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Twin-to-Twin Transfusion Syndrome: Definition, Staging, and Ultrasound Assessment

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Objective: The purpose of this article is to review the definition of twin-to-twin transfusion syndrome (TTTS) and the sonographic diagnostic assessment of these cases prior to therapy.

Materials and Methods: The article addresses the terminology used to refer to the condition and describes the systematic ultrasound assessment of the condition, including the ultrasound diagnosis, the staging of the disease, cervical assessment and pre-operative mapping.

Results: From an etymologic and medical point of view, the term ‘fetofetal transfusion’ is more appropriate than ‘TTTS’. However, as the latter, and its attendant acronym TTTS, have been widely adopted in the English language, it is impractical to change at this point. TTTS is defined sonographically in the combined presence of a maximum vertical pocket (MVP) of 8 cm or greater in one sac and 2 cm or less in the other sac, regardless of the gestational age at diagnosis. Staging of the condition using the Quintero staging system is practical, reproducible, and accepted. Transvaginal cervical length assessment should be an integral part of the ultrasound evaluation. Pre-operative mapping to anticipate the location of the placental vascular anastomoses and avoid injuring the dividing membrane is also discussed.

Conclusions: The term ‘TTTS’ can continue to be used in the English medical literature. The condition can be diagnosed and assessed following a systematic ultrasound methodology. The use of such ultrasound methodology breaks the examination into a distinct set of components, assuring a comprehensive examination and proper communication among caregivers.

Keywords Ultrasound, monochorionic twins, twin-twin transfusion syndrome

TTTS occurs in approximately 5–10% of monochorionic twins (Lutfi et al., 2004). Monochorionic twins themselves occur in approximately 0.7% of all pregnancies (Wenstrom & Gall, 1988). Therefore, TTTS occurs in approximately 0.07% of all pregnancies. This amounts to approximately 2,800 pregnancies in the US per year affected with TTTS (Mathews & MacDorman, 2011). The disease is thought to occur secondary to an imbalance in the transfer of blood between two monochorionic twins through placental vascular anastomoses (Quintero et al., 2000). Although proof of this etiology has proven somewhat elusive, a wealth of indirect evidence does suggest this to be the fundamental mechanism for the development of this condition (Ishii et al., 2004; van Gemert et al., 1997; Wieacker et al., 1992). The unbalanced exchange of blood between two monochorionic fetuses results in a set of hemodynamic alterations that ultimately place the pregnancy at risk of being lost (Mahieu-Caputo et al., 2000; Mahieu-Caputo et al., 2005). The recipient twin develops polyuria and polyhydramnios and is presumed to be hypertensive. The donor twin develops anuria and oligohydramnios and is presumed to be hypotensive. Loss of the pregnancy may result either from preterm delivery or miscarriage, or demise of one or both fetuses. Untreated, TTTS results in pregnancy loss rate is of approximately 95% (Kontopoulos & Quintero, 2007).

Significant achievements have been made in both the understanding of the pathophysiology as well as in the evaluation and treatment of patients with TTTS. Among those

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included in the achievements are standardization of the diagnostic criteria, the development of a staging system to assess the severity of the disease, the development of an effective laser surgical technique to ablate the vascular anastomoses, the scientific demonstration of the superiority of laser therapy over serial amniocentesis (Senat et al., 2004), and continuous improvements in the actual performance of the laser surgery. The purpose of this article is to review the definition of TTTS and the sonographic diagnostic assessment of these cases prior to therapy.

**Terminology**

TTTS is a disease that is derived from the unbalanced sharing of blood between fetuses via placental anastomosing vessels. Technically, the disease occurs between two or more fetuses. As such, the proper term to refer to the condition should be ‘fetofetal transfusion’. In fact, this is the medical subject heading (MeSH) used by the National Library of Medicine to index any article related to the subject. However, because the most common form is between two monochorionic twins, the terms ‘twin–twin’, ‘twin twin’ or ‘twin-to-twin’ transfusion syndrome have been widely adopted in the English language, with the acronym TTTS used to summarize all prior grammatical variations. Several other terms have been used in the literature to refer to the entity (e.g., poly/oli syndrome, FTS, Twin-oligohydramnios-polyhydramnios syndrome (TOPS), a fact that, unfortunately, can have a number of detrimental effects, including suboptimal yields in the literature searches, delay in the sharing of knowledge and data, as well as other negative research and clinical consequences. Although the term ‘fetofetal transfusion syndrome’ is perhaps technically more appropriate, the terms ‘twin–twin transfusion’, twin-to-twin transfusion’ or ‘TTTS’ have been widely adopted and used. For the purposes of this article, we will use twin-to-twin transfusion, or TTTS.

**Sonographic Definition of TTTS**

If we can agree on how to name this condition, the next important step is to define the condition medically. TTTS is an entity defined clinically by ultrasound (Quintero et al., 1999). In and of itself, this represents a remarkable milestone in the diagnosis of the disease. Prior to establishing ultrasound as the sole method to diagnose TTTS, other criteria had been proposed, such as differences in the hemoglobin concentration of the fetuses (Blickstein, 1990; Saunders et al., 1991) or neonates (Abraham, 1967; Rausen et al., 1965) or in the birthweight discordance >20% (Tan et al., 1979) of the twins, or surgical pathology analyses of the placental vascular anastomoses (Benirschke, 1995). Based on the classic and conclusive article of Danskine and Nelson (1989), in which only 4/178 twin pregnancies had a Hb difference > 5 g/dL and a birthweight discordance >20%, but none of which had evidence of TTTS, the neonatal criteria to diagnose TTTS were abandoned (Berry et al., 1995; Danskine & Nelson, 1989; Fisk et al., 1990; Saunders et al., 1991). Meanwhile, although ultrasound criteria were being proposed to diagnose TTTS with isolated case reports (Elejalde et al., 1983; Wittman et al., 1981), including conflicting reports on the results of Doppler examination of the umbilical artery (Erskine, 1944; Farmakides et al., 1985; Giles et al., 1990), it became necessary to define sonographic elements critical to the diagnosis versus heterogeneous presentations of the condition (Blickstein, 1990; Mari et al., 2001). For example, while significant weight discordance >20% may exist in up to 70% of fetuses (Quintero, 2007), it is no longer used as diagnostic criterion (Chmait, Kontopoulos et al., 2011; Chmait et al., 2008). Similarly, abnormal Doppler findings in the donor or in the recipient twin are not present in all cases of TTTS, and as such, are not suitable for inclusion as a diagnostic criterion (Rizzo et al., 1993). Therefore, standardization of the ultrasound criteria to define TTTS required selecting unique universal ultrasound parameters (i.e., present in all cases), followed by additional sonographic parameters to describe the heterogeneous nature of the disease.

The current sonographic definition of twin–twin transfusion syndrome by ultrasound requires, ideally, the demonstration of: (1) a single placenta, (2) same external genitalia in both twins, and (3) significant amniotic fluid volume discordance between the two fetuses, with a deep vertical pocket of 8 cm or more in the sac of the recipient twin and 2 cm or less in the sac of the donor twin.

**Single Placenta**

The diagnosis of monochorionicity requires the sonographic demonstration of a single placenta, and in the case of diamniotic twins, a thin dividing membrane and the absence of a ‘twin peak’ sign (Monteagudo & Timor-Tritsch, 2000; Monteagudo et al., 1994; Saunders et al., 1991; Sepulveda et al., 1996; Sepulveda et al., 1997). The diagnosis of chorionicity using the absence of a twin-peak sign is made best in the first trimester because the sensitivity and specificity decrease with advanced gestational age (Sepulveda et al., 1996; Sepulveda et al., 1997). The presence of oligohydramnios in one of the sacs may hinder significantly the diagnosis of chorionicity. Indeed, the demonstration of a twin peak sign (lambda sign) or a T sign requires the presence of fluid on both sides of the membrane. Patients with oligohydramnios or anhydramnios in one sac, by definition, may not have enough fluid on both sides of the membrane to accurately assess this sign. As a corollary, the diagnosis of chorionicity should be made with caution or not at all if the twin peak sign or its absence cannot be definitively established (Bajoria & Kingdom, 1997; Finberg, 1992; Rode & Jackson, 1999; Wood et al., 1996).

Although TTTS usually occurs in patients with a monochorionic placenta, the physician should be aware of important exceptions. These exceptions include bilobed placentas.
and dichorionic monozygotic twins (Benirschke & Masliah, 2001; Chmait, Floyd et al., 2011; Machin, 2001). In cases of bilobed placentas, vascular anastomoses between the two discs allow the development of the syndrome (Lopriore et al., 2006). Dichorionic monozygotic twins may also develop placental vascular anastomoses (Foscini et al., 2003). In these cases, TTTS may develop, just as in any other monochorionic diamniotic twin pair (Chen et al., 2013; Lage et al., 1989; Lopriore et al., 2006; Quintero et al., 2010). The ultimate exception is monochorionic–dizygotic twin pregnancies, in which a single placenta and a thin dividing membrane exist, but in which the fetuses may be of different sex. Such pregnancies presumably result from fusion of the morula of two dizygotic fetuses during the implantation process (Ekelund et al., 2008). These pregnancies may also develop vascular anastomoses and TTTS (Quintero et al., 2003). Lastly, though exceedingly rare, placental vascular anastomoses may also occur in dichorionic–dizygotic twins (Biran et al., 2011). Such anastomoses were only thought to occur in certain species, including cattle and marmoset (Benirschke, 1995), but have also been reported in human pregnancies (Biran et al., 2011). These patients may also develop TTTS. Therefore, while the demonstration of a single placenta and an absent ‘twin-peak sign’ is characteristic of most TTTS cases, rare exceptions do occur. Interestingly, these variations serve to confirm that placental vascular anastomoses are a sine qua non for the condition to develop.

Similar External Genitalia

The sonographic demonstration of similar external genitalia may be difficult in the presence of oligohydramnios in one of the sacs. As mentioned above, in rare cases, fetuses may also be dizygotic and still present with TTTS (Quintero et al., 2003). Therefore, although ideally the demonstration of similar external genitalia in the fetuses would aid in establishing the diagnosis, this is often not possible and therefore not a requirement for the diagnosis of TTTS.

Amniotic Fluid Discordance

The decision to use a MVP of 8 cm or greater in one sac and 2 cm or less in the other sac is based on the fact that these measurements are well above and below the 95th and the 5th percentile for a normal pregnancy, respectively. (Magann & Martin, 1999; Magann, Chauhan et al., 1995; Magann, Whitworth et al., 1995; Magann et al., 1997; Magann, Chauhan, Barrilleaux et al., 2000; Magann, Chauhan, Whitworth, et al., 2000; Magann et al., 2003; Magann et al., 2004) While some groups have suggested that the MVP of 8 cm should be changed to 10 cm above 20 weeks (Chalouhi et al., 2011), our group has shown that this recommendation results in an underestimation of the incidence of bona fide TTTS of 27% (Quintero, 2003; Quintero et al., 1999). The ultrasound assessment of the MVP in the sac of the recipient twin requires that the measurement be taken in an area free of fetal body or umbilical cord. Furthermore, the measurement technically should be obtained perpendicularly to the skin while the patient is lying in a dorsal position. The assessment of the MVP in the sac of the donor twin may be limited due to severe oligohydramnios, as mentioned above. Although most donor twins are tightly apposed to the walls of the uterus (stuck), the donor twin can move freely within the amniotic cavity in approximately 15% of cases despite a complete lack of amniotic fluid. This phenomenon results from folding of the dividing membrane around the body of the fetus and back to the wall of the uterus. On ultrasound, this folding of the membrane appears as a sling with which the fetus is attached to the uterus. If unrecognized, the MVP in the sac of this fetus could be mistakenly assessed as within the sac of the recipient twin. We have called this sonographic sign the ‘cocoon sign’ (Quintero & Chmait, 2004), which represents a potential pitfall in the assessment of the amniotic fluid volume in the sac of the donor twin.

The presence of oligohydramnios in the sac of the donor twin can impair the adequate visualization of the anatomy, fetal gender, and occasionally, the Doppler interrogation of the fetal vessels. The presence of polyhydramnios in the sac of the recipient twin, on the other hand, contributes to very mobile fetus, making anatomical evaluation and Doppler interrogation of its vessels particularly cumbersome. Nevertheless, if the sonographic evaluation of the fetuses is done in a systematic fashion, and in several distinct steps, the diagnosis, mapping, staging, and pre-operative assessment are possible.

Staging of TTTS

The heterogeneous ultrasound presentation of TTTS has been recognized by numerous investigators (Bromley et al., 1992; Ishimatsu et al., 1992; Lachapelle et al., 1997; Lees et al., 1998; Mari et al., 1998; Ohno et al., 1994; Pretorius et al., 1993; Reisner et al., 1993; Weiner & Ludomirski, 1994; Yamada et al., 1991). This included the presence or absence of hydrops, the presence or absence of abnormal arterial or venous Doppler studies, and varying levels of amniotic fluid volume discordance. An important step in the understanding of the ultrasound presentation of TTTS resulted from the realization that the disease could present with various degrees of severity, as opposed to with different risk factors. This led to the original development of the Quintero Staging System (Quintero et al., 1999). The Quintero Staging System was based on the empirical observation of the different sonographic presentations of the disease in the absence of modifications introduced by treatment. Thus, the Quintero Staging System was based on an unbiased sonographic description of the presentation and natural history of the disease.

For the purposes of the staging system, categorical (i.e., yes/no) variables were identified and preferably used. This avoided the use of nomograms that could hinder the
practical nature of the staging system. The staging system was also based on the natural assumption that the different sonographic presentations would represent different degrees of severity. Thus, demise was an obvious worse presentation than hydrops, which was a worse presentation than abnormal Dopplers, which was a worse presentation than lack of visualization of the bladder of the donor, which was worse than visualization of the bladder of the donor. For this, the staging system uses Roman numerals (I–V), to give an ordinal character to the classification. Stage I was defined as visualization of the bladder of the donor twin. Stage II was lack of visualization of the bladder of the donor twin in at least 60 minutes of continuous ultrasound examination. Stage III was defined as the presence of critically abnormal Dopplers, including absent or reverse end-diastolic velocity in the umbilical artery, absent or reverse flow in the ductus venosus, or pulsatile umbilical venous flow. Stage IV was defined as hydrops. Stage V was defined as demise of one or both fetuses. Stage III and Stage IV patients could present with a visible bladder or a non-visible bladder of the donor. In the classic presentation, the bladder of the donor twin would not be visible. In the ‘atypical’ presentation of Stage III or Stage IV, the bladder of the donor twin is visible (Quintero et al., 1999). In order for a patient to be classified as having Quintero Stage III TTTS, the critically abnormal Doppler findings need to be persistent. This is important, because donor twins may show intermittent absent/reverse diastolic flow, which can be more reflective of the presence of an arterio–arterial anastomosis rather than from true severe presentation. Similarly, intermittent absent or reverse flow in the ductus venosus during the atrial contraction does not qualify as Stage III. Pulsatile umbilical venous flow (single or double) is the only subjective ultrasound parameter in the Quintero Staging System. To avoid subjectivity, pulsatile umbilical venous flow can be defined as an umbilical vein resistance index > 0.15. $\text{UVRI} = 100 \ast (V_{\text{max}} - V_{\text{min}})/V_{\text{max}}$, where $V_{\text{max}}$ and $V_{\text{min}}$ represent the maximum and minimum deflection of the traced umbilical vein Doppler waveform (Russell et al., 2008).

The fundamental merit of the Quintero Staging System was to recognize the heterogeneous presentation of the condition and consider the pregnancy as a whole entity, rather than use individual risk factors for each twin. In addition, the system was proposed as a result of empirical observation of the natural history of the various presentations, rather than as a result of treatment. Although some authors have suggested modifying the Quintero Staging System to include the presence or absence of superficial anastomoses (Taylor et al., 2002) or different echocardiographic findings (Michelfelder et al., 2007; Rychik et al., 2007; Stirnemann et al., 2010), such recommendations are based mostly on an attempt to explain adverse surgical outcomes, rather than describe natural history. From its inception, the system did not pretend to indicate that cases could progress from one stage to the other in an orderly fashion as, by definition, the initial presentation can be Stage III in 50% of the cases. However, progression and regression have both been documented by different investigators, suggesting that in fact, cases may deteriorate or improve spontaneously or after therapy. There is no evidence to suggest that the Quintero Staging System would need to be modified or altogether changed, or substituted by any other staging system (Stamilo et al., 2010). That is not to say that echocardiographic information may not be useful in the assessment of TTTS patients. Indeed, the Quintero Staging System pertains to the preoperative evaluation, whereas fetal echocardiography may allow pre-operative and post-operative assessment of the fetuses. Therefore, the Quintero Staging System continues to be practical, reproducible, and used universally in the preoperative assessment and management of TTTS patients.

**Cervical Assessment by Ultrasound**

In general, a short cervical length, as assessed by ultrasound, has been associated with an increased risk of pregnancy loss and premature delivery (Cook & Ellwood, 2000; Owen, 2003; Rozenberg et al., 2002; Shennan & Jones, 2004; Slager & Lynne, 2012). A short cervix has also been identified as a risk factor for preterm labor and miscarriage in twins (Conde-Agudelo et al., 2010) and in patients with TTTS (Taylor et al., 2000). Therefore, ultrasound assessment of the cervical length is a fundamental step in the evaluation of patients with TTTS. In our lab, assessment of the cervical length is in fact the first step in the evaluation of patients with TTTS. Assessment of the cervical length is best performed using a transvaginal ultrasound, particularly since transabdominal assessment of the cervical length may miss a significant proportion of patients with a short cervix (Hernandez-Andrade et al., 2012). Prior to performing the transvaginal ultrasound assessment, the sonographer or physician must first inquire as to whether the patient has complained of leakage of fluid, which could represent premature rupture of membranes. When in doubt, the exam is performed via a transperineal approach (Jeanty et al., 1986). Approximately 6–7% of patients with TTTS will have a short cervix on presentation (Quintero, 2007). Although a cervical cerclage has not been conclusively shown to benefit patients with a short cervix in singleton pregnancies and may even be considered detrimental in twin gestations (Bergella et al., 2005; Hassan et al., 2001), our group and others have shown that the outcome of patients with a short cervix treated with a cervical cerclage is similar to that of patients with a cervix of normal length (Chavira et al., 2009). Thus, patients that present with a cervical length of 2.5 cm or less at our lab are offered a cervical cerclage. The timing of the placement of the cerclage may vary. The cerclage may be performed at the time of the laser surgery, or the day after the surgery (Chmait et al., 2013). Occasionally, ultrasound
may show a separation of the amniotic membrane from the periphery of the uterus at the level of the lower uterine segment. This sonographic finding has been dubbed ‘moon sign’ (Devlieger et al., 2003). It is unclear why such a sign would develop in patients with polyhydramnios. Presumably, the increase in size of the uterine walls may outdo the stretching capability of the amniotic membrane. The presence of a moon sign may or may not represent an increase risk for gross rupture the membranes or miscarriage after laser therapy (Chmait et al., 2013; Devlieger et al., 2003; Patel et al., 2014).

**Ultrasound Mapping**

The previous three steps in the ultrasound assessment of patients with TTTS can be performed at centers that do not necessarily offer surgical treatment. If the patient is to be assessed at a surgical center, the next step in the evaluation consists of pre-operative mapping. The goal of preoperative ultrasound mapping is to evaluate the exact location of the placenta and predict the location of the anastomoses, as well as the location of the dividing membrane. Prediction of the location of the anastomoses is important to properly and fully photocoagulate them. Missing the anastomosing vessels during surgery or having to use extreme maneuvers to coagulate them can create delay in the operating time and increase the likelihood of complications. Prediction of the location of the dividing membrane is important to also avoid injuring it upon entering the amniotic cavity. Injuring the dividing membrane results in a pseudo-monoamniotic twin pregnancy, with its attendant complications.

Ultrasound mapping begins by first noting the location of the placental borders. For example, it is important to know to which degree the placenta extends towards the lower uterine segment or towards the uterine fundus. Similarly, it is important to determine how much it extends to each of the lateral walls, in anticipation of where the trocar would be inserted through the abdominal wall. Second, the location of the insertion of the umbilical cords is also noted using color Doppler (Di Salvo et al., 1998). Naturally, the anastomoses are expected to be in an area of the placenta that lies between the two umbilical cords insertions. Although a critical short distance between the two umbilical cords (Hack et al., 2008) may seem like an obvious impediment for the performance of the laser therapy (Bajoria, 1998), an actual value for this measurement has not been established. Therefore, an arbitrary, short intercord distance should not be used as a disqualifying criterion for laser therapy. In general, the further apart in distance the umbilical cords are, the less likely it is that there will be either numerous or significantly large placental vascular anastomoses. The actual location of the umbilical cords may also herald the degree of difficulty that may be encountered during surgery. For example, if a velamentous insertion is identified, the operator must be careful not to use this area for the insertion of the trocar, as it may result in unintentional injury to velamentous vessels, with subsequent possible exsanguination and demise of one or both fetuses. Ultrasound documentation of the location of the umbilical cords is best done by using the icons provided by the ultrasound software. For these, the icon is placed on the monitor screen and the direction of the transducer and the location of the transducer relative to the umbilical cord is noted. This step is repeated for the other twin. Third, the position (i.e., longitudinal, transverse, oblique) of the donor twin and the prediction of the location of the vascular anastomoses as well as of the location of the dividing membrane may also aid. Since most donor twins are ‘stuck’ to the walls of the uterus, the dividing membrane follows the location of the donor twin in most cases. For example, if the donor twin is lying longitudinally, one can anticipate that the vascular anastomoses will run from left to right. Conversely, if the donor twin is lying transversely, one can anticipate that the vascular anastomoses will run in a superior to inferior direction. The location of the donor twin relative to the placental mass is also important to note. Indeed, the donor twin is ideally outside of the placental mass so that the anastomoses are not obscured by its presence. Alternatively, if the donor twin is lying over the placental mass, this may hinder significantly the identification of the vascular anastomoses, particularly if the degree of anhydramnios is such that displacement of the donor twin during surgery is minimal or impossible. Lastly, the position of the donor twin relative to the placenta-free area in patients with an anterior placenta is also important to note. In most cases, the placenta-free area is on the side of the recipient twin. However, if the donor twin is lying beneath the placenta-free area of the uterus, this may increase the likelihood of unintentional disruption of the dividing membrane during trocar entry. In our experience, unintentional septostomy during trocar entry occurs in approximately 15% of patients in patients with an anterior placenta and the donor covering the placenta-free area. At the end of the ultrasound mapping, it is recommended to depict these findings graphically on the patient’s abdomen by the use of a marker. The location of the umbilical cords is noted with a circle containing the letters ‘D’ and ‘R’. The position of the donor twin is also drawn on the patient’s abdomen. Lastly, the anticipated entry site for the surgery is marked with an X.

**Conclusion**

There is a need to standardize the definition and terminology used in TTTS. Although the term ‘fetofetal transfusion’ is a MeSH term and it is also medically and grammatically correct, ‘twin–twin transfusion syndrome’, ‘twin–to–twin transfusion syndrome’ and ‘TTTS’ are also widely used in textbooks and medical articles. TTTS is an ultrasound diagnosis. In diamniotic fetuses, the use of a MVP of 8 cm or more should be adopted,
regardless of gestational age. This avoids an underestimation of 20–25% of cases of TTTS after 20 weeks, which may have a deep vertical pocket between 8–10 cm. Oligohydramnios should be determined as a MVP of 2 cm and below.

The staging of TTTS is a necessary step to determine the severity of the syndrome and to have a means of accurate communication among caregivers. The Quintero Staging System has proven to be reproducible and reliable. The use of categorical yes/no outcomes for each variable in the staging system, rather than the use of continuous variables suggested in other systems, add to the reproducibility and the objectivity of the definition of each stage.

Cervical assessment and preoperative mapping constitute additional aspects of the sonographic evaluation of each case and should be instituted as part of the overall assessment of these patients at specialized centers.

The use of the ultrasound methodology proposed in this article to diagnose and evaluate patients with TTTS allows for a systematic and organized way of conducting the ultrasound examination. The ultrasound examination of patients with TTTS can seem overwhelming or daunting at first. However, the examination can be broken down into distinct steps to ensure that the assessment is both accurate and comprehensive. Standardization of the terminology and the sonographic diagnostic and assessment criteria have helped the communication between investigators, although work in this area remains to be done.

References


