

Diagnosis and Management of Twin-Twin Transfusion Syndrome

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ABSTRACT

Twin-twin transfusion syndrome (TTTS) is a complication unique to monochorionic twin pregnancies, in which the two twins share a common placenta and unequal blood exchange from one twin (donor) to the cotwin occurs through placental arterovenous anastomoses. The diagnosis is posed with the sonographic detection of oligohydramnios in the donor's sac, as a consequence of hypovolemia, and polyhydramnios in the recipient's sac, resulting from hypervolemia. The severity of TTTS is assessed according to Quintero staging system, which is based on five stages that range from visualization of the donor's bladder to intrauterine demise of one or both twins. Because laser therapy has revealed the optimal treatment for TTTS, management of twins affected with TTTS consists in preoperative and postoperative assessment of the twins by ultrasound examination. The aim of this review was to describe the diagnosis and management of TTTS and discuss controversies and limitations of current literature.

Keywords: Twin-twin transfusion syndrome, Laser therapy, Monochorionic pregnancies, Fetal management, Fetal ultrasound, Quintero staging system.

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INTRODUCTION

Twin-twin transfusion syndrome (TTTS) occurs in 10 to 15% of monochorionic diamniotic pregnancies. The syndrome is due to unequal blood exchange between one twin (donor) and cotwin (recipient) through placental vascular anastomoses. In almost all monochorionic pregnancies, placental anastomoses can be documented by placental histology and are classified in arteroarterious, venovenous and arterovenous anastomoses. The first two types seem to have a protective role, whereas the latter are responsible for the hemodynamic imbalance that leads to a net transfer of blood from the donor to the recipient. As a consequence, the donor twin is affected with blood depletion and hypovolemia resulting in growth restriction, oligohydramnios and intrauterine demise, whereas the recipient twin is affected with increased blood volume, polyhydramnios and cardiac failure. Therefore, the incidence of intrauterine fetal demise is 3 times higher in monochorionic than dichorionic pregnancies, in which the two twins do not share a common placenta.¹ Fetal death of one twin poses the

Table 1: Outcomes of laser therapy vs serial amnioreduction

Outcome	Laser therapy (%)	Serial amnio-reduction (%)	OR (95%CI)
Overall survival rate	66.4	47.7	2.04 (1.52-2.76)
Neonatal death	8.2	25.2	0.24 (0.15-0.40)
Neurologic morbidity	13.6	29	0.21 (0.13-0.34)

OR: Odds ratio; 95% CI: Confidence interval (significant, if it does not encompass 1)

surviving twin at increased risk of mortality and morbidity, mainly cerebral damage. Two theories attempt to explain the mechanism of fetal injury after death of one twin. The first theory proposes that passage of thromboplastic material from the dead fetus to the survivor through placental vascular anastomoses can lead to disseminated intravascular coagulation. The second theory suggests that blood pressure drops acutely in the dying twin and causes exsanguination of the survivor to the dying twin through placental vascular anastomoses.² The two theories share the common feature that placental anastomoses are functional and connect the two fetal circulations. Therefore, photocoagulation of placental anastomoses and restoration of the two fetal circulations represent the rationale for laser therapy. Laser therapy is also associated with better outcomes compared with serial amnioreduction (Table 1).³

In this review, the diagnosis, assessment and management of TTTS are described.

DIAGNOSIS OF TTTS

TTTS is diagnosed with the sonographic detection of oligohydramnios in the donor's sac and polyhydramnios in the recipient's sac. Oligohydramnios is defined as maximal vertical pocket ≤ 2 cm and polyhydramnios as maximal vertical pocket ≥ 8 cm.

Controversies exist with regard to the diagnosis of TTTS. These are due to the fact that TTTS is diagnosed according to the appearance of symptoms rather than the etiology, since actually it is not possible to detect when arterovenous anastomoses become functional leading to unequal blood exchange between the two twins. The standard diagnostic criteria of TTTS consist in the visualization of the oligo/polyhydramnios sequence. Because amniotic fluid

production changes by gestational age, some authors proposed to increase the threshold for polyhydramnios to 10 cm in the recipient's sac, if TTTS is detected after 20 weeks.⁴ In addition, the amniotic fluid is related to renal function, which develops in the second-trimester; hence, it is not possible to recognize if TTTS occurs in the first-trimester. In contrast, case reports of monochorionic twin pregnancies, which ended with spontaneous abortion, have shown the onset of TTTS as early as 13 gestational weeks. In particular, arterovenous anastomoses on the chorionic plate, a dark red fetus with cardiomegaly and a pale co-twin were documented at autopsy.⁵ Fetal hydrops has also been described in monochorionic pregnancies at 14 weeks of gestation.⁶ To support the hypothesis that TTTS may occur in the first-trimester, several studies have demonstrated that severe forms of TTTS can be predicted in up to 60% of cases by intertwin discordance of crown-rump length and nuchal translucency. Furthermore, the reversed a-wave (atrial conduction) of the ductus venosus may be detected at 11 to 13 gestational week in 38% of fetuses that develop TTTS in the second-trimester. We believe that if signs of TTTS are present since first-trimester, also the syndrome should be present. However, further studies are needed to investigate whether TTTS can be identified in the first-trimester.

Once the diagnosis is posed, severity of TTTS is classified according to Quintero staging system⁷ as follow:

1. *Stage I*: Visualization of donor's bladder and normal Doppler examination
2. *Stage II*: Not visualization of the donor's bladder during 1-hour examination and normal Doppler examination
3. *Stage III*: Presence of at least one of the following Doppler anomalies in at least 1 fetus:
 - a. Absence or reversed end-diastolic velocity of the umbilical artery;
 - b. Reverse flow in the ductus venosus;
 - c. Pulsatile umbilical venous flow;
4. *Stage IV*: Hydrops
5. *Stage V*: Intrauterine demise of one or both twins.

The efficacy of Quintero staging system is questioned, mainly because it does not reflect the pathophysiology of the syndrome. For instance, donor's bladder may be visualized in more advanced forms of TTTS, the assessment of cardiac function in the recipient twin is not included, and the mildest forms of TTTS, i.e. stages I and II, are limited to the donor twin, whereas the examination of the recipient twin begins from stage III. In addition, Doppler studies might not be accurate, since pulsatile umbilical venous flow is a subjective definition and umbilical artery velocity is considered a pathological sign if absent or reversed,

Table 2: Rossi staging system

	<i>Donor</i>	<i>Recipient</i>
Stage I	Growth restriction <20th percentile	Altered blood velocity in the umbilical artery and/or ductus venosus flow
Stage II	Altered blood velocity in the umbilical artery and/or ductus venosus flow	Cardiac hypertrophy expressed with altered myocardial perfusion index hydrops
Stage III	Fetal anemia expressed by increased middle cerebral artery velocity	
Stage IV	Donor demise	Recipient demise

although it is reasonable to assume that also cut-off values, rather than absolute definitions (absent/present/reversed flow) of the umbilical artery might be associated with poor outcomes. A possible explanation for the low association between Quintero staging system and prognosis of TTTS could be the lack of a control group. Moreover, it is based on the symptomatology of TTTS, which differs between the two twins. In fact, the donor is affected with hypovolemia leading to oligohydramnios, whereas the recipient is affected with hypervolemia leading to polyhydramnios. We previously proposed a double staging system, namely Rossi staging system, in order to assess the two twins independently (Table 2).⁸

MANAGEMENT OF TTTS

There is wide evidence that serial amnioreduction as treatment of TTTS is associated with poor perinatal outcomes and should be abandoned, whereas laser therapy has revealed to be the optimal therapy. Therefore, management of TTTS is mainly based on a preoperative and postoperative management.

Preoperative Management

Preoperative management of monochorionic twin pregnancies complicated with TTTS is based on sonographic assessment of the two twins. Firstly, severity of TTTS is determined by applying Quintero staging system.⁷ In TTTS treated with laser therapy, the overall survival rate for each stage is as follow: 83% in stage I, 71% in stage II, 67% in stage III and 68% in stage IV.⁸ The number of twins alive for each twin set is not different between mild (Stages I and II) and severe forms (Stages III and IV) of TTTS, being no survivors the less frequent and double survivors the most frequent outcome in all the stages.⁸ This finding shows that Quintero staging system

does not provide information about the prognosis of TTTS undergoing laser therapy.

Preoperative management of twins with TTTS obviously includes the assessment of fetal growth. Several studies suggest that fetal growth discordance rather than individual growth should be investigated. In particular, intertwin growth discordance can be accurately detected as early as 11 to 14 gestational weeks.⁹ An intertwin discrepancy in crown-rump length (CRL) up to 10 mm, or 14% or 4 days of gestational age indicate a normal finding with no need for further surveillance.²² In contrast, a discordant CRL >90th percentile is suspicious for structural or chromosomal abnormalities and development of^{9,10} and the earlier is discordance the earlier is the onset of TTTS. These findings confirm that TTTS might be present earlier than actually diagnosed, although further studies are needed to standardize diagnostic criteria for TTTS in the first-trimester.

In the second-trimester, selective intrauterine growth restriction (SIUGR) can be observed in approximately 10 to 15%¹¹ of monochorionic pregnancies and is associated with a high-risk of fetal demise and neurological morbidity. This condition manifests when one of the two twins presents estimated fetal weight <10th percentile at 20 gestational weeks.

Gratacos et al¹² proposed a new classification of SIUGR, which is based on Doppler investigation of the umbilical artery:

- *Type I*: Positive diastolic flow
- *Type II*: Persistent absent or reversed end-diastolic flow
- *Type III*: Intermittent absent or reversed end-diastolic flow.

These Doppler patterns depend on the placental territory shared between the two twins and type of placental anastomoses.¹² Better outcomes are observed in type I, which is associated with intrauterine demise in approximately 3% of cases,¹² no cerebral injury,¹² and an average gestational age at delivery of 36 weeks.¹³ Type II is secondary to placental insufficiency and unequal blood exchange between the twins and leads to fetal hypoxia of the smaller twin, cerebral injury in 14% of cases, perinatal death in 50% of cases and a short gestational age at delivery.¹² Type III has a clinical evolution that is less predictable probably because the presence of arteroarterial anastomoses is responsible for instable hemodynamic balance between fetal circulation.¹⁴ In type III, the larger twin is also exposed to brain injury and intrauterine demise.¹⁴ Umbilical cord occlusion or laser photocoagulation of placental anastomoses seem to protect the larger twin while increasing intrauterine demise of the smaller.¹⁴ The association between SIUGR and TTTS has not been

established yet. However, because SIUGR seems to be a manifestation of unequal blood exchange across placental anastomoses, it may be speculated that SIUGR represents a variant of TTTS and that the definition of TTTS as amniotic fluid discordance does not identify the precise moment in which placental anastomoses become pathologically functional.

Recently, echocardiography of the recipient has been introduced in the preoperative management of TTTS due to the observation that in up to 70% of recipients,¹⁵ cardiac function is compromised by ventricular enlargement,¹⁶ increased myocardial thickness,¹⁷ shortened fraction of the systolic function,¹⁸ predominantly in the right ventricle,¹⁸ shortening time of ventricular filling and tricuspid regurgitation. These findings can be observed in the mild forms of TTTS¹⁵ and some authors propose to include the assessment of cardiac function in Quintero staging system.

Postoperative Management

Laser therapy is considered the optimal treatment for TTTS because it divides fetal circulation and 'dichorionize' the placenta, creating two independent circulations. For this reason, biometrial and vascular parameters that are abnormal before the procedure improve or even resolve completely after the procedure.

Recipients' growth, which is regular before laser therapy, decreases after surgery, whereas donors' growth remains constantly below the 5th percentile.¹⁹ This finding indicates that laser treatment leads to a reduction of recipients' feeding vessels and maintenance of donors' growth. As a consequence, discordant birth weight is 18%.

Cardiac function of recipients drastically improves within 48 hours after surgery: Cardiac size, valvular regurgitation and ventricular inflow and outflow normalize in about 50% of cases.¹⁵ Approximately 6 weeks after therapy, most recipients present normal cardiac function.²⁰ With regard to donors, the blood volume overload secondary to the new circulation can temporarily worsen cardiac function with increased cardiac size, tricuspid regurgitation, and ductus venosus alterations.²⁰

Neurological assessment is essential at birth. In twins treated with laser therapy the incidence of major cerebral injury is approximately 6% without differences between donors and recipients.²¹ Cerebral palsy is the most common adverse neurological outcome.²¹ In addition, about 11% of twins affected with TTTS treated with intrauterine laser ablation manifest neurological damage during infancy.²¹

CONCLUSION

Definition and classification of severity of TTTS are very useful to standardize criteria and uniform studies for research

proposal and laser therapy has increased survival rates of twins compared with amnioreduction and septostomy. Despite significant improvements in understanding and treatment of TTTS, some aspects are still a challenge. This is probably due to the fact that TTTS was defined and classified in 1999, and after 13 years it is time to revise it in the view of the progression in ultrasound images acquisition and surgical technologies overtime.

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