Twin-twin transfusion syndrome (TTTS)

MARIOLA ROPACKA-LESIAK, GRZEGORZ H. BRĘBOROWICZ

Abstract

The etiology of TTTS is connected with the architecture of the placenta, and intertwine vascular connections known as anastomoses within the placenta. Actually all MC placentas have anastomoses that connect the fetal circulations. Fortunately, not all MC twins develop TTTS. Three main types of anastomoses might be distinguished: venovenous (VV), arterioarterial (AA), and arteriovenous (AV). The imbalance of blood flow through the placental anastomoses leads to volume depletion in the donor twin, with oliguria and oligohydramnios, and to volume overload in the recipient twin, with polyuria and polyhydramnios. There also appear to be additional factors beyond placental morphology, such as complex interactions of the renin-angiotensin system in the twins involved in the development of this disorder. There are no randomized trials to evaluate the effectiveness of antenatal monitoring or pregnancies complicated by TTTS. Weekly monitoring of the umbilical artery Doppler flow and MVP of amniotic fluid of each fetus may be considered. The evidence for effectiveness of serial (eg, weekly or twice/wk) nonstress tests, biophysical profiles, and other antenatal testing modalities is insufficient to make a recommendation, but these tests can be considered. The management options described for TTTS include expectant management, amnioreduction, intentional septostomy of the intervening membrane, fetoscopic laser photocoagulation of placental anastomoses, and selective reduction. There are no clinical trials regarding optimal timing of delivery for TTTS pregnancies. This depends on several factors, including disease stage and severity, progression, effect of interventions, and results of antenatal testing. Recommendations regarding timing of delivery with TTTS vary, with some endorsing planned preterm delivery as early as 32-34 weeks, and others individualizing care and allowing gestation to progress to 34-37 weeks, particularly in cases of mild disease (eg. stages I and II) with reassuring surveillance.

Key words: twin-twin transfusion syndrome (TTTS),

Twin-twin transfusion syndrome (TTTS) is a serious complication of monochorionic twins. The prevalence of TTTS is approximately 1-3 per 10,000 births [1, 2]. The presentation of TTTS is highly variable. The diagnosis of TTTS is based sonographic criteria: (1) the presence of a monochorionic pregnancy (MC); and (2) the presence of oligohydramnios defined as a maximal vertical pocket [MVP] of 2 cm in one sac, and of polyhydramnios (a MVP of 8 cm) in the other sac [3, 4]. This amniotic fluid discrepancy, that means the presence of poly and oligohydramnios is used to define stage I TTTS [5]. The growth discrepancy and intraterine growth restriction (IUGR) often may be observed in TTTS, however nor growth discordance itself or IUGR itself are not diagnostic criteria [6]. TTTS can occur in a MC twin pair in triplet or higher-order pregnancies. The TTTS staging system is base on sonographic parameters and was described by Quintero et al in 1999 [5]. The TTTS Quintero staging system includes 5 stages, ranging from mild disease with isolated discordant amniotic fluid volume to severe disease with demise of one or both twins [5]. The centers of fetal therapy report that about 11-15% of their cases at referral were Quintero stage I (probably underestimated), 20-40% were stage II, 38-60% were stage III, 6-7% were stage IV, and 2% were stage V [7, 8]. However this staging do not correlate perfectly with perinatal survival, but it is relatively simple to apply, and to communicate with patients [1, 9]. There are some attempts to modify this staging by the assessment of fetal cardiac function [10] or even to develop a new scoring system [11].

TTTS may develop at any time in gestation, however the majority of cases are diagnosed in the second trimester. TTTS often does not progress in a predictable manner. Natural history data are limited, especially for more advanced stages [5]. Over three fourths of stage I TTTS cases remain stable or regress without invasive therapy [12-14]. The natural history of advanced (eg. stage III) TTTS is bleak, with a reported perinatal loss rate of 70-100%, particularly when it presents 26 weeks
Without intrauterine therapy, the loss of at least 1 fetus is very common, with demise of the remaining twin occurring in about 10% of cases of twin demise, and neurologic handicap affecting 10-30% of cotwin remaining survivors [17-19]. Overall, single twin survival rates in TTTS vary widely between 15-70%, depending on the gestational age at diagnosis and severity of disease [1, 15, 18].

**Pathophysiology**

The etiology of TTTS is connected with the architecture of the placenta, and intertwine vascular connections known as anastomoses within the placenta. Actually all MC placentas have anastomoses that connect the fetal circulations. Fortunately, not all MC twins develop TTTS. Three main types of anastomoses might be distinguished: venovenous (VV), arterioarterial (AA), and arteriovenous (AV). AV anastomoses are found in 90-95% of MCDA placentas, AA in 85-90%, and VV in 15-20% [1]. Both AA and VV anastomoses are superficial connections on the surface of the placenta with the potential for bidirectional flow. The AV anastomoses are called deep anastomoses, because the anastomotic connections occur in a cotyledon, that means deep within the placenta. AV anastomoses can result in unidirectional flow from one twin to the other. The hemodynamic disequilibrium may lead to an imbalance of volume between the twins. Unlike AA and VV, which are direct vessel-to-vessel connections, AV connections are linked through large capillary beds deep within the cotyledon. AV anastomoses are usually multiple and the overall blood flow is balanced, so there is a hemodynamic equilibrium causing balanced intertwine blood flow without any signs of TTTS [1].

It is thought that these bidirectional anastomoses may compensate for the unidirectional flow through AV connections, thereby preventing the development of TTTS or decreasing its severity when it does occur [20]. It has been also described that mortality is highest in the absence of AA and lowest when these anastomoses are present (42% vs 15%) [21]. However, the presence of AA is not completely protective [22]. The imbalance of blood flow through the placental anastomoses leads to volume depletion in the donor twin, with oliguria and oligohydramnios, and to volume overload in the recipient twin, with polyuria and polyhydramnios. There also appear to be additional factors beyond placental morphology, such as complex interactions of the renin-angiotensin system in the twins involved in the development of this disorder [1, 23-25].

**Monitoring**

The ultrasound screening should be offered to all women with a MC twin pregnancy in the first trimester. It should include an evaluation of CRL, CRL discrepancy, chorionicity, and nuchal translucency.
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Fig. 4. Arterio-venous anastomoses on the placental surface in monochorionic pregnancy complicated by TTTS

Some authors also recommend to assess the blood flow through the ductus venosus and tricuspid valve. Usually, the signs of TTTS are diagnosed in the second trimester. One must remember that TTTS can be a very dynamic condition. It is very difficult to predict which pregnancies will stay stable, which occasionally regress spontaneously, progress slowly over a number of weeks, or develop quickly within a period of days with signs of rapid deterioration in fetal well-being. The present data suggest that all MC pregnancies should be monitored every 2 weeks [1, 26-28].

The monitoring usually begins around 16 weeks of gestation, until delivery, should be considered for all twins with MC placentation [27-29]. These serial sonographic evaluations should include at least MVP of each sac, and the presence of the bladder in each fetus. Doppler blood flow assessment is needed in later pregnancy. In addition to monitoring MC pregnancies for development of amniotic fluid abnormalities, there are several second- and even first-trimester sonographic findings that have been associated with TTTS [1].

The clinical utility of the sonographic findings has not been prospectively evaluated, and several require Doppler evaluation not typically performed in otherwise uncomplicated MCDA gestations. Thus, while they are associated with TTTS and may potentially improve TTTS detection. Abnormal umbilical artery waveforms in MCDA twins may represent placental insufficiency, but may also be secondary to the presence of intertwine anastomoses and changes in vascular reactivity typical of TTTS. Overall, the development of abnormal enddiastolic flow in the umbilical artery, especially absent or reversed, has been associated with later deterioration of fetal testing necessitating delivery in MCDA twins [1, 30, 31] but latency between Doppler and other fetal testing changes is increased in these gestations compared to singletons [32]. Frequent, eg, twice weekly, fetal surveilance is suggested for MCDA pregnancies with abnormal umbilical artery Doppler once viability is reached [31].

There are no randomized trials to evaluate the effectiveness of antenatal monitoring or pregnancies complicated by TTTS. Weekly monitoring of the umbilical artery Doppler flow and MVP of amniotic fluid of each fetus may be considered. The evidence for effectiveness of serial (eg, weekly or twice/wk) nonstress tests, biophysical profiles, and other antenatal testing modalities is insufficient to make a recommendation, but these tests can be considered. One reason for surveillance, even following laser therapy, is that not all anastomoses are ablated at the time of laser [1, 33, 34]. Residual anastomoses, either initially undetected, missed, or revascularized after laser, have been observed in up to a third of cases [35, 36]. Placental casting has also demonstrated the presence of deep, atypical AV anastomoses beneath the chorionic plate that would not be visible by fetoscopy [37]. Failure to coagulate all AV anastomoses can lead to persistent, recurrent or reversed TTTS. Persistent or recurrent TTTS has been reported in 14% of cases postlaser and reversed TTTS, with the recipient becoming anemic and the donor polycythemic, in 13% of cases [38, 39]. While TAPS can occur spontaneously in a MCDA gestation, it is a known iatrogenic complication of laser.

**Fetal echocardiography**

A functional assessment of the fetal heart may be useful in identifying cases that would benefit from therapy and in evaluating the response to treatment. Although fetal cardiac findings are not officially part of the TTTS staging system, many centers routinely perform fetal echocardiography in cases of TTTS and have observed worsening cardiac function in advanced stages [1, 10]. However, cardiac dysfunction can also be detected in up to 10% of apparently early-stage TTTS. The functional cardiac abnormalities that complicate TTTS occur primarily in recipient twins. Volume overload causes increased pulmonary and aortic velocities, cardiomegaly, and atrioventricular valve regurgitation. Over time, recipient twins can develop progressive biventricular hypertrophy and diastolic dysfunction as well as poor right ventricular systolic function that can lead to functional right ventricular outflow tract obstruction and pulmonic stenosis [1, 40, 41]. The development of right ventricular outflow obstruction, observed in close to 10%
of all recipient twins, is likely multifactorial, a consequence of increased preload, afterload, and circulating factors such as renin, angiotensin, endothelin, and atrial and brain natriuretic peptides [42-44]. The cardiovascular response to TTTS contributes to the poor outcome of recipient twins while recipients with normal cardiac function have improved survival [45].

In summary, scoring systems that include cardiac dysfunction have been developed, but their usefulness to predict outcome in TTTS remains controversial and further studies are needed to assess its meaning [1, 46].

Management

The management options described for TTTS include expectant management, amnioreduction, intentional septostomy of the intervening membrane, fetoscopic laser photocoagulation of placental anastomoses, and selective reduction. The interventions that have been evaluated in randomized controlled trials (RCTs) include intentional septostomy of the intervening membrane to equalize the fluid in both sacs, amnioreduction of the excess fluid in the recipient’s sac, and laser ablation of placental anastomoses. There have been 3 randomized trials designed to evaluate some of the different treatment modalities for TTTS, all of which were terminated prior to recruitment of the planned subject number after interim analyses [1, 47-49].

Consultation with a maternal-fetal medicine specialist is recommended, particularly if the patient is at a gestational age at which laser therapy is potentially an option. Expectant management involves no intervention. This natural history of TTTS, also called conservative management, has limited outcome data according to stage, particularly for advanced disease. Amnioreduction can be performed either as a 1-time procedure, as at times this can resolve stage I or II TTTS, or serially, eg, every time the MVP is 8 cm. It can be performed any time from 14 weeks. Amnioreduction is hypothesized to reduce the intramniotic and placental intravascular pressures, potentially facilitating placental blood flow, and/or to possibly reduce the incidence of preterm labor and birth related to polyhydramnios. Amnioreduction may be used also 26 weeks, particularly in cases with maternal respiratory distress or preterm contractions from polyhydramnios [1, 50]. Amnioreduction has been associated with average survival rates of 50%, with large registries reporting 60-65% overall survival [51, 52]. However, serial amnioreduction is often necessary, and repeated procedures increase the likelihood of complications such as preterm premature rupture of the mem-
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bined stage III and IV [47]. In recent nonrandomized large series, summarizing 1000 cases of TTTS (about 86% with stages II and III) treated with laser, the overall perinatal survival was about 65% [1].

Both double and single fetal demise are common complications in advanced stages of TTTS treated with laser. In a multicenter observational study, fetal demise occurred in 24% of donors and in 17% of recipients after laser [57]. Survival of 1 or 2 fetuses after laser may depend on coexisting unequal placental sharing that may not be visible before or even at the time of fetoscopy. Preoperative IUGR with absent or reversed end-diastolic flow in the umbilical artery has a 20-40% increased risk of postoperative donor demise [57, 58]. Recipient twin demise after laser is more common when the recipient has IUGR, reversed a-wave in the ductus venosus, or hydrops [57]. Improved recipient twin survival has been reported with the maternal administration of nifedipine 24-48 hours prior to laser photocoagulation in cases of TTTS cardiomyopathy [59] but more data are needed to suggest its use in this clinical situation. After successful laser photocoagulation, the cardiac function of recipient twins tends to normalize in about 4 weeks [60]. Pulmonic valve abnormalities, affecting about 20% of recipient also been observed to improve after laser with less than a third of surviving twins having persistent pulmonic valve defects requiring treatment after birth [61]. Overall, 87% of postlaser recipient twins who survived were reported to have normal echocardiograms at a median age just under 2 years [44]. Although procedure-related fetal loss is a recognized complication of fetoscopic laser photocoagulation, survival with neurologic handicap is also a serious long-term sequela of TTTS, with or without treatment. While the gestational age at delivery is a significant risk factor for adverse neurologic outcome, initial studies suggested that neurologic outcomes may be better for those cases managed with laser photocoagulation, compared to amnioreduction. Infants in the laser group of the Eurofetus trial had a lower incidence of cystic periventricular leukomalacia and were more likely to be free of neurologic complications at 6 months of age compared to those treated with amnioreduction [1, 47]. However, 6-year follow-up of 120 children from this trial found that laser therapy conferred no significant benefit in terms of difference in major neurologic handicap among TTTS survivors treated with laser vs amnioreduction [62]. Another recent study also reported no difference in neurodevelopmental outcome at 2 years of age among donors and recipients treated with laser or amnioreduction, although they did observe a trend of increased major neurologic impairment in survivors after amnioreduction compared to those treated with laser (9.5% vs 4.6%) [63]. Overall, rates of long-term neurologic sequelae in laser-treated stage I TTTS are reported to be about 3%, with rates of about 5-20% in survivors of any stage TTTS [1, 63-67]. The risk of abnormal neurodevelopment seems to be similar in donor and recipient survivors, and not drastically different between those treated with laser or amnioreduction.

In summary, even with the laser treatment option available, TTTS is still a severe condition in terms of perinatal outcomes. Given the 30-50% chance of overall perinatal death and 5-20% chance of neurologic handicap long-term, twin death or neurologic handicap is the outcome in up to two thirds of laser-treated TTTS [1, 68].

Delivery

There are no clinical trials regarding optimal timing of delivery for TTTS pregnancies. This depends on several factors, including disease stage and severity, progression, effect of interventions, and results of antenatal testing. Recommendations regarding timing of delivery with TTTS vary, with some endorsing planned preterm delivery as early as 32-34 weeks, and others individualizing care and allowing gestation to progress to 34-37 weeks, particularly in cases of mild disease (eg, stages I and II) with reassuring surveillance [1, 47, 49, 53, 69-71]. Cases treated with laser generally have more advanced disease, and they may be at risk for early delivery due to both TTTS and procedure-related complications. However, prematurity has been identified as an independent risk factor for neurodevelopmental impairment in the setting of TTTS [65]. Given the spectrum of disease associated with TTTS, many variables factor into decisions about timing of delivery, including disease stage, progression, response to treatment, fetal growth, and results of antenatal surveillance. Delaying delivery until 34-36 weeks may be reasonable even after successful laser ablation [1].

References


