Twin-twin transfusion syndrome: a literature review
Síndrome de transfusão feto-fetal: revisão de literatura

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ABSTRACT
Twin-twin transfusion syndrome is a complication of monochorionic twin pregnancies. In addition to commonly occurring in the second trimester, it has high fetal and neonatal morbidity and mortality and incidence rates ranging from 10 to 15% among all monochorionic pregnancies. This study aims to perform a literature review based on a bibliographic survey about the main epidemiological, clinical and therapeutic aspects of TTTS. The PubMed database was consulted, as the search terms used were "twin-twin transfusion syndrome", "diagnosis", and "treatment". Sixty-eight literature review and systematic review articles were obtained, and only twenty-nine were selected after applying the eligibility criteria. About the pathophysiology, the syndrome is explained by direct blood transfer between the twin fetuses through placental arteriovenous anastomoses, determining the existence of a recipient fetus and another donor. Although pregnant women are usually asymptomatic, the clinical fetal repercussions are often severe. Diagnosis is exclusively ultrasonographic and must be made as early as possible, emphasizing the importance of detecting chorionicity in twin pregnancy, in addition to serial ultrasonographic follow-up to track the development of the syndrome. Although there is still no well-established treatment protocol, endoscopic laser ablation of vascular anastomoses is considered the gold standard among the available therapeutic options. It has a high survival rate for at least one of the fetuses and low rates of neonatal neurological sequelae and can only be performed until the 26th week of pregnancy.

Keywords: Twinning, Monozygotic; Placental Circulation; Twin-twin Transfusion.
RESUMO
A síndrome de transfusão feto-fetal é uma complicação das gestações gemelares monocoriônicas. Além de ocorrer comumente no segundo trimestre, apresenta elevada morbimortalidade fetal e neonatal, e taxas de incidência que variam de 10 a 15% dentre todas as gravidezes monocoriônicas. O objetivo deste estudo é realizar uma revisão de literatura a partir de levantamento bibliográfico acerca dos principais aspectos epidemiológicos, clínicos e terapêuticos da STFF. A base de dados PubMed foi consultada, uma vez que os termos de pesquisa utilizados foram “síndrome de transfusão feto-fetal”, “diagnóstico” e “tratamento”. Obtiveram-se sessenta e oito artigos de revisão de literatura e/ou revisão sistemática, sendo que apenas vinte e nove foram selecionados após aplicação dos critérios de elegibilidade. Em relação à fisiopatologia, a síndrome é explicada pela transferência sanguínea direta entre os fetos gemelares através de anastomoses arteriovenosas placentárias, conceitualmente determinando a existência de um feto receptor e outro doador. Embora as gestantes comumente se apresentem assintomáticas, as repercussões clínicas fetais costumam ser graves. O diagnóstico é exclusivamente ultrassonográfico e deve ser feito o mais precocemente possível, ressaltando-se a importância da detecção da corionicidade da gestação gemelar, além de acompanhamento ultrassonográfico seriado para rastreio do desenvolvimento da síndrome. Apesar de ainda não haver protocolo de tratamento bem estabelecido, a ablação dos vasos placentários a laser é tida como o padrão-ouro dentre as opções terapêuticas disponíveis. Apresenta elevada taxa de sobrevida de pelo menos um dos fetos e baixos índices de sequelas neurológicas neonatais, podendo ser realizada somente até a 26ª semana de gestação.

Palavras-chave: Gemelaridade Monozigótica; Circulação Placentária; Transfusão Feto-Fetal.

INTRODUCTION
Twin-twin transfusion syndrome (TTTS) is one of the most severe complications that affect monochorionic twin pregnancies, whose incidence ranges from 10% to 15% among all of them, occurring more commonly in the second trimester of pregnancy. Considered a condition of high fetal and neonatal morbidity and mortality, TTTS is an unbalanced blood transfer between twin fetuses from placental arteriovenous anastomoses, one of which is considered the donor and the other is considered the recipient.

Twin pregnancies with identical fetuses occur in a proportion of one in 320 pregnancies, with about 70% of them being monochorionic diamniotic. In this context, it is crucial to understand the nomenclature around the process of placental formation. Depending on the period in which the endometrium receives the embryo, it can be classified as diamniotic dichorionic (two placentas and two amniotic cavities for fetuses, in 30%), diamniotic monochorionic (a single placenta and two amniotic cavities, in 70%), or monoamniotic monochorionic (a single placenta and an amniotic cavity for both concepts, in 1-2%). According to D’Antonio et al. (2019) apud Murgano et al. (2020), although the incidence of TTTS is 2.4 to 2.7 times greater in monoamniotic dichorionic pregnancy compared with monoamniotic monochorionic pregnancy, the latter presents a much more pronounced risk of perinatal morbidity and mortality.

The diagnosis of TTTS is performed during prenatal care through obstetric ultrasound (USG), which demonstrates, in general, the presence of polyhydramnios and oligohydramnios in the recipient and donor fetuses, respectively.

The preferred staging system to describe the evolution of TTTS remains that of Quintero, responsible for segmenting the severity of the disease into five different stages, relating them to their individual perinatal prognosis.

At the diagnosis time, if both fetuses have their vitality preserved and the expectant management is taken, the risk of mortality in at least one of them varies from 70% to 100%.

For this reason, a series of therapeutic modalities have been introduced to avoid the situation previously presented, thus having four main options as a treatment approach for patients diagnosed with TTTS: serial amnioreduction, septostomy, fetoscopic laser ablation of anastomotic vessels, and selective feticide.

The therapeutic modality recognized as the gold standard is fetoscopic laser ablation of anastomotic vessels. The other options are considered exceptional or even contraindicated in Brazilian territory, as is the case of selective feticide. Furthermore, fetoscopic laser ablation is, to date, the only therapeutic alternative responsible for interrupting the pathogenic pathway of the disease.

In this context, the present study aims to perform a literature review based on a survey of the scientific evidence of the last ten years (2010-2021) about the epidemiological, clinical, and therapeutic aspects of TTTS.
METHODS

This study is a narrative review that discusses the epidemiological, pathophysiological, and clinical aspects of TTTS. For this, a bibliographic survey was carried out from the PubMed database, which included the following terms to direct the search: “twin-twin transfusion syndrome”, “diagnosis”, and “treatment”.

As inclusion criteria for the selection of studies, the following were adopted: (a) articles in Portuguese and English; (b) a literature review or systematic review study; (c) year of publication from 2010 to May 2021; (d) relevance of the study developed; (e) presence of the terms “twin-twin transfusion syndrome” in the title or abstract. Regarding the exclusion criteria, the following were taken into account: (a) studies not related to the proposed theme; (b) articles published before 2010; (c) studies that do not include the other inclusion criteria. Thus, sixty-eight articles were found. In contrast, only twenty-nine were selected for this literature review after using the described eligibility criteria.

It is important to note that this article did not require approval by the research ethics committee (REC) because it is a literature review study (Resolution No. 510 of April 2016 of the Local Committee).

DISCUSSION

TTTS is an obstetric complication that mainly affects monochorionic twin pregnancies, whose incidence rate is around 15 out of 100 monochorionic pregnancies. Therefore, obstetricians must know the particularities of this syndrome, described below, due to the considerable impact on maternal and perinatal morbidity and mortality, in addition to providing better care to these pregnant women.

PATHOPHYSIOLOGY

Monochorionic twin pregnancies have a higher risk of obstetric complications when compared to dichorionic pregnancies, being responsible for approximately 30% of all causes of complications related to pregnancy. That occurs because monochorionicity involves the sharing of a single placental mass, in addition to the presence of numerous vascular anastomoses between fetuses.

Despite affecting up to 20% of monochorionic twin pregnancies, the pathophysiological process of TTTS is still not fully understood. In line with Mosquera et al. (2012), the composition of placental vascular anastomoses is one of the conditions that directly participate in developing the syndrome. In this perspective, there are three types of placental anastomoses in monochorionic pregnancies: arteriovenous (AV), which are deep and interconnect the arterial supply of one fetus with the venous drainage system of the other, allowing only a unidirectional flow due to the difference in hydrostatic pressure between the systems; and arterioarterial (AA) and venovenous (VV) anastomoses, which are superficial and interconnect vascular beds with similar pressures, thus generating a bidirectional flow.

It is known that the number, type, and diameter of these vascular communications are essential in determining the risk of developing the syndrome. The study of vascular patterns in pregnancies affected by TTTS shows that 95% of them have a predominance of AV anastomoses, having fundamentally unidirectional blood flow. Since the difference in hydrostatic pressure between the fetal vascular systems strictly determines the direction of flow and blood volume, the existence of an unbalanced vascular net with a predominance of AV anastomoses is the condition that explains the pathophysiological consequences of TTTS. In addition, the predominance of AA behaves as a protective factor concerning the development of the syndrome, with the disproportion of the ratio between AV and AA being the key to explain the occurrence of TTTS.

In general, TTTS is not explained only by sharing placental blood flow between the donor and recipient fetuses but also by the hemodynamic repercussions that the produced endocrine and vasoactive mediators generate. Thus, after establishing an unbalanced vascular microenvironment, where there is a direct blood transfusion from the donor fetus to the recipient, the clinical manifestations of the syndrome begin. In the donor fetus, to restore the physiological intravascular volume, there is an activation of the renin-angiotensin-aldosterone system (RAAS) and increased release of antidiuretic hormone (ADH). As a result of this hormonal action, occur: hypertension, decreased renal perfusion with consequent oliguria, hypovolemia with inherent damage to target organs, oligohydramnios, and intrauterine growth restriction (IUGR). Chronically, the state of hypoperfusion in the donor fetus associated with the constant action of RAAS can generate tubular atrophy and renal dysgenesis identified in the small percentage of the fetuses that survive until the end of pregnancy. On the other hand, when receiving a supraphysiological blood flow, which causes a significant increase in tidal volume, there is the consequence of the release of vasoactive substances (atrial and cerebral natriuretic peptides, for example) by the recipient fetus, leading to the development of hypervolemia, increased renal perfusion with polyuria and polyhydramnios, plethora, hydrops and heart failure.

STAGING

Although an ideal classification system has not been created yet, a staging system was proposed in 1999 to aim to describe in a standardized way the severity of TTTS based on ultrasound and doppler study findings, called the Quintero system. The Quintero staging system has five stages with increasing severities, which allows for a perinatal prognostic significance assignment and provides greater accuracy in comparing different treatment outcomes for TTTS. Due to its easy applicability and simplicity of interpretation, it remains the most used by professionals, including in large centers specialized in fetal medicine.

Generally speaking, in stage I (mild form), there is a difference in the size of the fetal bladders and the amniotic fluid volume (AFV) in the amniotic cavities, with the fetal donor bladder visible on ultrasound examination, in addition to doppler within the normal range.
Oligohydramnios is the maximal vertical pocket (MVP) less than two centimeters (≤2cm) in the donor fetus; on the other hand, polyhydramnios is an MVP greater than eight centimeters (>8cm) until the 20th week or greater than ten centimeters (>10cm) after this gestational age, in the recipient fetus.1,3,7,8,18. It is important to note that some authors prefer to standardize the cut-off point of eight centimeters regardless of gestational age to define the polyhydramnios in the recipient fetus11,18. In stage II, the donor fetus presents with a constantly empty bladder (not seen) and in severe oligohydramnios, which is known by the term “stuck twin” as long as it is wrapped in its membranes as if it rested inside a cocoon; in contrast, the recipient fetus has polyhydramnios, and the bladder is distended13-8,11,16,18,19. In stage III, it is already possible to observe doppler findings changes in the umbilical vessels or the venous duct of one or both fetuses, the main ones being: increased resistance of the donor’s umbilical artery (absent or reversed end-diastolic flow); increase in the pulsatility index of the ductus venosus; or absence/inversion of flow during atrial contraction in the recipient’s venous duct (negative a-wave ductus venosus)3,2,6,4,11. Finally, stage IV indicates that the recipient or donor fetus shows signs of hydrops, while stage V means that one or both twins have died8,11,16. There are many limitations present in the Quintero staging system, making researchers constantly seek to develop new systems to overcome such deficiencies1,12,13. In this sense, more than 50% of recipient fetuses show signs of cardiac impairment (structural or functional) still in the early stages of TTTS. Thus, new classifications were developed to include such cardiovascular parameters, as is the case with the modification of the Quintero staging proposed by Cincinnati1,9. In the Cincinnati classification, there was a subdivision of stage III depending on echographic signs of cardiomyopathy in the recipient fetus, being subclassified in IIIa, IIIb, and IIIc according to the fact that the heart disease is mild, moderate, or severe, respectively6. However, it is important to emphasize that fetal echocardiography does not significantly impact therapeutic decision-making in cases of TTTS1,17,18.

**DIAGNOSIS**

Although it can occur in any gestational period, TTTS occurs most frequently in the second trimester, between the 16th and 26th weeks.1,3,8,9,11,12,17. Thus, as an initial step in diagnosing the syndrome, it is indispensable to establish the chorionicity of twin pregnancies early for adequate prenatal surveillance. The determination of chorionicity by the first trimester USG, more precisely between the 10th and 14th weeks, can be done with 96% accuracy by identifying very specific additional ultrasound findings that may be present in the context of this obstetric complication and assist in diagnostic reasoning, such as fetal size discordance (greater than 20%); abnormal placental cord insertions, particularly velamentous insertions; and the intrauterine growth restriction of the donor fetus.

**CLINICAL PRESENTATION**

The clinical presentation of TTTS is entirely heterogeneous. Although it behaves like an entity with a broad spectrum of presentations, ranging from stable and indolent conditions to cases of fulminating progression, it is impossible to accurately predict the progression of TTTS in each pregnant woman. Even though it commonly behaves asymptomatically in pregnant women, the main maternal clinical manifestations, when present, occur due to uterine overextension by polyhydramnios, with emphasis on uteroplacental insufficiency, intrauterine infection, and premature rupture of membranes (PROM). As for the fetuses, since they share the same placental mass with unbalanced vascular anastomoses, they may present clinically with a picture of hypovolemia, oliguria, and oligohydramnios (donor fetus), and hypervolemia, polyuria, and polyhydramnios (recipient fetus). If the recipient is severely compromised, he may also have blood regurgitation in the mitral valve and fetal hydrops.
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Complications

If not properly treated, the main complications of TTTS are intrauterine fetal death, miscarriage, premature rupture of ovular membranes, and preterm delivery. In addition, twin pregnancies present an increased independent risk for the occurrence of preterm birth, and this is also present in pregnant women with TTTS. Although the syndrome has a progressively slow onset most of the time, it can manifest with the sudden death of one of the fetuses (usually the recipient). The fetal mortality rate in untreated pregnancies exceeds 80% if the disease has developed before the 28th week and mainly in stages II, III, and IV of Quintero. In addition, cardiovascular complications can also be present in fetuses affected by TTTS, especially pulmonary atresia or stenosis, diastolic ventricular dysfunction and insufficiency of atrioventricular valves in the recipient fetus, and hypertrophy middle and smooth muscle layers of the blood vessels of the donor fetus.

Treatment

Although there is no scientifically established consensus regarding treating the syndrome, the therapeutic options available are widely known, and, currently, fetoscopic laser ablation of placental vessels is considered the standard gold method. The available conducts are expectant, serial amnioreduction, septostomy, fetoscopic laser ablation of anastomotic vessels, and selective feticide. It is important to emphasize that regular monitoring and individualized therapy are imperative because if the syndrome is not treated and develops before the 26th week of pregnancy, perinatal morbidity, and mortality rates are greater than 90%. The risks and possible complications inherent to each method should always be considered with caution since the rates of disease progression to higher Quintero stages are 30%, 15%, and 0% in patients treated with amnioreduction, expectantly and with laser ablation of the placental vessels, respectively.

Expectant management

Expectant management can be adopted through careful and continuous monitoring of pregnancy, where there is no deterioration in the clinical condition of the fetuses under US and doppler flowmetry assessment. Thus, it can be adopted in cases classified as Quintero I, presenting survival rates of 86%. On the other hand, this therapeutic modality should not be considered for patients classified as Quintero II, III, or IV.

Serial amnioreduction

Amnioreduction is a palliative therapeutic procedure that consists of serial drainage of fluid from the amniotic sac of the recipient fetus, which can be adopted after the 14th week of gestation. Drainage promotes a reduction in pressure within the amniotic cavity. It decreases uterine distension, which in the first instance reduces the risk of preterm birth, which is closely related to several neonatal complications. The reducing impact on intra-amniotic pressure also generates a reduction in maternal symptoms related to hydramnios and the decompression of placental vessels. This improvement in perfusion, especially for the donor fetus, is indicated as increasing up to 74% in the uterine artery flow.

Serial amnioreduction is a palliative therapeutic option. It does not directly interfere in the pathophysiological process of the TTTS, limiting itself only to offering a measure that tries to reestablish the intra-amniotic pressure balance.

Septostomy

Septostomy is a procedure based on therapeutic rupture of the amniotic membrane at the site where the two amniotic cavities are divided. This approach aims to balance the fluid volume between the two amniotic sacs, which has the primary advantage of improving the hemodynamic state, mainly of the donor fetus, enabling oral rehydration and promoting more significant fluid reabsorption. Currently, septostomy has been neglected due to the intrinsic risk of completely breaking the amniotic membrane, which would generate a monoamniotic pregnancy.

Fetoscopic laser ablation of anastomotic vessels

Since 2004, after the publication of the multicenter randomized study “Eurofetus”, fetoscopic laser ablation of anastomotic vessels has been recognized as the gold standard for the treatment of TTTS, especially in the most severe cases. The technique was developed by obstetrician Dr. Julian DeLia and by the pathologist Dr. Kurt Benirschke, in 1984, and aimed to interrupt the placental vascular communication between the two fetuses. The procedure is based on the ablation of placental vessels using a fetoscope, which ultimately creates two independent functional circulatory systems in a single placenta, which “dichorionizes” the shared placental mass. After a careful scan, there is the identification of individual placental anastomoses, especially the VA, which are occluded using the laser. That said, at the end of the procedure, a line is drawn with the laser from end to end of the placenta. This method is called Solomon’s technique. The explanation for this is simple: it is known that more than one-third of placentas submitted to laser ablation may contain residual vascular anastomoses, usually with a caliber smaller than one millimeter (<1 mm), which may not be seen during fetoscopy. Thus, when compared to the standard technique, the Solomon technique has been shown to considerably reduce the recurrence of TTTS after laser ablation by promoting an essential reduction in these residual anastomoses. Comparative studies between selective ablation and the Solomon technique show a reduction in the occurrence of anemia-polycthemia sequence from 16% to 7%, in addition to reducing the chance of developing recurrent TTTS from 3% to 1%.

As the only procedure that acts directly on the interruption of the pathogenic pathway, significant scientific evidence indicates that laser ablation promotes survival from 61 to 83% of at least one of the fetuses, with neurological sequelae observed in only 1.2 to 7.6% of the neonates. It is usually performed on an outpatient basis, using local anesthesia and intravenous sedation.

As with any surgical procedure, laser ablation can pose risks of maternal and fetal complications. Maternal complications are observed in about 5.4% of the operations performed, the most commonly reported being: hemorrhage, placental detachment; chorioamnionitis; and accumulation of amniotic fluid in the peritoneal cavity. Early fetal complications include early rupture of membranes, amniochorial separation, and fetal death.
On the other hand, in some cases, the procedure ends with no apparent immediate complications. However, during follow-up of the late pregnancy, complications are observed, such as early rupture of membranes; placental detachment; recurrent TTTS; and anemia-polycthenia sequence, generated by the existence of small-caliber remaining placental anastomoses, which chronically causes anemia in the donor fetus and polycythemia in the recipient fetus. Laser photococagulation presents itself as an ideal therapeutic possibility, especially in cases classified as Quintero II, III, or IV21,22. This technique can be used, preferably, until the 26th week of pregnancy. After this period, the ablation technique using a fetoscope becomes more complex and with a higher risk of complications23,30. This happens because, in late pregnancies, there is more incredible difficulty in identifying the anastomoses due to turbidity of the amniotic fluid, larger placentas require more significant scanning and a greater number of ablations, and more developed vessels and larger caliber offer a higher risk of bleeding complications30.

Laser photococagulation has consistent data in the literature that supports its use, with an overall survival rate of approximately 60% for the donor fetus and 70% for the recipient fetus, with a risk of neurological sequelae of 9-10%25. It is important to emphasize that TTTS is a rare disease; because of this, more information is still needed from randomized clinical trials to reinforce the efficacy and expected outcomes of existing therapeutic proposals30.

Selective Feticide

Considered only in severe cases of TTTS, such as Quintero’s stages III and IV, selective feticide consists of the iatrogenic interruption of the umbilical cord blood flow of one fetus in an attempt to optimize the survival chances of the other conceptus2. Thus, for all the moral and psychological weight intrinsic to the decision for this therapeutic method, selective feticide should only be considered when the death of one of the fetuses is inevitable or highly likely15. Brazilian legislation prohibits any procedure involving an embryonic or fetal reduction in multiple pregnancies, making selective feticide for pregnant women with TTTS an unfeasible therapeutic alternative from a legal point of view in Brazil16.

Conclusion

TTTS is one of the most severe obstetric complications that affect monochorionic twin pregnancies. Once the pathogenic pathway of the disease is established, based on the presence of an unbalanced placental circulatory system, the clinical manifestations develop distinctly in each of the fetuses. The diagnosis is essentially ultrasonographic, so determining the chorionicity of twin pregnancies must be done early. In addition to early diagnosis, there is a clear need to perform, whenever possible, ultrasound screening and adequate monitoring of affected pregnant women. Fetoscopic laser ablation of anastomotic vessels has established itself, since 2004, as the gold standard for the treatment of TTTS. As the only modality that directly interrupts the pathophysiological mechanism of the disease, it presents expressive results in reducing morbidity and mortality, with high survival of at least one of the fetuses and low rates of neurological sequelae.

Author’s Contribution

We describe contributions to the papers using the taxonomy (CRediT) provide above: Conceptualization, Investigation, Methodology, Visualization & Writing - review & editing: Marcio Erlei Vieira de Sa Filho, Rafael Lauro Silva Lima e Fredson Guilherme Gomes. Project administration, Supervision & Writing - original draft: Marcio Erlei Vieira de Sa Filho, Rafael Lauro Silva Lima e Fredson Guilherme Gomes. Data curation & Formal Analysis: Marcio Erlei Vieira de Sa Filho, Rafael Lauro Silva Lima e Fredson Guilherme Gomes.

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