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Twin Anemia-Polycythemia Sequence (TAPS): From basic research to clinical practice

Joana Patrícia da Silva Rocha

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Twin Anemia-Polycythemia Sequence (TAPS): From Basic Research to Clinical Practice

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

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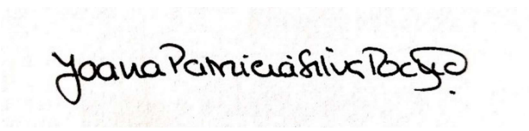
Estudante:



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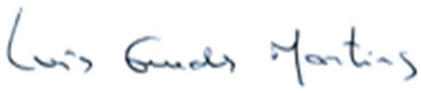

Dedicatória

À minha família, namorado e amigos pelo amor, força e apoio incondicional que me deram ao longo de todo o meu percurso.

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Resumo

A gravidez gemelar está associada a um risco acrescido de complicações perinatais e maternas, e o estabelecimento precoce do tipo de corionicidade define o perfil de risco. Nas gestações monocoriónicas (MC), os fetos partilham a mesma massa placentária e exibem anastomoses vasculares que ocorrem na superfície da placenta e na profundidade ao nível das vilosidades, sendo que a combinação e padrão das anastomoses determina o quadro clínico primário e a ocorrência de complicações futuras.

A sequência anemia-policitemia (SAP) foi descrita pela primeira vez em 2006, na sequência de avaliações efetuadas após cirurgia laser fetoscópica realizada para tratamento da sequência oligohidrâmnios-polihidrâmnios crónica, e em 2007, foram relatados os primeiros casos espontâneos, definindo a SAP como uma entidade vascular reconhecida como um dos síndromes de transfusão-fetal. Existem 2 subtipos de SAP: a forma espontânea (3-5%) ou iatrogénica (2-16%). Na SAP identificam-se anastomoses arterio-venosas de diâmetro muito pequeno (< 1 mm) e raras anastomoses arterio-arteriais (AA), de pequeno calibre, na ausência de discordância do volume de líquido amniótico. Existem critérios de diagnóstico pré e pós-natais que têm evoluído progressivamente ao longo do tempo. Foram propostos novos marcadores secundários adicionais cuja fiabilidade está a ser estudada. O melhor protocolo de rastreio de SAP em gémeos monocoriónicos ainda é uma questão de debate.

Esta revisão fornece um levantamento da literatura relevante sobre a epidemiologia, patofisiologia vascular, fatores hemodinâmicos e moleculares subjacentes que regulam as anastomoses vasculares, e critérios de diagnóstico desta doença, visando assim aumentar a sensibilização e o conhecimento sobre esta patologia recentemente identificada e frequentemente não reconhecida e mal diagnosticada.

Palavras-chave: Gravidez Gemelar, Gravidez monocoriónica, Sequência Anemia-Policitemia, Síndromes de Transfusão Feto-fetal, Sequência Oligohidrâmnios-Polihidrâmnios

Abstract

Twin pregnancy is associated with an increased risk of perinatal and maternal complications, and early establishment of the chorionicity type defines this risk profile. In monochorionic pregnancies, the fetuses share the same placental mass and exhibit vascular anastomoses crossing the intertwin membrane, and the combination and pattern of anastomoses determines the primary clinical picture and occurrence of future complications.

Twin Anemia-Polycythemia Sequence (TAPS) was first described in 2006 after a fetoscopic laser surgery in t*win-to-twin transfusion syndrome (*TTTS) twins, and in 2007, the first spontaneous cases were reported, recognizing TAPS as an individualized vascular identity in fetofetal transfusion syndromes. There are two types of TAPS: spontaneous (3-5%) and iatrogenic or postlaser (2-16%). TAPS consists of very small diameter arteriovenous anastomoses (< 1 mm) and low-rate, small-caliber arterioarterial (AA) anastomoses in the absence of amniotic fluid discordances. There are certain antenatal and postnatal diagnostic criteria, which have progressively evolved over time. New, additional secondary markers have been proposed, and their reliability is being studied. The best screening protocol for TAPS in MC twins is still a matter of debate.

This review provides a survey of the relevant literature on the epidemiology, vascular pathophysiology, underlying hemodynamic factors that regulate mismatched vascular connections, and diagnostic criteria of this disease and aims to increase the awareness of and knowledge about this recently identified and frequently unrecognized and misdiagnosed pathology.

Keywords: *Twin pregnancy, Monochorionic twins, Twin anemia polycythemia sequence, Fetofetal transfusion, Twin-to-twin transfusion syndrome, Twin oligohydramnios-polyhydramnios sequence*

Lista de Abreviaturas

Δ MCA-PSV, difference between Middle Cerebral Artery – Peak Systolic Velocity of Both Twins

AA, Arterioarterial

ACE2, Angiotensin-converting enzyme 2

Ang, Angiopoietin

ANG, Angiotensin

ARC, Absolute Reticulocyte Count

AV, Arteriovenous

CDR, Color Difference Ratio

Hb, Hemoglobin

LC3, Protein IA/IB Light Chain 3

MC, Monochorionic

MCA-PSV, Middle Cerebral Artery – Peak Systolic Velocity

MCDA, Monochorionic Diamniotic

MCMA, Monochorionic-monoamniotic

MoM, Multiples of the Median

MVP, Maximum Vertical Pocket

NO, Nitric Oxide

PE, PreEclampsia

PlGF, Placental Growth Factor

RASs, Renin-Angiotensin Systems

sFlt-1, soluble Form of Flt-1

TAPS, Twin Anemia-Polycythemia Sequence

TOPS, Twin Oligo-Polyhydramnios Sequence

TRAP, Twin Reversed Arterial Perfusion Sequence

TTTS, Twin-To-Twin Transfusion Syndrome

UA, Umbilical Artery

VEGFs, Vascular Endothelial Growth Factors

VV, Venovenous

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1. Introduction

Multiple gestation accounts for 2-4% of all live births [1,2], and its incidence has been increasing over the last four decades. [1,3,4] Twin pregnancy is associated with an increased risk of perinatal and maternal complications. [1,2,5] Early establishment of the chorionicity type defines the risk profile of the pregnancy and helps to estimate the possible future complications that may occur during gestation. [6] In monochorionic pregnancies, the two fetuses share the same placental mass and exhibit intertwin vascular anastomoses crossing the intertwin membrane, which could be associated with a 3- to 10-fold higher morbidity and mortality compared to that of dichorionic pregnancies. [1,7–11] Although intertwin anastomoses are a feature present in nearly all monochorionic placentas, it is the site, size, type and combination of anastomoses that determines the primary clinical picture. [9,10] In most cases, the intertwin blood transfers are balanced. [12] However, when imbalanced blood flow (with transfers of blood and, most likely, of numerous regulating factors) occurs and there is an asymmetry of the vascular communications between the two fetal circulations, this may lead to several complications, such as the classic "twin-to-twin transfusion syndrome" (TTTS) or twin oligohydramnios-polyhydramnios sequence (TOPS), twin anemia-polycythemia sequence (TAPS), and twin reversed arterial perfusion sequence (TRAP), whose epidemiology, pathophysiology and diagnosis criteria are briefly presented in *Table **1***. [3,5,16,6–8,10,12–15]

The first historical evidence suggesting the finding of "passing vessels in twin placentas" goes back to a study conducted in 1687 by Van Der Wiel. [17] In 1870, Hyrtl produced an atlas of injected twin placentas that demonstrated the existence of deep and superficial anastomoses. [17] However, only in 1875 did Schatz recognize the importance of these structures, finding that these vascular anastomoses only occurred in twins commonly referred to as "identical" and suggesting the concept of an active "hydraulic system" of the interfetal circulation. [10,17,18] During the 1920s, *Mutel* and *Vermelin* identified variable depths of anastomoses and reported that deep anastomoses caused an imbalance between the arterial and venous flow, and the superficial anastomoses were responsible for maintaining equal pressures between the two circulations. [17] *De Camillis* and *Tammeo* injected radiopaque dye into the vasculature of twin placentae and studied the number, volume, position, and nature of the anastomoses via X-ray in 1948. [17] Since then, numerous articles concerning the types of anastomoses, their frequencies and their effects on twins have been published. Using color dye injection, placental studies performed in monochorionic placentas have demonstrated three main types of anastomoses: arterioarterial (AA), venovenous (VV) or arteriovenous (AV). [3,5,16,19,6–8,10,12–15]

TAPS is a recently recognized clinical identity of a chronic, unbalanced fetofetal transfusion characterized by the presence of a large intertwin difference in hemoglobin and reticulocyte levels, with anemia in the donor and polycythemia in the recipient, in the absence of discordances in amniotic fluid levels. [9,16,20] The placentas of monochorionic pregnancies complicated with TAPS have an angioarchitecture quite distinct from those seen in uncomplicated monochorionic placentas.[21] The presence of only small and few unidirectional anastomoses supports the fact that this entity has a distinct pathophysiology from other fetal transfusion syndromes and, moreover, makes the application and performance of laser treatment quite challenging. [21]

The main prenatal diagnostic or screening tool for TAPS is Doppler measurement of the peak systolic velocity in the middle cerebral artery (MCA-PSV), which is a noninvasive standard test currently accessible for assessing the existence of fetal anemia present in a wide variety of pathologies. [16,22–27]

TAPS can still remain undetectable during pregnancy (especially when Doppler measurements are not performed), which can result in healthy neonates with no major comorbidities other than large hemoglobin discordances, or, on the other side of the spectrum, TAPS can lead to fetal death of both twins, particularly if not properly addressed and treated. [20] Approximately 40-63% of diagnoses of TAPS are not made prenatally but are only verified at birth; therefore, postnatal diagnostic criteria have also been proposed. [8,16,23]

Thus, the purpose of this narrative review is to compile relevant information from the current literature on the epidemiology, pathophysiology and angioarchitecture of the placenta and the prenatal and postnatal diagnostic criteria of TAPS.

2. Methods

To compose this review, a thorough literature search was repeatedly conducted in PubMed and Medline between July 2021 and March 2022, with a limitation of articles written in the English language. This literature review includes relevant articles from 1971 to 2021. The search terms used were *twin pregnancy, monochorionic twins, twin anemia polycythemia sequence, fetofetal transfusion, twin-to-twin transfusion syndrome, and twin oligohydramnios-polyhydramnios sequence*. Additionally, the references of all analyzed studies were searched to obtain necessary information. *Figure* 1 represents the flowchart of the search and selection process for the elaboration of this review.

3. Epidemiology

The copresence of an anemic and a polycythemic neonate in twin pregnancy was reported back in the 17th century (18), but it was not recognized as TAPS until the 21st century. (28,29) TAPS was first described in 2006 by Robyr et al (30), who reported cases that developed in a subgroup of twins with TTTS who had been treated with fetoscopic laser surgery. (7,16,30,31) Later in 2007, Lopriore et al. (28) reported the first cases of spontaneous TAPS, as well as the acronym, and a proposal of the pathophysiological process of the disease, based on the presence of tiny placental anastomoses that allowed slow transfusion. (7,16,23,31,32)

There are two subtypes of TAPS: the spontaneous form, which complicates up to 3-5% of monochorionic pregnancies (and typically presents after 26 weeks), and the iatrogenic form, with variable incidence (2-16%), which is a possible complication resulting from incomplete laser surgery treatments performed to treat chronic oligohydramnios-polyhydramnios sequence and arises from the presence of residual anastomoses present after the intervention. [6,9,35–42,11,16,20,21,30,31,33,34] TAPS can be erroneously discredited if we consider that only 3.5/1000 twin pregnancies are monozygotic, and only 70% of these pregnancies are monochorionic.[31] However, once a woman is diagnosed with a monochorionic pregnancy, her risks of TTTS, congenital anomalies and TAPS are no longer uncommon. [31] Up to 6% of monochorionic pregnancies can develop spontaneous TAPS, which represents 1 in 16 monochorionic pregnancies that may be affected by pathology with severe implications that may even culminate in fetal death. [6,8,9,16,20,21,31,33,34,43]

The existence of a wide spectrum of incidence may result from differences between laser surgical techniques, color dye placental injection techniques, differences in classification systems, or the existence of selection bias. [6,20,29,44] The more restrictive the diagnostic criteria that are applied, the lower is the incidence of TAPS. [20] By applying Solomon's technique, instead of a selective approach, in the treatment of TTTS, it is possible to reduce the incidence of iatrogenic TAPS from 16% to approximately 3%. [27,33,37,38] According to *Tollenaar et al*.[45], 81% of surgeons initially considered that the laser surgery was complete; however, approximately one-third of iatrogenic TAPS cases were TTTS treated with Solomon's technique, and although this technique has been proven to reduce the incidence of TAPS, it does not prevent its later development, which suggests that a “low index of clinical suspicion” can cause TAPS to occur unexpectedly and shows that operator-reported completeness cannot be relied upon.[36,38,45,46] Consequently, the International Society of Ultrasound in Obstetric and Gynecologic and several studies advocate that routine MCA-PSV Doppler follow-up should be performed in TTTS twins

treated with laser surgery throughout pregnancy to check for the presence of postlaser TAPS. [24,29,31,45,47]

4. Pathophysiology

4.1. Vascular anatomy in the monochorionic placenta

Almost every monochorionic (MC) placenta has vascular connections or anastomoses, and the adequate development of the chorionic vascular network of each twin individual placental circulation allows efficient fetomaternal exchange.[4,5,48–51] In the angioarchitecture of uncomplicated monochorionic placentas, there are often large-caliber anastomoses connecting the placental circulations of both twins, and blood flow transfers between them remain balanced; therefore, most MC pregnancies proceed well without complications. [5,6,16,52]

The fetal umbilical arteries branch into the chorionic arteries and course the placental surface in variable distribution patterns, with variable distances from the cord insertion site; then, they penetrate the chorionic plate perpendicularly toward the maternal surface. [50] The individual arteries supply the corresponding cotyledons and become terminal villous capillaries, which represent the site of fetomaternal exchange.[50] The capillary loops return the blood from the cotyledon to the umbilical cord by venules that progressively merge into larger-sized villous and chorionic veins. [50] On the surface of the chorionic plate, chorionic arteries can be distinguished from chorionic veins by their near-universal tendency to crossover the corresponding vein, and the chorionic artery and vein of each cotyledon exist in a 1:1 paired relationship. [50,53]

Generally, the key placental characteristics can be identified by simple gross examination of the noninjected placenta. [4] However, in selected cases, particularly when it is necessary to achieve an accurate delineation and categorization of smaller vessels, dye-based vascular injection studies may be necessary. [4,54,55]

In addition to evaluating intertwin vascular communications, it is possible to study the characteristics of vascular distribution patterns of individual monochorionic diamniotic (MCDA) twins. [56] The chorionic vascular patterns can be traditionally described as dispersed, magistral or mixed. [53,56,57] The ‘‘dispersed’’ or dichotomous pattern is characterized by a superficial fine network of regular vessels, with near-symmetric dichotomous branching out from the cord insertion to the various placental cotyledons, with progressive diminution of the vascular caliber.[53,56] The ‘‘magistral’’ or monopodial pattern has arteries of a relatively uniform and large

size that course across the placental surface nearly to the periphery without diminishing in diameter. [53,56,57] The ”mixed” vascular distribution consists of the combination of the two patterns without a predominant one. [56] De *Paepe et al*. [56] determined that the prevalence of magistral and mixed vascular types in MCDA placentas was higher than that previously reported for singletons (47% versus 38%). [56] The magistral/mixed vascular distribution pattern is associated with the presence of marginal/velamentous cord insertion, a lower number of intertwin anastomoses, uneven distribution of the vascular territories, and consequently, an increased risk of complications in MC pregnancies. [53,56]

Postdelivery placental examination injection studies have shown that vascular anastomoses may be located superficially (visible on the surface of the chorionic plate) or deeply (occurring at the capillary level within a shared placental lobule) within the placental mass, and there are three main types of anastomoses described: arterioarterial (AA), arteriovenous (AV) or venovenous (VV). [5,48,49,53,58] In noncomplicated MC placentas, the total number of vascular anastomoses varies in different studies from 2 to 7 (which may be due to the use of different techniques of placental examination), and the mean number of vascular anastomoses per placenta that has been reported is 8.3±5.2. [49,52] Ninety percent of monochorionic placentas have a combination of the three main types of anastomoses; in 5% of monochorionic placentas, there are only AV anastomoses present, and in the remaining 5%, there are no visible anastomoses. [14]

AV anastomoses are present in 95-99% of monochorionic pregnancies, are obligatorily unidirectional and occur deep within the parenchyma at the villous capillary level. [1,3,49,52,53,58,59,5–8,13–16] They are recognized on the chorionic surface by penetration of the chorionic plate of an unpaired artery of one twin, in close proximity (<0,5 cm) to an unpaired vein of the opposite twin (“nose-to-nose” contact), which supplies the underlying shared placental lobule. [1,3,59,60,5–8,13–16] In addition to the superficially detectable AV anastomoses, there are true deep/“hidden” AV anastomoses with an exclusively deep parenchymal course that have been documented by special placental casting techniques. These profound AV anastomoses may occur in more than half of monochorionic placentas; they are very small and are not believed to have hemodynamic consequences. [53] However, when flow through AV anastomoses is unbalanced, without compensation of bidirectional superficial anastomoses, they are responsible for the occurrence of the main complications of MC pregnancies. [5,33,48,49,53,56,60,61] Since these anastomoses are deep and are located inside the placental mass, it is difficult to evaluate their exact number, even under direct fetoscopic vision, which can explain some of the therapeutic failures observed with laser coagulation. [5,14,46]

AA and VV anastomoses are usually superficial, bidirectional, and form direct communications between the arteries or the veins from the two fetal circulations, hence allowing flow in either direction, according to interfetal vascular pressure gradients in a balanced manner.[5,6,60–62,7,13,14,16,23,49,56,59] However, in rare cases, superficial anastomoses can act as a functional AV when a disturbance in vascular pressures or vascular blockage results in unidirectional flow.[33,48]

Generally, due to the characteristics of AA anastomoses and their (20-times) lower resistance compared to AV anastomoses, they have the capacity to compensate for any imbalanced flow, and they seem to be associated with a protective effect against many of the complications of monochorionic pregnancies. [5,14,64,33,52,53,56,58–60,63] Their frequency is variable, but they are usually present in 85-91% of MC placentas. [5,49,52] Seventy-five percent of AA anastomoses can be detected antenatally using Doppler ultrasound imaging studies, as they demonstrate typical bidirectional pulsatile spectral Doppler waveforms, where there are cyclic changes in systolic velocities together with the intermittent reversal of end-diastolic velocities. [5,13,14,65] This typical wave pattern results from the combination of two pulsatile waves of blood flow with opposite directions and different velocities and frequencies. [5,13]

VV anastomosis is the rarest of the three types and is only present in one quarter (25-28%) of MC placentas. [5,14,49,52] In the absence of VV anastomoses, each twin has its own placental territory defined by the venous vessels that drain oxygen-rich blood back to its owner, but in the presence of these anastomoses, there is no longer an individual but rather a common flexible venous drainage area. [14] Their clinical significance is still inconclusive and controversial. [5,14,33,48,52,53] The venous vessels, due to their lower pressure compared with arterial vessels, may be more influenced by external factors (such as the fetal position), which can cause them to act as functional AV anastomoses and therefore be associated with an increased risk of developing complications in MC pregnancies, especially in the absence of AA anastomoses. [33,66]

Monochorionic-monoamniotic (MCMA) placentas have a higher number of AA anastomoses (usually such that have a large diameter and are presented between the 2 umbilical cord circulations), a lower number of AV anastomoses and a similar number of VV anastomoses compared with monochorionic-diamniotic (MCDA) placentas. [5]

4.2. Vascular anatomy in TAPS

The typical angioarchitectural pattern associated with TAPS consists of very small diameter arteriovenous anastomoses (< 1 mm), which allow a unidirectional, slow (5-15 ml/24

hours) and chronic well-compensated fetofetal transfusion. [9,16,68,20,21,32–34,51,52,67] It is believed that the absence of amniotic fluid discordances in TAPS may be due to the slow chronic character of the intertwin blood transfusion, which does not cause a hormonal imbalance, since it allows hemodynamic compensatory mechanisms to take place. [9,20,21,51,64]

Furthermore, the mean number of AV anastomoses (3-4) is lower than what is verified in uncomplicated monochorionic placentas and from those complicated with other fetofetal transfusion syndromes. [21,23,33,34,52,54,67,69]

Bidirectional AA anastomoses are also less frequent in TAPS placentas (even less frequent in the iatrogenic form) than in uncomplicated MC pregnancies; they are present in 11-20% of cases and have a reduced caliber (<1 mm) [5,16,71,20,21,23,33,34,52,64,70] According to Poiseuille's law, blood flow resistance depends linearly upon the viscosity and length of a vessel but is inversely proportional to the fourth power upon the radius. [67] The low rate and small caliber of AA anastomoses may thus have a high flow resistance, consequently inadequately compensating for any flow imbalance caused by AV anastomoses and thus failing to prevent the development of TAPS. [21,52,64,67] VV anastomoses are even less common in TAPS placentas, having only been detected in 7% of iatrogenic cases, and no cases have been reported in the spontaneous form. [16,33]

There are also differences between the angioarchitecture of placentas with spontaneous TAPS and those with iatrogenic TAPS, namely, regarding the mean number of anastomoses and their locations. [16,23,33,61] The spontaneous form displays a greater number of total anastomoses (mean of 4 vs. 2 in the iatrogenic form) and more compensating AV or AA anastomoses, which are located alongside the entire vascular equator and at the margins of the placenta. [16,23,33,61] In the postlaser form, there may be only one tiny (< 1 mm) residual AV anastomosis (without compensating AA or VV anastomoses), which is probably located at the margin or in the depth of the placenta, where they are easily missed. [5,16,19,21,33,45,61,69]

In uncomplicated monochorionic pregnancies, the individual proportion of placental territory correlates with fetal growth, and generally, the larger the corresponding placental area, the greater the newborn weight. [72] In spontaneous TAPS, this rule does not seem to be applied, since the donor usually has the lowest weight (90% of the cases) but, paradoxically, generally has the largest placental sharing area (65%) compared to the recipient. [16,21,23,33,72,73] This finding occurs only in TAPS twins, and its cause is still unknown. [16,21,72] The existence of chronic hypoxia and nutritional depletion (hypoalbuminemia and hypoproteinemia) seen in the donor, caused by the placental share discordance between twins, may theoretically stimulate compensatory

placental expansion to increase the nutritional and oxygen supply. [21,72] However, it has been theorized that these stimuli would not be able to promote growth in the donor since its placental insufficiency limits growth and that, therefore, these stimuli would be transferred to the recipient through vascular anastomoses, resulting in its increased development since its placental function is not impaired.[21,72] This process is called the "growth factor sequence" and may play a role in the development of TAPS, although this has not been proven. [21] Another, most plausible, explanation may come from selection bias, since the placentas studied are always from fetuses with TAPS that were born (since those who die in utero have a damaged placenta, making it impossible to calculate the placental territory area and hemoglobin levels). [72]

It has been reported that in some atypical cases of TAPS, only a tiny AA or VV anastomosis was detected (although their bidirectional character), which suggests that under certain conditions, they may act like unidirectional AVs. [41,47] *Tollenaar et al.* [47] also verified 7 cases of TAPS without any evident placental anastomoses, and in 3 of these, the TAPS resolved spontaneously (possibly due to spontaneous thrombosis of the AV anastomoses), while the others were probably caused by hidden deep anastomoses or by tiny anastomoses that were not seen by suboptimal color-dye injection techniques, which in TAPS is often technically more challenging. [45,47] Monoamniotic twins usually have proximate cord insertions connected by large intertwin anastomoses, and therefore, it seemed virtually impossible for TAPS to develop in this type of gestation. [33,52,74] However, one case of TAPS in monoamniotic twins that was subsequently treated with laser surgery was reported, and during the procedure, the absence of large anastomoses and the presence of only very thin AV anastomoses were confirmed. [33,74]

The incidence of velamentous cord insertion and TAPS was similar to that in normal MC pregnancies; nonetheless, in a larger series, there was a tendency toward a lower incidence of velamentous cord insertion in TAPS. [33,52] Another striking feature of TAPS placentas is the color difference on the maternal side, with a very pale placental area belonging to the donor/anemic twin and an extremely dark red placental share belonging to the receptor/polycythemic twin. [33,52]

In sum, TAPS placentas have a unique angioarchitecture, clearly distinct from that of noncomplicated monochorionic pregnancies, and the main characteristics are their minuscule size, their small number of AV anastomoses and their deficiency or (when present) low rate and small caliber of AA anastomoses, which tend to be localized near the margin of the placenta [52,75]

4.3. Molecular changes

The correct development of the fetal vascular tree is crucial for the development of an efficient fetomaternal exchange; however, it is remarkable how little is known about the factors regulating the growth and development of the chorionic surface vessels. [50] Genetic, mechanical (hemodynamic) and trophic factors are considered to play a role, yet the exact mechanisms that regulate these underlying vascular phenomena remain unknown. [50] The understanding of uteroplacental (decidual and villous capillary) vasculogenic and angiogenesis regulation is increasing, but knowledge about the regulation of fetoplacental (umbilical and chorionic) angiogenesis remains limited. [56]

Fetal–placental circulation is established approximately between 6 and 7 weeks post-conception (p.c.) through the connecting stalk, which later becomes the umbilical cord. [76] The cotyledons represent an anatomic unit and a closed chorionic villous system that contains fetal blood and are separated by the placental septa (partitions of maternal decidua covered by a trophoblastic layer). [76] The fetal capillary blood is separated from the maternal blood by a thin vasculosyncytial membrane, wherein the capillary membrane is surrounded by the thinned syncytiotrophoblast membrane. [76] Deoxygenated blood is delivered from the fetus to the placenta through paired umbilical arteries from which eight chorionic arteries originate and traverse the fetal plate crossing over the chorionic veins, which are responsible for delivering richly oxygenated blood to the fetus. [76]

Placental vasculature development is accomplished by two distinct mechanisms: vasculogenesis – the formation of new blood vessels from mesodermal-derived hemangioblastic stem cells that can be detected up to the 10–12th week of gestation; and angiogenesis - the formation of blood vessels from existing vessels that occurs between Day 32 (p.c.) and the 24th week, first with branching angiogenesis (expansion of the placental vascular system) followed by nonbranching angiogenesis (elongation of the existing vessels), which dominates in the 3rd trimester. [76–78]

Some studies suggest that placental angiogenesis is coordinated by the interaction of angiogenic vascular endothelial growth factors (VEGFs) and their coreceptors (Flt-1, KDR, Flt-4), angiopoietin (Ang), and antiangiogenic factors jointly with local paracrine mediators, such as nitric oxide (NO). [56,76–78] VEGFs and their relative placental growth factor (PlGF) are critically required for all steps of placental vascular formation and development from vasculogenesis to nonbranching angiogenesis later in gestation, and they also contribute to a dramatic increase in uterine vascularization and blood flow. [76–79] The threshold levels of VEGF must be achieved to

accomplish normal vascular development.[78] VEGFs activate angiogenesis by binding to two receptors: VEGFR-1 acts as an endogenous inhibitor by reducing the binding of VEGF to VGEFR-2, therefore reducing the proliferation and branching of endothelial cells and the capillary network; VGEFR-2 promotes vascular branching and the proliferation of vascular cells. [79] A soluble form of Flt-1 (sFlt-1), presented on trophoblasts, is also involved in both normal and pathological vascular development and is considered antiangiogenic in that it antagonizes the stimulatory functions of VEGF-A and PlGF. [76] Additionally, Ang is responsible for the establishment, remodeling and maturation of the vessel wall, and NO is also a regulator of angiogenesis since angiogenic factors require NO to induce new vessel formation due to its major local vasodilator effect. [76–78,80]

Physical factors, particularly vascular pressure and flow and/or oxygen tension, may influence early vascular patterning, and it has been demonstrated that oxygen gradients across the placental lobule have differential effects on uteroplacental angiogenesis. [56] These proangiogenic mediators are regulated by oxygen tension, which is low in early pregnancy and sharply increases after the first trimester. [76] The relatively hypoxic environment is physiologically ideal for proper placental development, since it constitutes a stimulus for cytotrophoblastic proliferation while inhibiting differentiation to an invasive phenotype that subsequently begins to occur at 10 weeks gestation by the remodeling of the arterial wall of uterine vessels; this results in a low-resistance state that allows for increased blood flow. [76] Low levels of oxygen upregulate VEGF, Ang-2, and Flt-1 and suppress PGF, which promotes vasculogenesis and branching angiogenesis over nonbranching angiogenesis in the earlier stages of pregnancy, a sequence that, if altered, results in abnormal villous growth and maturation. [76] Early hypoxia stimulates endothelial NOS, while chronic hypoxia inhibits it, confirming that early hypoxia followed by increased oxygen pressure is critical for development of the villous tree. [76]

Vascular anastomoses in monochorionic twin placentas develop as the fetal–placental circulation is established during the first trimester. [76] Some studies discovered higher levels of VEGFR-1 and lower levels of VEGFR-2 in MC pregnancies compared with singletons during the first trimester and that the levels of VEGFR-1 were decreased in the 2nd trimester compared to the first.[79,80] These results indicated that VEGFR-1 plays an important role during the development of the placental and fetal vascular systems, and these differences may be related to the relative size of the placenta (compared to that of singletons) rather than an angiogenic response to relative hypoxemia. [79,80] Nevertheless, VEGFR-1 levels have been reported to be inversely correlated with fetal weight at birth and Apgar score in patients with gestational hypertension. [79]

The underlying factors that cause mismatched connections and are associated with the development of MC vascular complications are not fully understood. [76,79] Studies performed in TTTS placentas verified an antiangiogenic state and that the donor usually expresses higher levels of VEGFR-1, Flt-1 and KDR, while the mother's serum shows an increase in sFlt-1 and a decrease in both sVEGR-1 and PLFG. [76,79–81] However, these data are variable, and it is not known how this correlates to the pathophysiology of the disorder. [76,81]

Mao et al. studied the intertwin differences in placental oxygenation and autophagy in TAPS. [82] The oxygenation of the respective twin territories was measured by quantifying the expression of CAIX protein (an indirect marker of chronic hypoxia), and consequently, higher levels were demonstrated in the anemic twin territory compared with their polycythemic counterparts. [82] Simultaneously, autophagy was studied by measuring the levels of antibodies (LC3-I, LC3-II) connected to the microtubule-associated protein IA/IB light chain 3 (LC3), although the conversion of LC3-I to LC3-II is recognized as a hallmark of autophagosome formation. [82] The donor territory showed higher levels of LC3-I and II as well as other markers of higher lysosome content and function, whereas the receptor had very low LC3-I and undetectable LCA-II, indicating autophagosome accumulation in the anemic shares of TAPS placentas. [82] To distinguish whether autosome activity was a result of enhanced autophagosome synthesis or reduced autophagosome turnover, we measured the levels of p62 protein (a selective marker of reduced autophagosome degradation), which were significantly higher in the anemic shares than in the polycythemic shares, suggesting inhibition of autophagosome turnover, defects in autophagy, and accumulation of lysosomes and autophagosomes in the anemic shares. [82] The exact clinical implications of this finding remain to be determined; however, it was speculated that the inhibition of placental autophagy may be attributable, at least in part, to differential tissue oxygenation, which could be implicated in the growth restriction that is commonly verified in anemic TAPS twins (since this is a common finding in other pregnancies complicated by fetal growth restriction, such as that occurring in implantation disorders and preeclampsia (PE)). [82]

On another note, the maternal and fetal circulating and tissue renin-angiotensin systems (RASs) are important for a successful pregnancy outcome and have many functions since they regulate maternal and uteroplacental blood pressure and promote placentation. [83] Angiotensin-converting enzyme 2 (ACE2) has the key role of transforming angiotensin (ANG) II to Ang-(1–7), consequently reducing the imbalance toward increasing levels of ANG, which in turn protects against ANG II-induced oxidative stress, vasoconstriction, and proinflammation, playing a protective role in end-organ damage. [83] Pregnancy complications such as fetal growth

restriction and PE are associated with increased levels of the ANG II pathway [83] *Mao et al.* demonstrated that TAPS placentas display intertwin discordance in the expression of ACE2 and its associated cellular proteases (TMPRSS2 and cathepsin-B). [84] In vitro and in animal models, hypoxia affects ACE2 expression in trophoblastic cells, and therefore, this group speculated that discordance of the ACE2/TMPSSR2 expression in TAPS placentas may be attributable, in large part, to differential tissue oxygenation and that hypoxic conditions may enhance the functionality of the RAS axis. [84]

5. Diagnostic criteria

5.1. Prenatal Diagnosis

The diagnosis of TAPS can be made either prenatally or postnatally. [23,34,51] TAPS can develop across a wide range of timepoints during pregnancy and is not restricted to a certain trimester; however, in most cases, it develops after 26-30 weeks. [11,33,47] Generally, most iatrogenic TAPS cases develop between the 1st and 5th weeks after the first laser intervention (50% of those, up to the 2nd week) but can be detected up to the 17th week after this intervention. [16,33,45]

The absence of oligohydramnios in the donor twin and polyhydramnios in the recipient twin in antenatal ultrasound is an essential prerequisite for the diagnosis of this pathology. [8,20] Prenatal diagnosis for TAPS is based on Doppler measurement of the MCA-PSV, a noninvasive test that is the standard test to assess the existence of fetal anemia present in a wide variety of pathologies [9,16,22–24,32,41,75] In TAPS, the MCA-PSV is increased in the donor (suggesting anemia), while in the recipient, there is a decrease (indicating polycythemia). [8,12,16,23,47]

The antenatal diagnostic criteria have progressively evolved over time. [23] Initially, an MCA-PSV value >1.5 MoM in the donor as well as an MCA-PSV value < 0.8 MoM in the recipient were necessary criteria for prenatal diagnosis of this condition. [16,23] *Slaghekke et al*. (and several subsequent studies) evaluated the acuity of the cutoffs of the MCA-PSV method in predicting the development of TAPS and concluded that using a cutoff lower than 0.8 MoM for severe polycythemia overlooks many cases and causes severe consequences, since some polycythemic twins maintain their velocity above this threshold. [22] Subsequently, a more conservative approach regarding the cutoff for the recipient (MCA-PSV < 1.0 MoM)) was proposed. [9,16,20,22,23,31,44]

Fishel-Bartal et al. demonstrated that twin differences in MCA-PSV values were positively correlated with postbirth hematocrit discordances and that polycythemia could not

be excluded even if the MCA-PSV was not low. [25,29,85] On this premise, several subsequent studies have stated that the difference between a peak maximum systolic velocities of both twins (ΔMCA-PSV) superior to 0.5 multiples of the median (MoM) could have greater diagnostic accuracy for predicting TAPS than the current MCA-PSV cutoff criteria and that ΔMCA-PSV is a good predictor of the neonatal intertwin hemoglobin concentration difference and potentially of TAPS. [25,27,29,85] *Tollenaar et al.* demonstrated that twins with Δ MCA-PSV > 0.5 MoM had neonatal morbidity and mortality outcomes similar to those of the group meeting the MCA-PSV cutoff criteria, indicating that even when MCA-PSV values are normal, obstetricians should be aware of the pathological and therapeutic implications associated with TAPS. [25,26,44,86] Additionally, *Tavares De Sousa et al*. stated that a delta of >0.373 MoM was the best predictor of twin Hb discordance of the >90th percentile at birth. [27,44] Furthermore, there has been an emerging trend of favoring ΔMCA-PSV over absolute MCA-PSV values, and the former is now considered the best and most reliable reference for the diagnosis of antenatal TAPS. [16,25,26,31,87] Subsequently, Tollenaar et al. has proposed a new antenatal classification system for TAPS [*Table **2***]. [25]

Additionally, the application of other secondary markers (based on echographic signals) in prenatal diagnosis has been studied and together may help identify most cases of TAPS when MCA-PSV values are not routinely evaluated. [31,88,89] The placenta in TAPS may show a dichotomous appearance with respect to its thickness and echogenicity on ultrasound evaluation [9,16,23,90,91] The donor side may be hyperechogenic, hydropic and enlarged, while the recipient counterparts may be hypoechogenic and flattened or without relevant changes. [5,16,20,33,91,92] Placental dichotomy is more prevalent in spontaneous than in iatrogenic TAPS. [89] Chronic anemia may lead to the accumulation of excessive fluid in the fetal circulation that precedes fetal hydrops, and several studies point to a positive correlation between discordant placental echogenicity and a greater severity of TAPS. [88,89] Chronic hypoxia in the donor requires an increasing cardiac output, leading to cardiac remodeling and the development of cardiomegaly [16,89,90] Finally, the recipients' liver may exhibit the "starry-sky" echographic sign in which the portal venules ("stars") are hyperechogenic and congested together with the hypoechogenic liver parenchyma ("sky"), mimicking a starry sky. [16,23,89,90,93] This marker is extremely important because it is the only one that can predict polycythemia; however, it may also be reported in acute hepatitis and other conditions, such as liver failure, but none of these conditions are usually present in TAPS recipients. [23,89,93] To evaluate the usefulness of these criteria, recent studies demonstrated that placental dichotomy was present in only 44% of twins with TAPS, 70% of donors had cardiomegaly, and the starry-sky sign was seen in 66% of

recipients. [44,89] Most twins with TAPS (86%) had at least one of these echographic signs present, and there was a tendency for the joint prevalence of the three criteria in the higher prenatal stage of TAPS. [16,89,90] Moreover, these secondary markers together can identify most cases of TAPS when MCA-PSV values are not routinely assessed, but 14% of cases may only have discordant MCA-PSV values without any additional criteria [88,89]

The prenatal surveillance of monochorionic pregnancies with systematic monitoring of MSV-MCA values for TAPS screening is still not consistent. [29,31,90] The best prenatal diagnostic criteria are still a matter of debate since the incidence of TAPS is relatively low and the available data come from retrospective studies with small populations, which limits the reliability of the proposed diagnostic criteria. [26,32] Consequently, additional, large prospective studies are necessary to assess the accuracy of the MCA-PSV criteria. [16,26,32]

Nonetheless, the scientific evidence, although limited, is increasingly favorable and suggests that early detection of TAPS may allow for appropriate prenatal interventions that will improve the long-term outcomes of the disease, which otherwise may culminate in neurodevelopmental impairment and very high morbidity and mortality (approximately 15%, and even higher in the donor [22%]). [31,44,47,88] Therefore, in current practice, it is pragmatic to continue routine serial surveillance with antenatal monitoring of MCA-PSV in MCDA twins, from the beginning of the second trimester (ranging from 16 weeks to 28 weeks) and especially after laser treatments, to anticipate possible complications inherent to MC pregnancies. [8,20,26,31,41,47,68,90] The results should be interpreted with caution and the consideration of other echographic signs of TAPS during ultrasound surveillance. [26,31,47]

5.2. Postnatal diagnosis

Approximately 40-63% of TAPS diagnoses are not made prenatally and are only verified at birth; thus, postnatal diagnostic criteria have been proposed. [16,23,68] Early postnatal diagnostic criteria used cutoffs for anemia in the donor and had the disadvantage of not correlating fetal hemoglobin levels with gestational age (which are known to increase linearly) and consequently required the use of specific gestational age-related nomograms. [7,9,20,51,94,95]

Currently, the postnatal diagnosis of TAPS is based on 3 criteria. [16,27,33] The first that must be fulfilled is the existence of an intertwin hemoglobin difference of more than 8 g/dL. [8,9,96–98,16,27,33,42,51,82,87,95] However, there is another condition, acute peripartum TTTS, that is believed to develop during labor and presents as a large hemoglobin discrepancy along with hypovolemic shock due to exsanguination from large caliber anastomoses, which may require

blood transfusion and resuscitation with fluid therapy in the first hours after birth. [7,16,23,28,99] Both pathologies have a distinct therapeutic approach, since TAPS donors benefit more from a conservative approach, which in cases where there is still effective erythropoiesis, may not even require transfusions. [16,23,99]

To differentiate between both entities, 2 additional criteria have been proposed, and at least one of them must be present: the existence of a reticulocyte count ratio greater than 1.7 between both twins (the win reticulocyte ratio is calculated by dividing the reticulocyte count of the donor by the reticulocyte count of the recipient) and the verification of the presence of only minuscule placental anastomoses (diameter <1 mm) that are detected through dye-based vascular injection studies. [8,9,87,91,95–99,16,20,23,27,28,33,42,51] In TAPS, the donor exhibits a higher reticulocyte count due to increased erythropoiesis (as a consequence of chronic anemia), while in acute TTTS, the reticulocytes are normal, given the rapidity of the phenomenon and the inability to activate compensatory mechanisms. [7–9,16,20,23,28,33,51,100] The finding of small caliber anastomoses contrasts with the presence of large caliber, low resistance AA and VV anastomoses that allow the exchange of large blood volumes acutely and directly in acute peripartum TTTS. [16,23,28,33,99]

Since the reticulocyte count is not routinely measured and dye-based vascular injection studies can sometimes be difficult to perform (it is a time-consuming procedure and thus performed mostly by specialized medical centers), other additional postnatal diagnostic criteria that are faster and easier to use have recently been studied. [23,99,101] In addition to the distinct skin color of TAPS twins at birth (the pale donor and the plethoric recipient), there are also differences in the coloration of the maternal placental surface after birth. [16,23,101] The anemic donor area is very pale, while the polycythemic recipient portion appears extremely dark, allowing calculation of the color difference ratio (CDR) (measured with the "ImageJ" processing program) by dividing the mode of color intensity of the anemic twin by that of the polycythemic twin. [16,23,33,92,99,101] The mean CDR in acute peri-partum TTTS placentas is usually much lower (CDR < 1.5) than that in TAPS placentas (CDR > 1.5) [16,23,99,102] The difference in coloration is thought to be directly proportional, not only to the discordances in hemoglobin values but also to the time of exposure of the placenta to high red cell counts. [99,102] The sensitivity and specificity of this method (and whether it can be added to the list of postnatal criteria) is still a matter under investigation, but new evidence supports its usefulness, especially when the other criteria are inconclusive, because it is an accessible, timesaving, cost-effective, and free tool requiring only a few precautions. [23,99,101,102]

6. Discussion

TAPS can develop across a wide range of gestational ages and has been managed heterogeneously. [47] This pathology may be associated with diverse outcomes, ranging from mild anemia and polycythemia to severe perinatal and long-term morbidity and mortality, especially in donors, who have an increased risk for hearing loss (15%) and mild-to-severe cognitive impairment (34%). [31,39,47,75,103,104] Recipients might also experience severe consequences, such as limb ischemia, skin necrosis, and severe cerebral damage. [31,39,47,75,103,104] In rare cases, the damage may be severe enough to cause death in either twin. [31]

The knowledge of rare cases of fetofetal transfusion in dichorionic pregnancies, particularly one case of TAPS with the presence of a small, deeply hidden VV anastomosis after placental injection, demonstrates that the distinction between monochorionic and dichorionic twins is not as strict as previously thought and that anastomoses may potentially lead to fetofetal transfusion pathology with severe consequences. [103] Therefore, the clinical picture, rather than the establishment of the type of chorionicity, should be the leading factor in medical decision-making regarding the required perinatal diagnostics and treatment. [103,105]

In regard to prenatal diagnosis, there is currently no consensus on when to start MCA-PSV surveillance; however, the perinatal outcome is greatly dependent on the TAPS stage, and timely detection is of utmost importance, as it allows the consideration of antenatal treatment. [47] Studies show that MCA-PSV Doppler is a noninvasive tool that has high and acceptable sensitivity and specificity for detecting fetal anemia, polycythemia, and TAPS. [31] False-positives and negatives can be reduced by adhering to the proper scanning technique, performing serial readings, and remaining mindful of additional conditions, such as gender, cardiac status, uterine contractions, fetal behavioral state, advanced gestational age, abnormal placentation and intrauterine growth restriction, that may alter the readings. [31] The antenatal classification system using delta cutoffs has greater diagnostic accuracy for predicting a significant difference in hemoglobin levels between twins, maximizing the value of MCA-PSV Doppler screening. [25,31] Based on the mounting evidence of serious effects of TAPS, studies suggest that to improve early detection and outcomes, routine MCA-PSV examination should be included in the standard biweekly follow-up visit in all uncomplicated MC pregnancies starting in the early second trimester. [40,41,47] Cardiac assessment could also be considered a monitoring tool [40]

The postnatal diagnosis of TAPS depends upon two factors: analytic values - based on hemoglobin levels and reticulocyte counts - and the performance of dye-based vascular injection studies.[40] It is generally believed that TAPS results from intertwin blood transfusion through

small vascular anastomoses. [75] Unfortunately, placental histological assessment (which should be mandatory in monochorionic twin pregnancies complicated by TAPS or TTTS) is not routinely performed in all centers, and in some reports, it was performed in only 39% of cases. [75] Even when it is performed, placental examination might fail to demonstrate patent vessels (probably due to thrombotic events or the existence of small hidden anastomoses); therefore, their absence is not a requirement for excluding the diagnosis of TAPS. [75]

During normal gestation, the hemoglobin concentration and erythrocyte count increase linearly, the erythroblast count decreases exponentially, and the reticulocyte count decreases linearly. [94,95] The absolute reticulocyte count (ARC), defined as the number of reticulocytes/μL, reflects bone marrow function and effective erythropoiesis. [106] On the day of birth, the reticulocyte count is higher than at any time during healthy life, caused by a relatively high blood concentration of erythropoietin before and at birth. [107]

The reticulocyte count is essential for the postnatal diagnosis of TAPS, but in recent review articles, there was no consensus about the units or values that should be used. [75] The reticulocyte count is reported as a percentage in some articles [104,108] and as an absolute value in others [40] or is not reported at all, making it difficult to pool data. [28,75,109]

A normal ARC both at pediatric (after the first 3 months of life) and adult ages is ∼25,000 to 75,000/μL (1.0 ± 0.5 percent of the 5 million red cells/μL) and is calculated and reported by many automated cell counters even though there are no standardized cut offs in the newborn. [106] Some authors that tried to study reference intervals for reticulocyte parameters in newborns provided information predominantly from term and late-preterm infants (⩾34 weeks gestation), mainly from the first week or two after birth; therefore, robust reticulocyte parameters remain largely undetermined for early-gestation preterm neonates. [107] Furthermore, it is not known how reticulocyte parameters of neonates are affected by conditions such as iron deficiency or hemolytic disorders.[107]

Hemoglobin levels and reticulocyte count can be measured at birth in all monochorionic twins obtained primarily from umbilical cord blood. [95,110] If cord blood is not available, samplings can be obtained on Day 1 through heel stick or venous puncture. [95,110] Reticulocyte parameters are obtained on a very small sample of blood as part of the complete blood count and do not require additional phlebotomy. [106] Reticulocyte parameters provide useful information to pediatricians and neonatologists for the diagnosis and management of hematologic diseases. [106,111]

7. Conclusion

Due to the relatively low incidence of monochorionic pregnancies and their complications, large multicenter studies are required to investigate the natural history, pathophysiology, and best diagnostic criteria and to develop standards for the management of these pathologies. [16,23,29,75]

Nevertheless, during the last 15 years, our knowledge about TAPS has grown exponentially, and the disease has been recognized as a distinct entity in intertwin transfusion processes, with a unique angioarchitecture, with the presence of small unidirectional anastomoses in the absence of TOPS and with its own diagnostic criteria, classification systems, and short- and long-term outcomes. [16,21,23]

To improve care for patients with TAPS, there are still major challenges. [16] One of them is the implementation and standardization of serial MCA-PSV Doppler screening to promptly diagnose this pathology. [16,23,47] Without this screening, TAPS can remain undetectable during pregnancy, which can result in healthy neonates with no major comorbidities, other than large hemoglobin discordances, or, on the other side of the spectrum, it can lead to fetal death of both twins, particularly if not properly addressed and treated. [20] Additionally, all centers that monitor TAPS pregnancies should perform a complete postnatal diagnostic evaluation that should include the measurement of hemoglobin values, reticulocyte counts, placental histological assessments and dye-based vascular injection studies to diagnose and distinguish TAPS from other conditions, such as acute peri-partum TTTS, and simultaneously assess whether laser therapy (when performed) is successful. [16,23,33] In addition, the evaluation of new pre- and postnatal diagnostic criteria based on secondary echographic signs (placental dichotomy, fetal cardiomegaly, “starry-sky sign”) and the color difference of the maternal side of the delivered placenta requires further investigation in a larger series of placentas with and without TAPS. [23,89] Research on the best treatment options is vital to prevent severe outcomes. [16,23] Short-term and long-term outcomes should also be assessed to estimate treatment effects. [16,23,112]

Molecular studies on monochorionic placentas can increase the knowledge about basic phenomena involved in numerous clinical situations. It is an exceptional research object, as it can eliminate numerous confounding factors, namely, certain maternal characteristics and comorbidities, uterine environment conditions, and genetic profiles. [81–83]

Finally, guidelines need to be swiftly updated with the latest available research, since consistent clinical guidelines influence clinical practice and prenatal screening, which ultimately

will help to produce more reliable data and a better understanding of monochorionicity and improvement of its outcomes.[31,90]

Apêndice

Table **I** - Differences between TTTS, TAPS and acute TTTS.

Hb – hemoglobin; UA- umbilical artery; TAPS – twin anemia-polycythemia sequence; TOPS – twin oligo-polyhydramnios sequence; TTTS – twin-to-twin transfusion syndrome; MVP - maximum vertical pocket; * percentage (%) of monochorionic pregnancies; ** Critically abnormal Doppler is defined as absent or reversed end-diastolic flow in the umbilical artery, pulsatile flow in the umbilical vein, increased pulsatility index or reversed flow in the ductus venosus. (16)

Complication	**Epidemiology**	**Pathophysiology**	**Diagnosis criteria**	
TTTS or TOPS	15-20%* (1,13,28)	Chronic intertwin transfusion through large AV anastomoses (7)	Ultrasound identification of polyhydramnios in the recipient twin (by MVP of amniotic fluid >8 cm in the first 20 weeks of gestation and more than 10 cm after 20 weeks) and oligohydramnios for the donor twin with an MVP <2 cm. (6,7,12,53)	
Acute peripartum TTTS	1.5-2.5%* (7,14,39,49,89,113)	Acute intertwin transfusion through large anastomoses AA or VV during delivery (7)	Intertwin hemoglobin difference ≥ 8 g/dl; Reticulocyte count ratio < 1.7% between both twins; Numerous large anastomoses (diameter >1.0 mm), with at least one AA or VV anastomoses. (7,16)	
TAPS Spontaneous TAPS (3-5%*); Iatrogenic or postlaser TAPS (2-16%*) (6,8,44,112,9,16,20,21,31,33,34,43)	2-16%* (6,16,31)	Chronic intertwin transfusion through small AV anastomoses (< 1 mm) (5,7,61,70,9,16,20,21,23,33,34,45)	**Antenatal:** A delta MCA-PSV > 0.5 MoM Without other signs of fetal compromise ** in the absence of discordances in amniotic fluid levels. (6,16,20,25)	**Post-Natal:** Intertwin hemoglobin difference ≥ 8 g/dl. (16,27,33) Plus 1 of the following: - Reticulocytosis in the donor and intertwin reticulocyte count ratio ≥1.7%; *or* - only minuscule AV placental anastomoses (diameter <1 mm) in color-dye-injection placental studies. (16,20,23,28,33,99)
TRAP	1% (3)	Blood flows from an UA of the pump	Presence of an AA anastomosis and discordant development or	

		twin in a reversed direction into the UA of the perfused twin, via an AA anastomosis and returns via a VV anastomosis back to the pump twin. [14]	intrauterine demise of one of the monochorionic twins allowing for reversal of blood flow. [14]

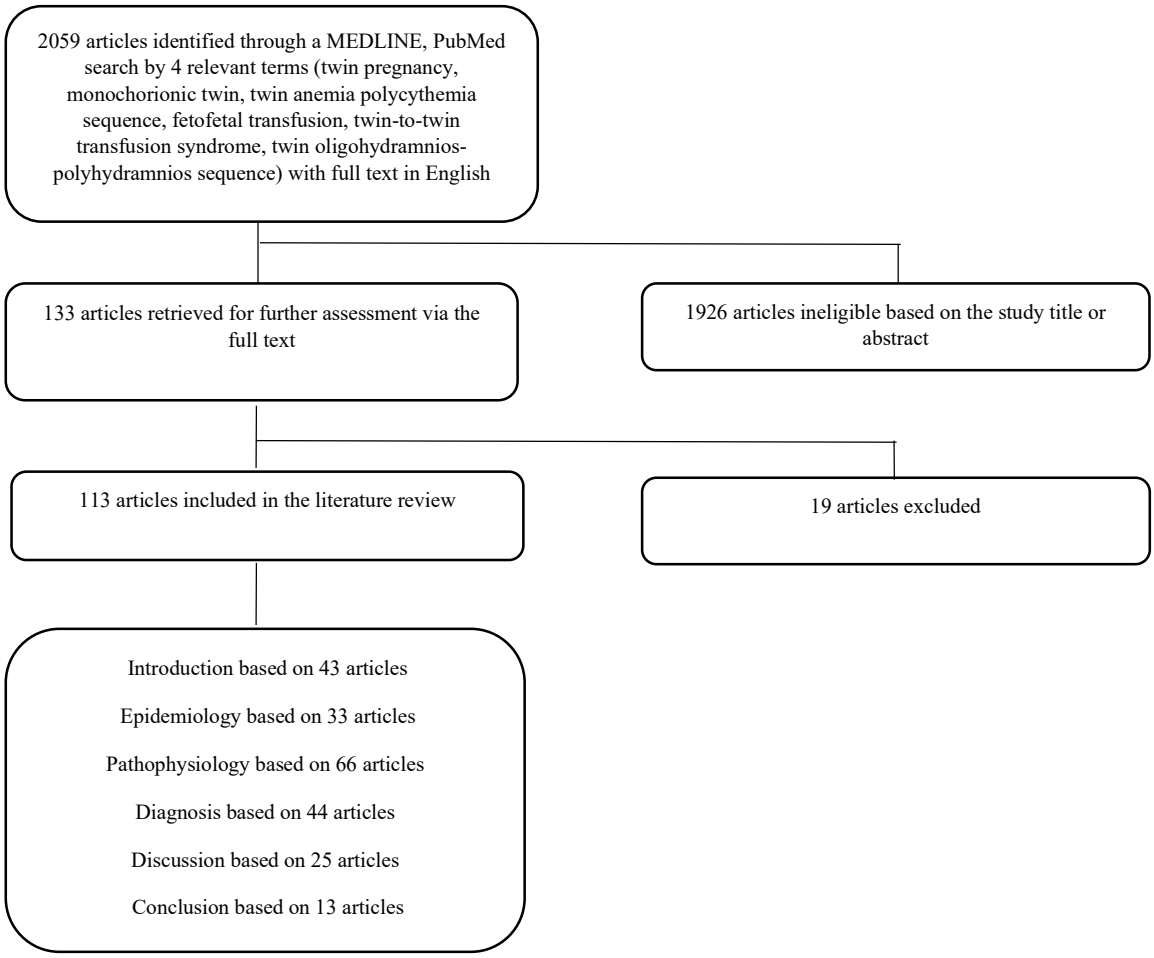

Figure 1 - Flow diagram of the literature review.

Table II – Antenatal classification system for twin anemia–polycythemia sequence (TAPS)

TAPS – twin anemia-polycythemia sequence; MCA-PSV-middle cerebral artery peak systolic velocity; MoM-multiples of the median. * Defined as critically abnormal flow: Doppler shows absent or reversed end-diastolic flow in the umbilical artery, pulsatile flow in the umbilical vein and/or increased pulsatility index or reversed flow in the ductus venosus

	Previous criteria[19,20,23]	**Proposed criteria** [25,85]
Stage 1	MCA-PSV donor > 1.5 MoM, recipient < 1.0 MoM; without signs of fetal compromise	Delta MCA-PSV > 0.5 MoM; without signs of fetal compromise
Stage 2	MCA-PSV donor > 1.7 MoM, recipient < 0.8 MoM; without signs of fetal compromise	Delta MCA-PSV > 0.7 MoM; without signs of fetal compromise
Stage 3	As Stage 1 or 2; with cardiac compromise of the donor*	As Stage 1 or 2; with cardiac compromise of the donor*
Stage 4	Hydrops in the donor	Hydrops in the donor
Stage 5	Intrauterine demise of one or both fetuses preceded by TAPS	Intrauterine demise of one or both fetuses preceded by TAPS

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Suplementos

1. Submission Acknowledgement

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Submission Title: Twin Anemia-Polycythemia Sequence (TAPS): From Basic Research to Clinical Practice

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