Acta Obstet Ginecol Port 2012;6(2):67-74

Review Article/Artigo de Revisão

Revisiting twin-to-twin transfusion syndrome: from screening to treatment

Revisitando o síndrome de transfusão feto-fetal: do rastreio ao tratamento

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ABSTRACT

Monochorionic diamniotic twin pregnancies have an almost 15% risk of developing twin-to-twin transfusion syndrome (TTTS) and a higher rate of perinatal mortality. The TTTS occurs due to placental anastomoses that create an unbalanced exchange of blood between twins, leading to hypervolemia, polyuria and polyhydramnios in the recipient twin and hypovolemia, oliguria and oligohydramnios in the donor twin.

Diagnosis is defined by an oligo/polyhydramnios sequence and bladder filling. TTTS can be predicted by ultrasound and Doppler evaluation, based on increased nuchal translucency and abnormal blood flow waveform in the Ductus Venosus. The Quintero staging system is the most frequently used, but new classifications have been developed based on the severity of cardiac dysfunction in the recipient twin. The gold standard for treatment is endoscopic laser ablation of the vascular anastomoses, although septostomy and amnioreduction are also used in this setting. Numerous intrauterine and perinatal complications are associated with TTTS, including fetal death, preterm delivery, low birth weight and premature rupture of membranes, but long-term neurologic and cardiac complications are also a matter of major concern.

Keywords: twin twin transfusion syndrome; monozygotic twins; Doppler ultrasonography; laser therapy; perinatal complications

INTRODUCTION

The main goal of this review is to revisit the literature from the last 10 years in relation with epidemiology, pathophysiology, prediction, screening, staging, treatment and complications of twin-to-twin transfusion syndrome (TTTS).

A search in Pubmed was performed using the query *"twin-to-twin transfusion syndrome"[All Fields] OR "twin-twin transfusion syndrome"[All Fields] OR "fetofetal transfusion"[All Fields]*. The search was limited to the last 10 years, to humans, to MEDLINE articles and to English and Portuguese languages. The inclusion criteria were: articles related with pathophysiology, prediction, screening, staging, treatment and complications of TTTS. Letters, case reports and reviews were excluded. Articles primarily focused in other subjects than TTTS, in triplets or in monoamniotic pregnancies were also excluded. A total of 30 articles were included in this review.

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DEFINITION

Twin-to-twin transfusion syndrome affects 9% to 17%[1-4] of all monochorionic diamniotic twin pregnancies and it is associated with high perinatal morbidity and mortality rate[5]. Monochorionic diamniotic pregnancies are defined using ultrasonography during pregnancy identifying absence of the lambda sign, one single placenta and fetuses of the same gender[2,4,6]. An unbalance exchange of blood through vascular anastomoses is thought to be the leading cause of the disease. As a result hypovolemia, oliguria and oligohydramnios are documented in the donor twin, in contrast with hypervolemia, polyuria and polyhydramnios in the recipient twin[6]. If left untreated, TTTS is expected to be lethal for both fetuses[5].

PATHOPHYSIOLOGY

a) Vascular Anastomoses

The pathophysiology of TTTS is usually explained on an angioarchitectural basis. There are four types of placental anastomoses described: arterioarterial (AA) and venovenous (VV), which are superficial and bidirectional anastomoses on the chorionic surface; arteriovenous (AV) and venoarterial (VA) that are deep and unidirectional anastomoses, piercing the chorionic plate to supply the cotyledon, at a capillary level[6].

In 2002, Bermúdez et al.[6] showed that placentas without anastomoses do not develop TTTS and placentas with only superficial anastomoses are unlikely to develop the syndrome. They also reported that TTTS is present in 80% of placentas with only deep anastomoses and 20% of placentas with combined superficial and deep anastomoses. Unidirectional AV anastomoses can create unbalanced exchange of blood between two monochorionic twins, causing hypervolemia in the recipient twin and hypovolemia in the donor twin: a shared cotyledon receives its arterial supply from one twin and gives its venous and well oxygenated blood to the other twin. They defend a possible protective role for superficial anastomoses and there is evidence that TTTS is higher in pregnancies with no AA anastomoses[7]. Although the real mechanism is unknown, bi-directional AA anastomoses may allow some compensation during the early stages of TTTS.

b) Renin-angiotensin System (RAS)

TTTS is associated with maternal hyperaldosteronism with aldosterone levels ten-fold higher than non-pregnant women and two-fold higher than normal mid-trimester twin pregnancies. Apparently, these changes are dissociated from renin and angiotensin II levels, since they remain in normal levels[8]. Six hours after TTTS correction, there is a significant decrease of aldosterone levels, associated with increased levels of atrial natriuretic protein (ANP), while angiotensin remains constant. This suggests the hypothesis of Pseudo Primary Aldosteronism, possibly related to a placental factor. It is also noted hemodilution with decreased hematocrit, hemoglobin and plasma protein levels, not related with changes in aldosterone but with the volume of amniotic fluid[8].

In the donor twin, it seems that RAS up-regulation, in response to hypovolemia, leads to oliguria, exacerbating oligohydramnios and causing intrauterine growth restriction. In contrast, RAS is down-regulated in the recipient twin. However, angiotensin II may be transferred through placental anastomoses resulting in RAS paroxysmal activation in the recipient twin resulting in fetal vascular disturbances and cardiomyopathy[9].

c) Atrial natriuretic protein

Other authors suggest that ANP can be implicated in the pathophysiology of polyhydramnios/oligohydramnios sequence in TTTS. Bajoria et al.[10] showed that fetal concentrations of ANP were significantly higher in the recipient twin than in the donor twin, while ANP levels of donor twin were comparable to non-TTTS twins. This could be explained by transference of ANP by placental vascular anastomoses from the donor to the recipient twin. They also showed that maternal ANP concentrations are lower in TTTS than non-TTTS pregnancies. Immunolocalization of ANP in fetal kidney shows that immunoreactivity is more intense in distal convoluted tubule cells and in the cytoplasm of intercalated cells, in the recipient than in the donor twin. In fetal heart, immunoreactivity is most intense in the perinuclear and subendocardial position. Atrial distension responding to chronic cardiac overload seems to be the most plausible explanation to increased ANP synthesis in the recipient twin. As ANP promotes sodium excretion and diuresis, high ANP concentrations may lead to polyuria and consequently explain the pathophysiology of polyhydramnios in the recipient twin. ANP concentrations in the donor twin similar to non-TTTS twins imply that other mechanism than ANP may regulate fetal fluid balance[10].

d) Velamentous cord insertion/unequal placental sharing

It was suggested that velamentous cord insertion and unequal placental sharing may have implications in the pathophysiology, considering its higher incidence in monochorionic twin pregnancies (13%). Velamentous cord insertions is defined as cord insertion in the fetal membranes, instead

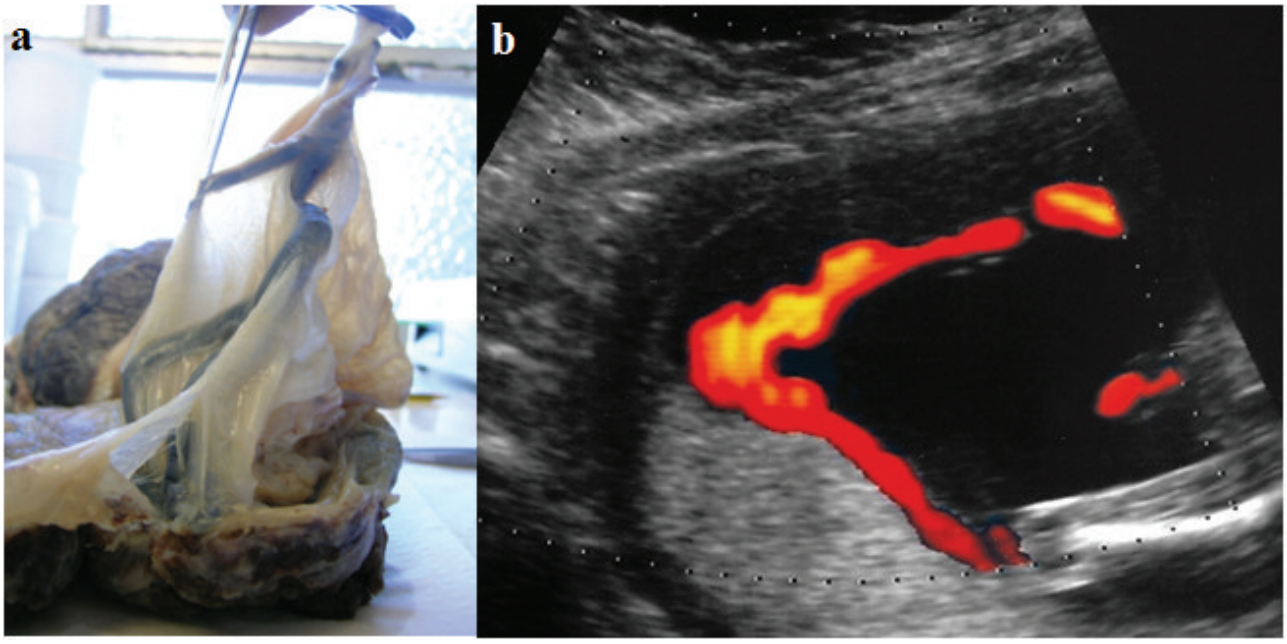

Figure 1. a) Velamentous cord insertion *in vivo* (courtesy of Otília Brandão MD); b) Velamentous cord insertion in ultrasonography (courtesy of Nuno Montenegro PhD MD).

of the placental disc[11] (Figure 1). Recent studies[12] found no significant difference in the incidence of velamentous cord insertion and unequal placental territories between placentas with or without TTTS, concluding that velamentous cord insertion and unequal placental territories have no implications in the pathophysiology of TTTS. However, other studies[11] showed a higher incidence of velamentous cord insertion in TTTS placentas (33%) compared with non-TTTS placentas (10%). The reason for this discrepancy remains unclear.

SCREENING AND PREDICTION

The routine screening in monochorionic twin should include ultrasound and Doppler carried out every two weeks after 16 weeks. If TTTS eventually develops, immediate treatment should be offered. The examination must include the following parameters: A-wave in the Ductus Venosus (DV), nuchal translucency (NT) thickness in the first trimester; folding of the intertwin membrane; deepest vertical pool (DVP) of amniotic fluid for both fetuses; bladder filling and end-diastolic flow of the umbilical artery in both recipient and donor twins[2,13].

The criteria for diagnosis are defined by oligo/polyhydramnios sequence in monochorionic pregnancies. Oligohydramnios is defined as a DVP < 2cm. Polyhydramnios is defined as a DVP > 8cm before 20 weeks and >10 cm after that [2,13,14].

Patients should be informed about the symptoms of TTTS and advised to seek medical care in case of sudden increased of abdominal size or premature contractions[2]. If TTTS is diagnosed, a series of sonographic evaluation, with Doppler flowmetry of umbilical artery, DV and middle cerebral artery peak systolic velocity (MCA-PSV)[13].

Until recently, TTTS was only diagnosed when it was established with discrepant amniotic fluid volume between donor and recipient. But with the identification of some predictors, monochorionic twin pregnancies can be anticipated as high risk to develop TTTS and can have a closer follow-up in order to diagnose the syndrome earlier and avoid serious complications. The prediction of TTTS is based in the characteristics of the ultrasound and Doppler examination and includes discrepancy in crown-rump length (CRL), increased NT thickness[1] and abnormal blood flow waveform in DV in the first trimester of pregnancy[15].

However, DV blood flow evaluation seems to be the most powerful predictor of TTTS. When at least one of the fetuses had an abnormal DV waveform (Figures 2c, 2d), the relative risk (RR) of developing TTTS was 15.5 with a sensitivity of 75% and a specificity of 92%. There was also a positive association between a difference in NT thickness ≥ 0.6 mm and TTTS, with a RR of 1.61, with a sensitivity of 50% and a specificity of 91% [15]. This is consistent with a previous studies which suggested that a discordance in NT of ≥ 20% at 11 to 13+6 weeks implicated a risk of 30% of

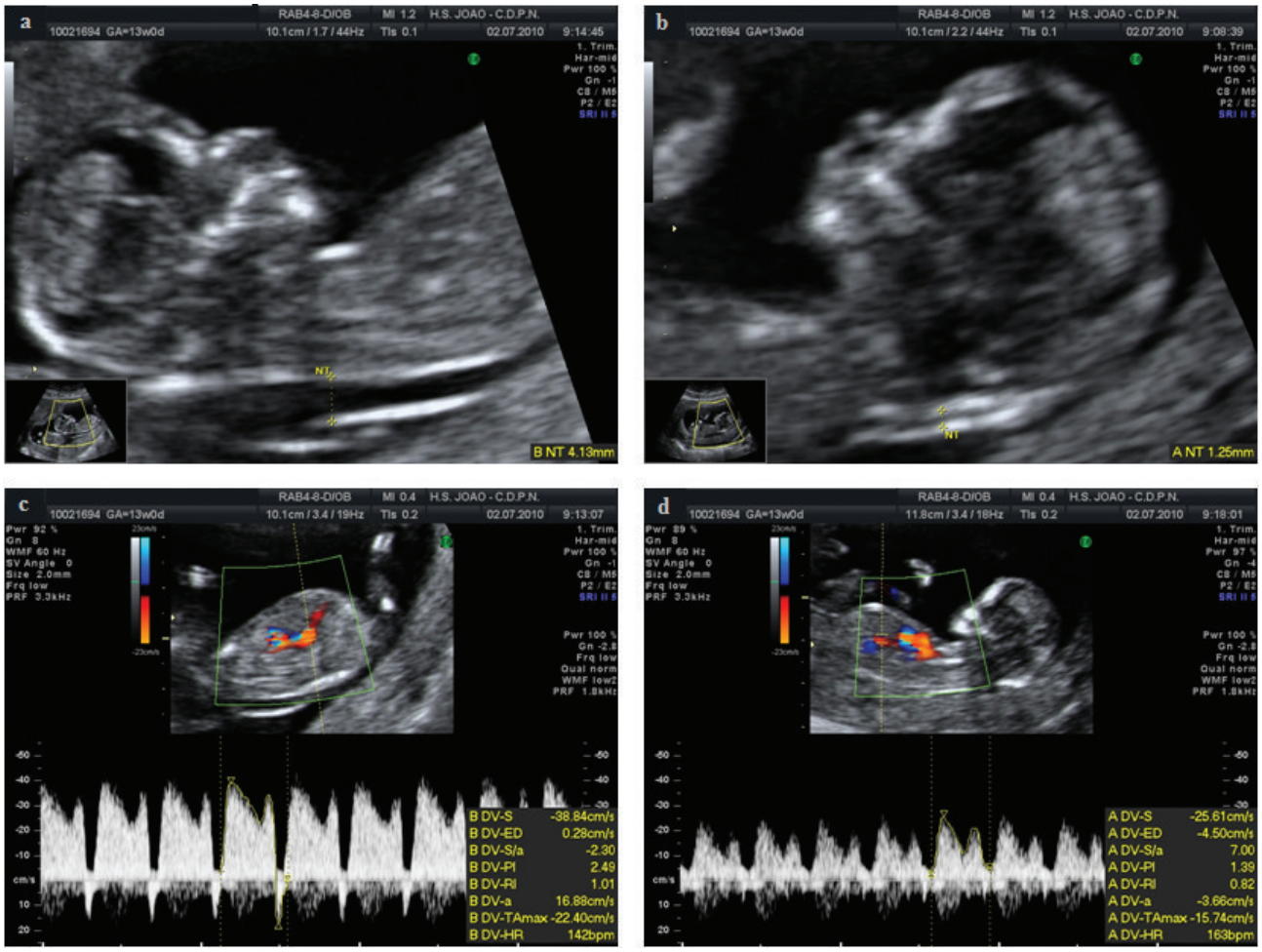

Figure 2. Ultrasound images from a monochorionic diamniotic twin pregnancy diagnosed at 13 weeks' gestation. There is a nuchal translucency (NT) discrepancy (NT = 1.25, 4.13 mm) (a,b). One of the fetuses presents abnormal flow in the ductus venosus (DV) with reversed A-wave (c), whereas the other has normal blood flow waveforms in the DV (d).

developing TTTS, contrasting with a smaller risk of 10% in those pregnancies with NT discrepancy < 20% [4].

Furthermore, when combing NT and DV blood flow, fetuses with NT < 0.6 mm and abnormal DV blood flow in at least one of the fetuses the relative risk for TTTS was 10.37. When at least one of the fetuses has abnormal DV blood flow and NT ≥ 0.6 mm, the relative risk to develop TTTS increased to 21 [15].

Lewi et al[1] suggest that CRL could be used in the first trimester as a predictor of TTTS. However, CRL discrepancy ≥ 6 mm had a sensitivity of 52%, with many false positives (23%) and a positive predictive value of 19%. In the other hand, Matias et al[15] as well as Kagan et al[4] showed that there was no significant association between the intertwin difference in CRL or the intertwin CRL ratio and the development or TTTS, showing a low sensitivity rate of 8.3% [15].

STAGING

In 1999, Quintero et al. proposed a classification of TTTS based on two-dimensional ultrasound and Doppler flowmetry (Table 1) [cited by [16]]:

Quintero et al. (2003)[16] suggested that patients in stage I or II benefit from serial amnioreductions, especially with a gestational age > 22 weeks. They also proposed that stage II diagnosed before 22 weeks and stages III and IV probably have a better prognosis with endoscopic laser surgery. Senat et al. (2004)[14] disagreed, saying that stages I or II can also benefit from laser therapy and that staging should not be taken into account when the treatment modality is chosen.

Muratore et al (2009)[5] in their study, obtained a similar survival for stages I, II and IV after the treatment (be-

Table I. Quintero's stages

Stage I	Donor's bladder visible and Doppler studies normal
Stage II	Donor's bladder not visible, but Doppler studies not critically abnormal
Stage III	Absent or reverse end-diastolic velocity in the umbilical artery, reverse flow in Ductus Venosus, or pulsatile Umbilical Venous Flow
Stage IV	Presence of ascites, pericardial or pleural effusion, scalp edema or overt hydrops
Stage V	Death of one or both twins

tween 75 and 80%), while stage III had a significant lower survival (55%). This seems to be a limitation of this staging system. It can be explained by the possible existence of an unknown subgroup within stage III with specific characteristics that make this group more vulnerable for the adverse effects of laser ablation. In the other hand, the higher survival of stage IV comparatively to stage III can be explained by a possible compensated state as the disease progresses. It can also reflect the inadequacies of Quintero Staging.

Several authors defend that Quintero staging does not properly feature the cardiovascular aspects of the disease[17-19]. Different studies have been made in order to create a new staging system based on the severity of cardiac dysfunction in the recipient twin. The Children's Hospital of Philadelphia (CHOP) Cardiovascular Score is the most complete score and includes 12 variables, evaluated by fetal echocardiography, which, with experience, may be accessed in 30-45 minutes. The variables include ventricular hypertrophy, cardiac dilation, ventricular dysfunction, tricuspid valve regurgitation, mitral valve regurgitation, tricuspid valve inflow, mitral valve inflow, pulsatility in the umbilical vein, right-sided outflow tract and pulmonary regurgitation on the recipient twin and blood flow in the umbilical artery on the donor twin[17]. Posteriorly, Shah et al. (2008)[18] proposed another scoring system, Fetal Cardiovascular Profile Score (CVPS), also assessed by fetal echocardiography, enhancing the important association between cardiovascular abnormalities and the outcome of recipient twin. Finally, Stirnemann et al (2010)[19], suggested that profiling fetal cardiac function in TTTS could lead to a quantitative assessment of cardiomyopathy in the recipient twin, using echocardiography, and that cardiomyopathy assessment could be used as a marker of severity and a tool for staging the disease.

TREATMENT

Nowadays there are three main treatment modalities available for TTTS: Septostomy, Amnioreduction and Endoscopic Laser Surgery.

Septostomy consists in the perforation of the intertwin membrane, puncturing just one time with a 22-gauge needle, guided by ultrasound. The needle is introduced over the donor's gestational sac to the recipient's sac. The patients repeat ultrasound 48 hours after the procedure to evaluate if amniotic fluid volume is equilibrated in the two gestational sacs. If this does not occur Septostomy is repeated. Sometimes Septostomy can be performed along with Amnioreduction. This occurs if the oligohydramnios is not resolved or if the DVP in the recipient twin increases 30% over the baseline value 48 hours after Septostomy. Then, a 22-gauge needle is inserted through the 18-gauge needle required for the Amnioreduction, in order to avoid more than 1 puncture in the amniotic cavity. In most of the centers this technique is not currently adopted[20] and the Template produced by the Working Group on Multiple Pregnancy does not recommend Septostomy as a treatment for TTTS[13].

Amnioreduction is performed when recipient twin sac registers polyhydramnios (DVP > 8.0 cm before 20 weeks and > 10.0 cm after that). The procedure is performed under continuous ultrasonographic guidance[14,16,20]. Special attention is required to avoid the intertwin membrane and donor's sac so to prevent an unintentional Septostomy[20]. 18 to 20-gauge needle is introduced within the polyhydramniotic sac and connected to a vacuum suction bottle, a syringe aspiration or a wall suction, to accelerate the procedure by actively draining of the amniotic fluid. The amniotic fluid is drained to the point where DVP is less than 5 to 6 cm. The Amnioreduction is repeated whenever the recipient shows recurrence of polyhydramnios[14,16,20]. It could also be repeated when the pregnant has excessive uterine activity or respiratory compromise[20].

However, the **gold standard** for the treatment of stage II/III is laser ablation of vascular anastomoses[14,21]. Guided by continuous ultrasonographic, a 3.3 mm 3 port fetoscope, with a lent port and two working ports, is placed by a 4 mm incision that allows access to the intertwin membrane's insertion on the placenta. One of the working ports is for the 600 µm laser endostat and the other is used to cleaning the amniotic cavity with physiologic saline[21]. The next

step is to identify anastomotic vessels in the recipient's sac by following vessels that cross the membrane. As soon as anastomotic vessels are identified they are coagulated with a 30 to 60 watts power[14,21] with endostat at 1 cm from the vessel[21]. If the vessels belong to just one twin, they are left intact[14]. Finally, the amniotic fluid is drained to the point where DVP is less than 5 to 6 cm[14,21]. In the removed amniotic fluid, karyotype is always assessed.

PERINATAL COMPLICATIONS

Failure of the treatment is considered when polyhydramnios reappears or when it occurs cardiac failure with imminent fetal demise. The following criteria define cardiac failure after treatment: «1) development or progression of severe atrioventricular valve (mitral or tricuspid) regurgitation, 2) reversal of A-wave of DV in the donor twin, 3) reversal of diastolic flow in the umbilical artery of the recipient twin, or 4) development or progression of severe biventricular dysfunction.»[21]

Moise et al[20], in 2005, in a randomized trial compared Amnioreduction with Septostomy. 73 patients were included in this study, 97% in stages I to III and 3% complicated with hydropsia (stage IV). 36 patients were included in amnioreduction group and 37 patients were included in septostomy group. There were no significant differences between both techniques regarding the survival of at least one or both twins, the overall fetal and neonatal deaths, the gestational age at delivery and the birth weight of donor and recipient twin. However, in the Amnioreduction group, patients were more likely to require more than one procedure (46% for Septostomy versus 69% for Amnioreduction). They concluded that, in spite of Septostomy having advantages over Amnioreduction, both techniques are a viable treatment for Stages I and II.

Endoscopic laser ablation is nowadays considered the main treatment for TTTS. However it can have many complications for both mother and fetuses. The complications include fetal demise, preterm delivery, preterm premature rupture of membranes and postoperative contractions[5].

Senat et al[14], in 2004, performed a randomized, controlled trial to compare Amnioreduction and Endoscopic Laser Surgery. In this study the survival of at least one twin in the perinatal period was significantly higher in the laser group (76%) versus Amnioreduction (56%). The same occurred after 6 months, with 76% survival in the laser group and 51% in the Amnioreduction group. In contrast, a posterior study by Combleholme et al[21], in 2007, showed no significant survival of one or both twins (60% for Amnioreduction versus 45% for Endoscopic Laser Surgery), suggesting that none is superior in this study. When they considered Quintero stages, in Senat's study those pregnancies classified as Stages I or II has a higher survival (73%) than Stages III or IV (55%). When they compared the two procedures, Endoscopic Laser Surgery had a higher survival rate than Amnioreduction in all stages (86% for Endoscopic Laser Surgery and 58% for Amnioreduction in Stages I or II; 66% for endoscopic laser surgery and 44% for Amnioreduction in Stages III or IV)[14]. This totally contrasts with Cromblehorme's study in which there was a significant difference in stages III or IV survival after 30 days with a 67% survival for Amnioreduction opposing to 12.5% for endoscopic laser surgery[21].

In Senat's study[14], there was no significant difference in maternal complications (intra-abdominal leakage of amniotic fluid and placental abruption) and premature rupture of membranes after the procedure for both laser and amnioreduction group. Although pregnancy loss before 24 weeks of gestation was higher in the laser group (17%) than in the amnioreduction group (11%), there was no significant difference. The higher pregnancy loss in laser group could be explained by the placental vessels damage during the laser procedure. The median gestational age at delivery was significantly higher in Endoscopic Laser Surgery (33.3 weeks) than in Amnioreduction (29.0 weeks). The birth weight was also higher in the laser group than in the amnioreduction group (1757 g and 1359 g respectively, $P < 0.001$). The lower neonatal death rate in the laser group can be explained by the older gestational age in that group and the differences in gestational age can be explained by the repeated invasive procedures and recurrent polyhydramnios in the amnioreduction group.

Although TTTS can be resolved with the coagulation of all visible anastomoses on the chorionic surface, in case of missed anastomoses, related with failed surgery, double intrauterine fetal death, discordant hemoglobin values that requires intrauterine transfusion and recurrence of TTTS can occur[22]. Failed surgery occurs when the procedure is difficult (small anastomoses not seen during fetoscopy; anastomoses not coagulated to spare cotyledons; the donor's placental vessels collapsed by hypovolemia and vasoconstriction which were not detected; anastomotic flow obstruction caused but insufficient coagulation or anastomoses too large to coagulate) or in the presence of velamentous cord insertion[3,23]. There is no relation between failed surgery and placental location[3,23]. Missed large AV and VA anastomoses result in double intrauterine fetal death and recurrence of TTTS but can be compensated by

large AA anastomoses. Missed small AV and VA anastomoses result in isolated discordant hemoglobin values[22].

In order to identify early recurrence of TTTS or blood transfusion from the former recipient to the former donor, the follow-up should include a weekly ultrasound even after successful treatment in cases of TTTS before 26 weeks[3]. Since residual anastomoses are more frequently associated with hemoglobin differences between the two fetuses and anemia or polycythemia at birth, it is recommended serial measurement of MCA-PSV after laser surgery[3,23].

Transient hydropic signs are frequently observed after Endoscopic Laser Surgery. The signs include skin edema, pleural effusion, ascites and pericardial effusion. It occurs in 5.5% of the recipients and in 27% of the donors[24]. When it occurs in the recipient it is associated with congestive heart failure and with a poor prognosis [cited by [24]]; recipients who develop hydrops usually die a few days later. On the other hand, donors with transient hydrops after laser treatment usually do not have a poor prognosis. This could be explained by increased arterial resistance and impaired diuresis which leads to a transient hypervolemia after treatment and it may be a sign of a successful resolution of TTTS. Pregnancies with hydropic donor are associated with a significantly higher gestational age at delivery and birth weight for recipient and donor. In some cases hydrops is associated with a poor prognosis in the donor, but in these cases the fetus shows signs of severe hypoxia by Doppler flowmetry[24].

LONGTERM COMPLICATIONS

Neurodevelopment impairment affects 12 to 17% of all children born of treated TTTS pregnancies[25, 26] and includes cases of Cerebral Palsy (quadriplegia, diplegia and hemiplegia), severe mental development delay, deafness and severe psychomotor development delay[25]. Regarding neurological and physical examination it could be classified as: normal physical and neurological examination (N1), neurologic deficiencies with perspectives of normalization (N2), and major neurological impairment (N3), for example cerebral palsy[26]. Senat et al[14] reported that pregnancies treated with endoscopic laser surgery have better neurological outcome and higher survival rate at 6 months of age than those who are treated with serial amnioreductions. Posterior studies[25] are in good agreement with the previous results. It is also consistent that the survival rate does not change after 6 months, so they suggest that the children with the most severe complications die spontaneously or immediately after birth due to serious brain lesions[25,26]. Hemodynamic and hematological imbalance, associated with prematurity and low birth weight, may explain the pathophysiology of the cerebral injury[27]. There is no significant difference between neurological impairment of both donor and recipient twin, which may suggest that both twins have the same risk to have a poorer outcome[25,26].

As stated previously, TTTS induces a hemodynamic unbalance state in both twins, with hypovolemia in donor twin and hypervolemia in the recipient twin who also registers signs of pressure overload[6,17]. The most common echocardiographic findings in recipient twins are ventricular dilation, hypertrophy and tricuspid regurgitations, probably related with the pressure overload in the right ventricle. The donor twins are more likely to have abnormal umbilical artery diastolic blood flow[17]. Acquired right ventricular outflow tract obstruction occurs in 9% of the recipient twins, probably as a consequence of myocardial hypertrophy which causes direct obstruction of pulmonary blood flow. As a result, the blood redirection from the right ventricle will cause progression to pulmonary stenosis and right ventricular hypoplasia. Pulmonary stenosis may only appeared later in childhood[28]. In a 10-year follow-up[29], both former donor and recipient twins had normal cardiac dimensions, systolic and diastolic function, although recipient twin has a slight reduction in early diastolic ventricular relaxation.

Donor twin has a pulse wave velocity (PWV) in the brachioradial artery two fold higher than recipient twin, probably caused by donor's chronic hypovolemia. This shows the increased arterial stiffness in donor twin. Although treatment doesn't alter this intertwin arterial wall stiffness discordant, PWV discordance seems to decrease, resembling the one seen in dichorionic twins[30].

CONCLUSION

In summary, TTTS is a condition that complicates many monochorionic diamniotic twin pregnancies and is associated with high perinatal mortality and morbidity. It is diagnosed using ultrasonography based on oligo/polyhydramnios sequence and bladder filling and it can be predicted measuring NT and DV wave form at 11-14 weeks. The Gold Standard for treatment is Laser Endoscopic Ablation of the placental vessels, although Amnioreduction or Septostomy can be used. TTTS is associated with a high rate of perinatal and long-term complications.

Conflict of interest statement: None declared.

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