusion who did not fully meet the TOPS criteria.

A study by Rossi et al.[19] suggested that TTTS and TAPS might be a single entity that occurs in sequence: mild inter-twin transfusion would cause selective intrauterine growth restriction; moderate inter-twin transfusion would cause abnormal renal function leading to amniotic fluid discordance (it is, to TTTS); and severe inter-twin transfusion would cause abnormal cerebral perfusion, and thus, TAPS. However, to our knowledge there are no cases reports that follow this proposed sequence.

It is interesting to note that amniotic fluid discordance(AFD) >3cm (and that does not fulfil the TTTS criteria) has been showed to increase the risk for TAPS; moreover, in the group with AFD, women who developed TAPS had significantly higher AFD compared with women who did not develop TAPS (7,3 cm vs 4,2 cm, $p<0,01$).[58] Patients with AFD also delivered earlier and had more neonatal morbidity than the control group.[58]

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

Table I – Differences between TTTS, TAPS and acute TTTS. Adapted from "Hematological disorders at birth in complicated monochorionic twins" by L.Verbeek *et al.*[51]

	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 (>8g/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.

Staging of TTTS and TAPS

TTTS has established staging, the so-called "Quintero Stages", which divides the severity of TTTS into five stages. Several studies support Quintero stage at presentation as a determinant of fetal outcome[18], although others note that progression through these stages has never been documented[3].This staging system relies only on fetal ultrasound and Doppler characteristics, neglecting significant prognostic factors such as intrauterine growth restriction, as well as obstetrical factors such as gestational age and cervical length, but, probably owing to its simplicity, remains widely used by most centers.[3,18]

In stage 1 TTTS, the donor bladder is still visible. As the disease progresses, the donor becomes more hypovolemic and the bladder is not longer seen (stage 2). In stage 3, critical abnormal Doppler measurements (such as absent/reverse end-diastolic velocity in the umbilical artery, reverse flow in the ductus venosus or pulsatile flow in umbilical vein) are seen. Stage 4 TTTS is characterized by the presence of fetal hydrops in the receptor, mainly due to progressive cardiac failure. Stage 5 is characterized by intrauterine fetal demise of one or both fetus.[9] The "stuck twin" phenomenon is seen in cases where the donor twin has anhydramnios, and thus has the amniotic membrane tightly wrapped around its body.[18]

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

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.Djaafri *et al.*[3], "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*[41], and "Twin Anemia Polycythemia Sequence: Current Views on Pathogenesis, Diagnostic Criteria, Perinatal Management, and Outcome." by L.Tollenaar *et al*[4].

	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 >8g/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 >11g/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 >14g/dL
Stage 4	Presence of hydrops in either twin	Presence of hydrops on donor	Presence of hydrops on donor	Inter-twin Hb difference >17g/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 >20g/dL

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

A prenatal and postnatal classification system of TAPS has been proposed[4] and thus updated due to new prenatal diagnostic criteria based on delta MCA-PSV.[41] In these prenatal classifications, stage 1 consists on a MCA-PSV donor over 1,5 MoM and MCA-PSV recipient under 1,0 MoM (old criteria) or a delta MCA-PSV >0,5 MoM (new criteria), without further signs of fetal compromise. Stage 2 implies a MCA-PSV donor >1,7 MoM and MCA-PSV recipient <0,8 MoM (old criteria) or 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, likewise the stage 5 of Quintero stages, implies the dismise of one or both foetuses, 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 foetuses (assuming that another criterion, such as the reticulocyte count ratio, is met for the diagnosis of TAPS to be made, as discussed in the section “Diagnosis – postnatal) : an inter-twin hemobglobin difference >8g/dL is the inferior limit for stage 1, >11g/dL for stage 2, >14g/dl for stage 3, 17g/dl for stage 4 and 20g/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.[23]

Cardiac descompensation of the donor, hidrops 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.[22,51] As already discussed in this paper, donor twins have chronic anemia with highly increased reticulocyte counts, reflecting the chronic blood loss characteristic of TAPS.[51] A blood transfusion is often needed in the first 24h of birth in around 57% to 80% of cases, but, given the chronic nature of the anemia, is not necessary immediately at birth or in the delivery room.[51]Recipients of TAPS may be severely polycythemic and require partial exchange transfusion (PET) in 40–71% of cases.[51]

Thrombocytopenia (platelet count <150 × 10^9/L) occurs more often in twins affected by TAPS compared to MC twins.[51] Thrombocytopenia in TAPS is mostly self-limited, but in severe cases might require platelet transfusion.[51] Thrombocytopenia is more common in the recipient twin, with several studies reporting lower platelet count in recipients than in donors.[51] Platelet count in recipient twins is also negatively correlated to hemoglobin level at birth.[51] Some explanations proposed to this low platelet count in polycythemic recipients are impaired production secondary to tissue hypoxia, slow spleen blood flow, and decreased plasma fraction with normal concentrations.[51]

Postnatal short-term renal dysfunction was described in TAPS cases[59], and it was found to be more common in donors, who had significantly higher levels of creatinine compared to recipients in the first week of life, suggesting that chronic blood loss in donor twins may not only lead to anemia and hypoalbuminemia but may also affect short-term renal function. Long-term renal consequences considering renal pathology or systemic hipertension in TAPS donors require further investigation.[59] There was a case report of a TAPS donor with hyponatremic hypertensive syndrome, a rarely described pathology in prenatal term infants in which the unilateral ischemic kidney induces the activation of the renine-aldosterone-angiotensin system; TAPS could theoretically have contributed to the unilateral ischemia, but the connection is not clear.[60]

A study[61] 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. In fact, TAPS was diagnosed in eight of the 22 cases (29%) that developed brain lesions and in 91/1001 (9%) of those that did not develop brain lesions (p<0,001).[61] This study included fetal brain magnetic resonance imaging (MRI), and highlighted that normal serial targeted ultrasound examination could miss 13% of cerebral anomalies diagnosed by MRI.[61] There is also a case report of a prenatal brain lesion in a spontaneous TAPS recipient, thought to be caused by hyperviscosity/polycythemia[62]. Bilateral deafness and spastic paralysis have also been reported.[63] The recipient of TAPS seems to be at greater risk for brain damage.[36]

Prenatally acquired limb ischemia, including multiple limb ischemia, not explained by other factors (e.g. amniotic bands) has been reported in recipients of TAPS.[64] On the other hand, there is also a case report of a upper limb vascular occlusion in a MC pregnancy without any risk factor associated.[65] Skin necrosis has also been reported on the recipient twin.[23]

Chronic fetofetal transfusion syndromes, such as TAPS, are considered a possible independent risk factor for the development of retinopathy in either the donor and/or the recipient twin, because of relative hypoxia.[66]

A study reported two cases of severe post-laser TAPS associated with critical maternal morbidity, including one suspected case of mirror syndrome due to increasing placental thickness, excess maternal body weight gain and significant edema.[63] To our knowledge, there is no study comparing maternal complications between TAPS pregnancies and other type of pregnancies.

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] Outcomes of all the interventions that will be described are also significantly influenced by the cervical length measured before the procedure.[9]

- ***Laser surgery***

Laser coagulation of the vascular anastomoses is the only curative treatment for TAPS.[4,28] Moreover, laser therapy in TAPS can be technically more challenging than in TTTS[28,29] because of the possible absence of polyhydramnios and of a 'stuck twin', and difficult visualization of the very small communicating anastomoses.[33] When considering laser therapy for TAPS, preoperative amnioinfusion (injection of isotonic fluid into the amniotic cavity) is thus advisable. 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[8,67], and in obesity[67], which can therefore influence management choices[67]. Laser surgery is contraindicated with active labour, prelabour 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.[8]

Gestational age at presentation in TAPS seems to influence differences in management. In a study for laser-surgery as a management option for TAPS cases[28], gestational age at diagnosis in the group that was later subjected to laser surgery was significantly lower at 19 weeks (range: 17–24) comparing to 26 weeks (range: 19–29) in the intrauterine-transfusion group and 25 weeks (range: 17–34) in the expectant-management group (p=0,02). One possible reason is that fetal surgeons probably felt that laser treatment was more justified in cases in which TAPS presented early and well before delivery; another explanation could be that these early cases were seen as more favourable and feasible for laser treatment because of the smaller size of the uteri and fetuses.[28] Moreover, the same study observed a

tendency towards more intrauterine interventions for TAPS in recent years, eventually due to an increasing awareness on TAPS and its adverse events.[28]

A study[28] 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 in the laser group compared with 72% in the intrauterine-transfusion group and 52% in the expectant-management group ($p<0.01$).[28] The median time between diagnosis and birth was 11 weeks in the laser group compared to 5 weeks after intrauterine transfusion and 8 weeks after expectant management ($p<0.01$).[28] The study also observed a reduction of mortality and severe neonatal morbidity in the laser-treated group, but it did not reached statistic significance ($p=0,3$ and $p=0,17$, respectively).[28] Moreover, an improved outcome after laser treatment might also be the reflex of a selection bias, as laser treatment may have been performed preferably in the more favourable TAPS cases.[28]

When performing the laser treatment it is also advisable to use the Solomon technique.[4,29] See the section of "Prevention" for a detailed discussion on this subject.

Moreover, if there was any previous laser treatment (as in, by definition, in all the cases of post-laser TAPS), careful consideration should be made before attempting a new laser procedure: if the anastomoses were not visualized during a technique-appropriated first laser treatment for TTTS, it is unlikely that they will be identified any better during a second procedure.[68] However, changing the access route may be helpful, since it may be easier to visualize persisting anastomoses from a different view-point.[68] Furthermore, in a second laser-surgery there is risk of dehiscence of the amnion and of the presence of cloudy amniotic fluid.[28]

Complications after placental laser surgery are common, with PPROM being the most frequent; post-laser CAS is a major risk factor for its occurrence.[8] Disruption of the amnion (with or without perforation of the intertwin membrane) can result in pseudoamniotic constrictions on the distal extremities of one fetus, which is estimated to occur in 2% of postlaser pregnancies.[8] In TAPS, where limb occlusions without risk factors have been reported[65], this makes it even more essencial to pay attention to the limbs during ultrasound vigilance.

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] Very early cases of TAPS, which are

inaccessible to any in-utero therapy, should to be monitored before any decision is made, in order to perform the appropriate treatment at the appropriate time.[68]

- ***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 and 2; if TAPS progresses to further stages, other management options should be considered.[4] This is also a valuable treatment option in presentations after 30 weeks' gestation with a stable fetal condition.[28]

To our knowledge, in the past 5 years there have been no reports on spontaneous resolution of TAPS. Some studies[4,69] mention a 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.[28]

A big disadvantage of all invasive procedures (including intrauterine blood transfusion, laser treatment, and even selective feticide), and therefore an advantage for the expectant management, is that a hole in the amniotic membranes needs to be made to perform these interventions, which is associated with significantly increased risks of preterm prelabour rupture of the membranes, chorioamnionitis, miscarriage, or preterm delivery.[9]

One study by Baschat et al.[29] wrote the expectant management of TAPS is associated with 75% survival, while laser treatment or intrauterine transfusion is associated with 100% survival (because pregnancy prolongation to a viable gestational age is more likely), but gave absolutely no reference to these number claims.

In a literature review of 29 cases of TAPS expectant management was the choice made for 13 of the pregnancies.[15]

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

In-utero transfusions are usually carried out using leukocyte-free, irradiated, cytomegalovirus-negative, ABO type O, Rhesus-negative red cell concentrates compatible with the maternal blood group.[70] Treatment with IUT can be performed in the donor either intravascularly (in the umbilical vein of the anemic twin) or intraperitoneally.[4,70] 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.[4,29,67] This is especially important as a potential side effect of IUT treatment is worsening of the polycythemia hyperviscosity syndrome in the recipient.[4,71] Indeed, antenatally the main challenge is to cope with the polycythemic twin, rather than the anemic one.[22]

To reduce the risk of increasing polycythemia hyperviscosity, combining an IUT in the donor and iPET in the recipient can be of additional value to help decrease the viscosity of the blood of the polycythemic recipient.[4] iPET consists of, after taking a sample for the determination of hematocrit, taking 3–5 mL of fetal blood–from the umbilical vein of the recipient twin and then replace with 3–5 mL of normal saline (0.9% NaCl).[70] The goal is, at the end of the iPET, to have a target hematocrit of 50% for the polycythemic twin.[70] iPET for the recipient and IUT for donor are performed during the same procedural session, starting with the iPET.[70] They can also be done several times during the course of a pregnancy.[68,70]However, rapid recurrence of anemia following the initial transfusion might suggest a vascular pattern that allows the rapid transfer of blood between the twins, and a second transfusion would thus carry the risk of marked polycythemia with hyperviscosity in the recipient twin, without any added therapeutic benefit to the donor.[29]

Before 30 weeks of gestation, some have advocated to consider a rapid transfusion of the anemic twin to prolong gestation.[29] However, a disadvantage of choosing IUT as the first management option in TAPS cases presenting early in gestation is that a relatively large number of transfusions are needed to reach a reasonable gestational age for survival until induced (preterm) delivery.[28]

In a report of 3 cases treated with IUT+iPET, the authors believe it prolonged the pregnancies, and reinforce the importance of MCA-PSV as a clinically useful tool to monitor for progress or regression.[70] In another case report of a dichorionic triamniotic triplet pregnancy complicated by TAPS[25], an IUT allowed this pregnancy to continue for an additional 17 days, on a vital age for survival (from 28 weeks to 30+6 weeks). However, other authors say their experience suggests that IUT neither improves the condition of the affected fetuses nor allows clinically meaningful prolongation of the pregnancy.[15]

A study[71] involving a computer model simulation of IUT vs IUT+iPET showed that the addition of iPET to IUT reduces the severity of polycythemia in the recipient, supporting the claim that iPET is thus important to prevent complications of hyperviscosity.

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, which are small (residual) anastomoses[4]; nevertheless, if laser surgery is not feasible, IUT in combination with PET might be a good alternative to prolong the pregnancy while temporarily improving the condition of both twins.[28,71] IUT might be specially useful as a management option when fetoscopic 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.[67]

It is possible to combine laser surgery with IUT, as reported in a case from TAPS where the woman underwent laser surgery with the Solomon technique – even though no anastomoses between the donor and the recipient were seen during fetoscopy – followed by IUT of the donor twin.[72] The MCA-PSV in the donor twin normalized immediately after the UIT, but it took several weeks for the MCA-PSV of the recipient twin to return to normal values.

In a study by Sananès et al.[68] that primarily aimed to compare the outcome of laser or IUT therapy versus a 'non-treated group' (including cases managed in-utero with expectant management and cases only diagnosed postnatally), antenatal treatment was associated with a higher resolution rate of TAPS and a longer time between diagnosis and delivery, though at the account of a rise in PPROM; overall, there was no difference in terms of overall mortality. This is, however, a very small study (20 TAPS cases, 9 of them in the in-utero therapy group) with a rather strange group design.

- ***Pregnancy termination/delivery***

If none of the above management strategies are successful, further clinical progression then necessitates preterm delivery.[29] Indications towards delivery, taken into account the gestational age, include worrisome Doppler[22], nonreassuring fetal heart rate[15,22], severe intrauterine growth restriction[26], fetal hydropsis[26,63], fetal cardiac failure[63] or active labour.[25] In a literature review of 29 cases of TAPS, 23 of them were delivered by caesarean section.[15]

- ***Selective feticide***

Selective feticide, through umbilical cord occlusion, might be an option in severe cases of TAPS[8,68]. For instance, it has been reported in prenatally diagnosed brain lesions.[28,61]

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 been 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.[4,28] When laser treatment is not feasible and gestational age is below 30 to 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]

In one study the authors said that, once TAPS was diagnosed, inpatient management was initiated, given the rarity of this complication, the heterogeneity of the diseases and parental anxiety[22], but, to our knowledge, there are no studies on the advantages and cost-effectiveness of inpatient management in TAPS.

Postnatal management

A study[22] on perinatal outcome and management found that major neonatal morbidities were similar between the TAPS group and the control group, except for hematologic complications, which were almost ubiquitous in the TAPS group. In 55% of TAPS twin pairs (11/20), either a blood transfusion or a partial exchange transfusion was required during the first day of life. Other neonatal organ systems did not seem to be affected, but the results should be interpreted with caution since every pregnancy with single or dual fetal demise was excluded from the study.[22] In a systematic review of 28 prenatally diagnosed TAPS pregnancies[19], blood exchange was required in seven of polycythemic twins (30%) and blood transfusion was required in nine anemic twins (39%).

The first case of postnatal syngenic PET by using the polycythemic twin as a blood donor (instead of a foreign donor) for the anemic twin was successful, as reported in 2014.[69] The team made this decision because the hematocrit of the polycythemic infant (81%) was as high as that of a packed red blood cell unit (assumed hematocrit: 75%). This syngenic approach has some advantages: since they were monochorionic twins (and thus monozygotic), the donor sibling was transfused with her own blood and stem cells without any risk of rejection, the hemodynamic instability was prevented as soon as possible, and donor exposure and the risk of any blood infection was avoided.[69] Preventive measures for blood clotting and serologic screening of the donor twin for blood-transmitted infections can also be taken.[69]

Prevention

There are no known prevention measures for spontaneous TAPS, to our knowledge. However, when it comes to post-laser TAPS (which can ultimately be considered iatrogenic[29,47]), there has been some discussion on the specific techniques used on the laser

procedures for TTTS (or TAPS) that could diminish the rates of complications such as post-laser TAPS. The ideal best treatment for TTTS is fetoscopic laser coagulation, whose goal is to coagulate all anastomoses.[73] As discussed before on this paper, residual anastomoses might occur. These might cause complications such as TAPS (in 13-16% of cases of twin double survival) or recurrent TTTS (7-14%).[73] The technique on laser surgery has evolved. If in the beginning laser photocoagulation was perfomed using a laparotomy incision, soon laparoscopy was being used.[20] The first techniques aimed to coagulate any vessel crossing the intertwin membrane, but as, due to TOPS, the intertwin membrane often folds into the donor share of the placenta, more 'normal' vessels from the donor would be coagulated.[20]

These observations led to the advancement of techniques aimed at preserving donor twin placental territory.[20] The location where the abnormal vascular communications are found is often called the "vascular equator" and is identified using the fetoscope by tracing vessels from each fetus and visualizing where they terminate; vessels that leave the cord root as an artery (easily distinguish from a vein as the artery always crosses over the vein), insert into a cotyledon in the deep placenta, and then exit and return to the same fetus as a vein are considered functional and not pathologic.[20] In contrast, a vessel that travels from one fetus, inserts into a cotyledon, and then appears to exit and go to the cord root of the other fetus is considered nonfunctional and pathologic, and thus, photocoagulated.[20] This technique is usually named selective fetoscopic laser photocoagulation.

An improvement to this technique was the use of the sequential selective laser photocoagulation technique, which is, to coagulate first the AV anastomoses from the donor artery to the recipient vein; then the AV anastomoses from recipient artery to donor vein; and in the end any AA and VV anastomoses.[20] Like in the selective technique, nonpathological vessels are also spared. The theory behind this sequence is to limit hypotension in the donor fetus during laser by first interrupting the vessels from donor to recipient (e.g., donor artery to recipient vein) and then treating the rest.[20]

The most recent modification is referred as the "Solomon technique" and its randomised controlled trial was known as the "Solomon trial".[74] The Solomon technique consists of, after coagulating all the visible anastomoses, coagulating a thin line of tissue at the placental surface from one edge of the placenta to the other, to connect the white areas that resulted from coagulation of the anastomoses.[74] The purpose of coagulating along this line is to completely and physically separate the two parts of the chorionic surface of the placenta at the level of the vascular equator, including tiny anastomoses that might had not been visualised during the procedure.[74,75]

The Solomon trial reported less cases of TAPS and recurrent TTTS in the Solomon group compared to the control group, and, as the Solomon technique did not seem to be associated with an increase in any identifiable adverse effect or complication, it was suggested that the procedure with Solomon technique was at least as safe as the procedure without it.[74] Another analysis from the same authors[73] aimed to study the number and characteristics of residual anastomoses in placentas included in the Solomon trial, and concluded that the percentage of placentas with residual anastomoses in the Solomon group and control group was 19% (14/74) and 34%, respectively (p=0,04). Moreover, in the cases where the surgeons had considered the laser photocoagulation to be "complete", the percentage of placentas with residual anastomoses was 12% in the Solomon group and 32% in the control group, but the diameter of the residual anastomoses in the Solomon group was significantly higher.[73] The risk of TAPS in the group with residual anastomoses was 21% (3/14) in the Solomon group and 62% (16/26) in the standard group (p=0,02).[73] Interestingly, the risk of TAPS or recurrent TTTS was lower in the Solomon group with residual anastomoses compared with the control group with residual anastomoses (29% vs 73%, respectively), which could be explained by a trend towards higher rates of residual arterioarterial anastomoses in the Solomon group, thought to be protective of the development of TAPS or TTTS.[73] The study also states that the main reason for residual anastomoses in the Solomon group was the fact that the laser-line along the vascular equator was not continuous, and in 8 placentas in which the procedure was deemed as "complete" by the surgeons the residual anastomoses were spread along the vascular equator.[73] A possible explanation could be that the energy used to coagulate the surface of the placenta was not always sufficient for the desired coagulation; however, too much energy would cause too much tissue damage, so more studies on the subject are needed.[73]

A retrospective study[75] comparing the standard selective laser coagulation group (control group) with the ones who also underwent the Solomon technique (Solomon group) found that the Solomon group had a significantly higher survival rate for both twins (84.6 vs 46.1%; p<0,01) and a higher overall neonatal survival rate (45/52 (86.5%) vs 94/152 (61.8%); p< 0,01). Another study[30] on the Solomon technique suggested its use to be associated with significantly lower recurrence of TTTS (3,9% vs 8,5%), twin anemia polycythemia sequence (2,6% vs 4,2%), and amniotic fluid abnormalities (0% vs 5,6%); double survival at 6 months of age was also significantly higher with the Solomon tecnnique. They noted that Solomon technique specifically abolished amniotic fluid discrepancies, and proposed that eventually the closure of microanastomoses or creation of a dead placental zone could have decreased intertwin transfer of vasoactive substances that are important in the evolution of TTTS.[30]

Although the previous mentioned retrospective studies[30,75] only included surgeons with some experience in the procedure, the improvement of complication rates observed could be due to the increased experience with fetoscopic laser in general and not specifically due to the use of the Solomon technique.[21]

A systematic review[76] included the three above mentioned studies[30,74,75] about the Solomon technique and concluded that the Solomon technique is certainly equivalent to, and has some advantages over, the standard selective technique, with no increase in other adverse events, and is thus recommendable. Another review study[29] also recommended to adopt the Salomon technique, unless the treatment center has a recurrence rate of TTTS and TAPS that is significantly below the international average.

The surviving children who were included in the Solomon Trial were subjected to a study concerning their neurodevelopment outcome at 2 years-old and no difference in survival without neurological impairment was found between the Solomon and standard laser technique (11% and 9%, p=0,61).[77] This negligible effect on longterm outcome could be due to small sample size and statistic power, effective treatment of short-term complications (such as recurrent TTTS or TAPS) from the standard laser technique, or bias caused by the neonatal withdraw of care due to severe brain injury. Due to the reduction of short-term complications and the absence of increased adverse long-term effects, the authors recommend the use of the Solomon technique in the treatment of TTTS.[77]

The diameter of the cannula used in the procedure also seems to have an impact on the success of the procedure, with the use of 10 and 12 Fr cannulas (and their corresponding fetoscopes) being associated with less cases of TAPS and recurrent TTTS, as well as lower rates of residual anatomoses.[78]

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 Doppler ultrasound measurements of the MCA-PSV, as well as measurements of amniotic fluid volumes of both twins still remains crucial.[8,21,73] A literature review found that TAPS may occur at any time after laser surgery, with reported interval ranging from 1,2 to 11,2 weeks.[15]

On another perspective, postnatal complications of TAPS could theoretically be prevented, or at least mitigated, with appropriate timing of cord clamping, given its importance on hemoglobin values at birth.[51] 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.[51] More research is needed on this topic.

Prognosis

- *Prenatal*

A review of 28 prenatally diagnosed TAPS pregnancies[19] found that diagnosis from 15 to 23 weeks of gestation and active treatment in-utero were associated with the highest mean levels of hemoglobin in anemic twins (p=0,021), the lowest levels in polycythemic twins (p=0,025), and the lowest frequency of postnatal procedures (p<0,001). The survival rate was independent of gestational age at diagnosis and prenatal therapy. This is because a diagnosis of TAPS made at >29 weeks was more likely to be conservatively managed than with earlier diagnosis, but postnatal procedures were more frequently performed.[19] Twins with TAPS following twin-to-twin transfusion received in-utero therapy more frequently than spontaneous TAPS twins (p=0,030) and required a postnatal procedure less often (p<0,001).

- *Postnatal*

  - **Short-term outcome**

A literature review of TAPS cases[15] reunited 29 cases of TAPS (14 spontaneous, 15 post-laser) and stated that perinatal death was reported in 19% of the 58 newborns (4 with spontaneous TAPS and 7 in post laser group). 5,2% of the children (all spontaneous TAPS) developed intraventricular haemorrhage and one developed cerebral damage (in the post-laser TAPS group). In 70% of cases (40/58, 20 in spontaneous TAPS group, 20 in post-laser group) there was survival to discharge without significant complications.

In a systematic review of 28 prenatally diagnosed TAPS pregnancies[19], the overall survival rate was 82% (46/56); of these survivors, 50% (23/46) were the anemic twin and 50% were the polycythemic twin. For each twin set, there were no survivors in 3% of pregnancies. Neonatal morbidity affected five newborns (9%) and was represented by thrombocytopenia, neurologic disease, skin necrosis, mild hypotonia, and respiratory distress. In two cases, neonatal morbidity was fatal.[19]

  - **Long-term outcome**

Long-term outcome in surviving twins is not yet very well studied, due to the relatively new discovery of this pathology and scarce data.

A study evaluated the long-term neurodevelopmental outcome in children who had had post-laser TAPS.[79] In 53 survivals of post-laser TAPS, follow-up assessments were made to 47 children when they were at least 24 months old. Neurodevelopmental impairment was detected in 9% and at least mild-to-moderate cognitive delay was detected in 17% of the

children (both with no differences between donors and recipients), which is within the range of the incidence of neurodevelopmental impairment reported in case series of TTTS treated with laser.[79] Risk factors for low cognitive scores were low gestational age at birth (p=0,02) and low birth weight (p<0,01). Of the children in which it could be assessed, there was mild-to-moderate motor delay in five children (19%) and severe motor delay in one child (2%). There was also a diagnosis of one cerebral palsy (2%) and severe cognitive delay in 2 children (4%). Mild-to-moderate cognitive delay was detected in 8/47 (17%) and mild-to-moderate motor delay in five (19%) children in whom it could be assessed. In a analysis of antenatally detected/managed TAPS cases, the subgroup treated with IUT had the lowest median cognitive score, possibly because these cases were born at a lower gestational age of 29 weeks (due to induced labour or planned caesarean section for severe anemia or polycythemia).[79] The small sample of this study reinforces the need to further research on the area.[79]

A study aimed to review long-term cardiovascular and neurodevelopmental sequelae after IUT treatment, whether it was made for TAPS or for other indications.[80] As far as TAPS is concerned, they suggested cerebral injury (in the anemic or in the polycythemic twin) in TAPS cases treated with or without IUT is more common than initially thought, and reinforced the need of more studies on the subject.

Discussion and conclusions

TAPS is a pathology exclusive to monochorionic pregnancies, characterised by a striking difference of haemoglobin values between two foetuses: 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 diagnosis 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 foetuses. The value most used in the last 5 years literature is 1,5 MoM MCA-PSV for the anemic twin and 1,0 MoM MCA-PSV for the polycythemic twin (frequently 0,8 MoM in more restrictive criteria), but recently it has been noted that the difference between the twins' MCA-PSV might be a better diagnosis criteria. 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, but still often ignored, criterion for the prenatal diagnosis of TAPS. Postnatally, differences on hematocrit between the two newborns are essential for the diagnosis: a cut-off of >8 g/dl is the most widely used on recent literature. Moreover, to differentiate TAPS from pathology such as acute TTTS, other criteria have been proposed: a reticulocyte count ratio >1,7 or placental examinations revealing the presence of small AV anastomoses. How small these anastomoses are is also not completely unanimous, as most papers quote a limit of <1 mm (based on a review paper by the Leiden group, the biggest research group on TAPS) but in our five years' literature review the only study we found on the subject claimed that the mean diameter of the AV anastomoses in TAPS was 2,26 mm. This discrepancy might eventually be due to slightly different methods of measurement of the anastomoses, and caution is recommended on excluding suspected cases of TAPS solely because the diameter of AV anastomoses is slightly above 1mm. More recently, a third additional criterion has been proposed: the colour difference on the maternal side of the placenta between the anemic twin part (seen as pale) and the polycythemic part of the placenta (dark red). An objective quantitative cut-off for this discrepancy is still on discussion.

TAPS and TTTS are by definition separate entities (though some literature does not support this claim), but it is up to discussion whether there are some cases that are somehow in a spectrum between this two pathologies. The idea that TTTS might be only a prior stage from TAPS (i.e. that TTTS and TAPS would be a single entity that occur in sequence) is a

hypothesis that is not supported by cases reports and that contradicts all the studies about the placental anastomoses differences of TAPS and TTTS and normal MC pregnancies that we have discussed in detail.

Prevention of spontaneous TAPS is unknown, but advances on the laser surgery technique for TTTS – the Solomon technique, where a coagulation line of tissue at the placental surface from one edge of the placenta to the other is made at the end of the surgery – have been shown to decrease the rates of recurrent TTTS and TAPS, with no rise on complications on short or long term, and is thus nowadays recommended. After laser surgery for TTTS, follow-up evaluation with echographic measurement of MCA-PSV and amniotic fluid values is essential for early recognition of TAPS (or recurrent TTTS) and consequent management.

It is clear that 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, as the knowledge about this pathology and its management develops, it is recommended to measure MCA-PSV in all MC pregnancies, at least from 20 weeks onward, and at least every two weeks.

Prenatal and postnatal staging of TAPS has been proposed, but more research is needed to understand if this classification is helpful for management and prognosis.

Prenatal complications include prenatal brain injury, prenatal limb occlusion, fetal hydropsis, cardiac descompensation and fetal death. Postnatal complications include persistence of prenatal existing injuries, complications related to prematurity and, specially, haematological complications caused by the anemia and polycythemia. Short-term renal impairment has also been described.

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. Other prenatal management options include expectant management, intrauterine transfusion (to the anemic twin) with or without further partial exchange transfusion (for the polycythemic twin – suggested to improve the outcome of intrauterine transfusion), termination of pregnancy/delivery or selective feticide. Expectant management is more common in less advanced cases of TAPS. Moreover, as the awareness about this condition and its complications grows and management options advance, there seems to be a growing tendency towards more interventive measures, with special emphasis on laser surgery. A fluxogram of management has been proposed, but more research is needed to see whether it has any clinical value.

Postnatally, management of the hematological complications commonly includes blood transfusion for the anemic twin and partial exchange transfusion for the polycythemic twin. A synergetic transfusion of blood between the polycythemic and the anemic twin has already been described.

Prognosis and outcome are especially difficult to measure due to the accumulating differences on diagnosis, management and outcome criteria spread across literature. Long term studies are especially scarce – and perhaps the most important, as long term survival without severe morbidity is the ultimate goal of fetal medicine.

As a rare and newly described pathology, further research on TAPS, especially involving a big number of cases, is essential to increase sample size and the quality of the studies. To help this, the Leiden group (the most active research group on TAPS) has recently created a web-based registry of TAPS cases (https://www.tapsregistry.org) to gather information on short and long term outcome in TAPS, and allow future better study designs for the management of this condition.

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"Ninguém faz um curso de Medicina sozinho."
[popular saying]

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