THE SONOGRAPHIC EVALUATION OF TWIN-TO-TWIN TRANSFUSION SYNDROME

INTRODUCTION
The increased perinatal mortality and morbidity associated with monochorionic/diamniotic twins is due to the presence of vascular communications between the two fetal circulations. While these vascular anastomoses are generally always present, it is predominantly the deep artero-venous anastomoses without sufficient superficial artero-venous or arterio-arterial compensating anastomoses that result in the 15% incidence of twin-to-twin transfusion syndrome (TTTS)\(^1,2\).
The determination of chorionicity in the first trimester is, therefore, critical in determining the subsequent management of a twin pregnancy.

DETERMINING 1ST TRIMESTER CHORIONICITY
The improved resolution of transvaginal sonography permits, not only an early identification of twin pregnancies, but also a detection of chorionicity and amnionicity. The presence of two distinct gestational sacs (Fig. 1) is evidence for a diachorionic/diamniotic twin pregnancy. The thickness of the dividing decidua between the gestational sacs is determined by the distance between implantation sites.

 Twins with a single gestational sac and a thin dividing membrane between the twins are diamniotic/monochorionic (Fig. 2).
The presence or absence of the amnion can be determined by 6 to 7 weeks’ gestation (Fig. 3).

During the first nine menstrual weeks, the diameter of the amniotic cavity is almost equivalent to the crown-rump length\(^3\)(Fig 3). As a result, there is also a correlation between cord length and crown-rump length\(^4\). Hence, prior to visualization of the amnions (< 6-7 menstrual weeks), if two embryos are separated by more than two times the crown-rump length, the pregnancy is monochorionic/diamniotic...
(Fig. 4). If the two embryos are closely approximated then determination of amnionicity (monoamniotic or diamniotic) must wait until the amnions can be clearly visualized.

**Figure 4 - 6 week monochorionic/diamniotic twins. The yolk sacs are at opposite ends of the gestational sac.** To view an enlargement, click on the image.

**DIZYGOTIC MONOCHORIONIC TWINS**

Although rare, dizygotic monochorionic twins may occur after assisted reproductive technologies. It is postulated that this is due to the fusion of the outer cell mass of two separate eggs before day fourteen.

1st Trimester Sonographic Findings in Twin-To-Twin Transfusion Syndrome (Table I)

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A. Nuchal Translucency

First trimester screening in singletons for trisomy 21 and trisomy 18 utilizing maternal age, B-hCG, pregnancy-associated plasma protein, and the nuchal translucency measurement identifies approximately 90% of fetuses with trisomy 21 and 100% of trisomy 18 fetuses.

In chromosomally normal twin pregnancies, the prevalence of an increased nuchal translucency (Fig. 5) is higher in monochorionic (8.4%) versus dichorionic (5.4%) twins. The increase false positive rate with monochorionic twins is due to the association between a thickened nuchal translucency and twin-to-twin transfusion syndrome. The likelihood ratio of an increased fetal NT at 10-14 weeks’ gestation for the development of severe twin-to-twin transfusion syndrome is 3.5. A 20% discordance in NT measurements is present in 25% of monochorionic/diamniotic twins. In this group the risk of an early fetal death or severe twin-to-twin transfusion syndrome is > 30%. 
B. 1st Trimester Amniotic Fluid Discrepancy
A subjective disparity in amniotic fluid volume between monochorionic twins with twin-to-twin transfusion syndrome has been detected by 13 weeks’ gestation.\textsuperscript{11}

C. Placental Cord Insertion
The prevalence of velamentous cord insertions is much higher in monochorionic twins with twin-to-twin transfusion syndrome (64%) versus monochorionic twins without twin-to-twin transfusion syndrome (19%). Placental cord insertions should, therefore, be documented in the late 1st or 2nd trimester.\textsuperscript{12}

2ND TRIMESTER SONOGRAPHIC FINDINGS IN TWIN-TO-TWIN TRANSFUSION SYNDROME

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<tr>
<td>◦ Abnormal MCA</td>
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<td>◦ $\uparrow$ diastolic flow, $\uparrow$ PI</td>
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<td>◦ $\uparrow$ PSV</td>
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<tr>
<td>◦ Abnormal flow ductus venosus</td>
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<td>• Cardiac effects</td>
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<td>◦ Cardiomegaly</td>
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A. Inter-twin Membrane Folding
Twenty-five percent of monochorionic twins have membrane infolding (Fig. 6); half of these cases progress to severe twin-to-twin transfusion syndrome and half have moderate twin-to-twin transfusion syndrome\textsuperscript{13}.

![Figure 6 - Inter-twin membrane folding associated with twin-to-twin transfusion syndrome (arrow = dividing membrane)](image)
To view an enlargement, click on the image.

B. Polyhydramnios/Oligohydramnios (Fig. 7)
Discrepancies in amniotic fluid volumes is a hallmark of early twin-to-twin transfusion syndrome. Polyhydramnios/oligohydramnios have been defined as single maximum vertical pockets of amniotic fluid $\geq 8$ cm and $\leq 2$ cm, respectively\textsuperscript{14}. 

C. Absent Bladder in Donor Twin/Enlarged Bladder in Recipient
The discrepancy in bladder size between monochorionic twins with TTTS is due to the hypovolemia in the donor and hypervolemia in the recipient\textsuperscript{15}.

D. Velamentous/Eccentric Cord Insertions
13\% of monochorionic twins have velamentous cord insertions – a risk factor for twin-to-twin transfusion syndrome (Fig. 8)\textsuperscript{16}.
E. Abnormal Dopplers

Absent (Fig. 9) or reversed (Fig. 10) diastolic flow in the umbilical artery is an indication of worsening twin-to-twin transfusion syndrome. Cardiac diastolic dysfunction results in abnormal ductus venosus waveform pattern (Fig. 11).

Figure 9 - Absent diastolic flow in the umbilical artery. Absent end diastolic velocity is approximately 40% of one cardiac cycle [in brackets].

Figure 10 - Reversed diastolic flow in the umbilical artery
F. Growth Discordancy
A 20% difference in fetal weights or an abdominal circumference difference of > 20 mm (Fig. 12) has been used to define discordant growth\textsuperscript{17}.

G. Significant Difference in Umbilical Cord Diameters

H. Cardiac Hypertrophy/Failure (Fig. 13)
The assessment of myocardial performance evolved after the publication of the Quintero staging system\textsuperscript{18}. As a result, fetal echocardiographic findings have not, to date, been incorporated into the staging system.
It is mainly the recipient that shows a progressive deterioration in cardiac function. Cardiac dysfunction in the recipient may be due to increased afterload that results from increased systemic resistance and pressure. The renin-angiotension system is upregulated in the donor to counteract hypovolemia. However, the transfer of angiotension II to the recipient through placental shunting may result in cardiomyopathy due to peripheral vasoconstriction and a direct effect on the myocytes\textsuperscript{19,20}. This mechanism explains the development of recipient cardiomyopathy in some cases without the Doppler changes noted in Quintero stage III\textsuperscript{21}.

I. Fetal Hydrops (Fig. 14)
QUINTERO STAGING OF TWIN-TO-TWIN TRANSFUSION SYNDROME

Quintero and co-workers\textsuperscript{18} evaluated 50 cases of TTTS to develop a staging system that utilizes various poor prognostic factors (Table III). As the severity of TTTS increases, so does perinatal mortality. Survival is also worse when the stage increases over serial studies. The Quintero stage at presentation has not been associated with survival\textsuperscript{14}.

| Table III. Sonographic staging of twin-to-twin transfusion syndrome\textsuperscript{18} |
|---------------------------------|---------------------------------|-----------------|-----------------|-----------------|
| Stage                          | Polyhydramnios/Oligohydramnios | Absent bladder in donor | Abnormal Dopplers* | Hydrops | Demise |
| I                              | +                               | -                | -                | -                | -                |
| II                             | +                               | +                | -                | -                | -                |
| III                            | +                               | +                | +                | -                | -                |
| IV                             | +                               | +                | +                | +                | +                |
| V                              | +                               | +                | +                | +                | +                |

* One of the following: 1) absent/reversed diastolic flow in the umbilical artery; 2) absent/reverse diastolic flow in the ductus venosus; 4) pulstile umbilical venous flow.

O’Donoghue et al\textsuperscript{22} have reported that 28.3% of stage I twin-to-twin transfusion syndromes remain stable and 41.3% regress. Of the cases that progress, 80% did so within two weeks. Treatment with reduction amniocentesis at presentation did not influence progression or regression of stage I twin-to-twin transfusion syndrome\textsuperscript{22}.

The difference between stage I and stage II may, in part, be dependent upon the duration of observation for bladder filling. Cases of stage I or stage II may progress to fetal demise without progressing through the other stages\textsuperscript{23}.

Quintero originally subclassified stage III into III “classical”, i.e. abnormal Doppler in either twin without a visible donor bladder and stage III “atypical”, abnormal Doppler in either twin and a visible donor.
The incidence of arterio-arterial anastomoses is 72.9% in atypical stage III versus 17.8% in classic stage III (p < 0.01). The arterio-arterial anastomoses may function by permitting bi-directional blood flow to protect against transfusion imbalance. Hence, the donor could receive a sufficient volume of the recipient’s blood to permit renal function and bladder filling. Arterio-arterial anastomoses provide a survival advantage independent of Quintero stage. The arterio-arterial anastomoses can be detected with Doppler because of their characteristic bi-directional waveform pattern. The survival of donor twins at 6 months is significantly lower in stage III “atypical”. A possible explanation for the worse prognosis after laser ablation of the arterio-arterial anastomoses in stage III atypical may be severe hypotension in the donor.

**MONOAMNIOTIC TWINS**

The almost 100% incidence of arterio-arterial anastomoses in monoamniotic twins explains the relatively low incidence of twin-to-twin transfusion syndrome when compared to diamniotic/monochorionic twins. TTTS in monoamniotic placentas has a 2.6 times lower incidence than in diamniotic/monochorionic placentas (3.8% vs. 10%). In monoamniotic pregnancies TTTS cannot be initially detected by polyhydramnios/oligohydramnios (stage I). Since 50% of TTTS are stage I, the manifestations of twin-to-twin transfusion syndrome would only be apparent in stage II, or greater, disease. Hence, the detectable rate of TTTS in monoamniotic twins would be approximately 2%.

**CLINICAL COURSE**

The clinical course of TTTS is highly variable. Progressive polyhydramnios in one sac and oligohydramnios in the other is the rule. Pre-term delivery may occur soon after diagnosis or the process may gradually evolve over several months. Factors that independently predict poor survival in TTTS include: absent or reversed diastolic flow in the donor’s umbilical artery; pulsatile umbilical venous flow or reversed diastolic flow in the ductus venosus of the recipient; and an absence of arterio-arterial anastomoses. When Doppler was compared to placental injection studies for the detection of arterio-arterial anastomoses, Doppler had an 85% sensitivity and a 97.3% specificity. The detection of an arterio-arterial anastomoses reduces the risk of TTTS nine-fold. If TTTS does develop, there is an increased chance of both twins surviving when an arterio-arterial anastomosis is detected.

**THERAPEUTIC AMNIOCENTESIS**

Ultrasonically guided therapeutic amniocentesis of the severely polyhydramnic gestational sac was the first, and still most frequently employed, treatment for TTTS. The goal of the procedure is to reduce the amniotic fluid volume in the polyhydramnic gestational sac to normal. The amount of fluid that is drained may vary from 1 to 7 liters. The removal of large volumes of fluid is usually performed in stages. The speed with which amniotic fluid re-accumulates varies from case to case. Spontaneous resolution of TTTS after a single therapeutic amniocentesis has occurred. There has also been documented resolution of fetal hydrops after therapeutic amniocentesis. The reported outcomes with treatment of twin-to-twin transfusion syndrome is primarily dependent upon the severity of the cases in the study group. Early severe (onset 16-18 weeks) TTTS occurs in approximately 1% of monochorionic twin pregnancies; moderate (onset 24-30 weeks) and mild (onset in the 3rd trimester) TTTS is, therefore, more common. The survival rate with reduction amniocentesis in cases of severe early onset TTTS is in the vicinity of 70%, in contrast to 20% without intervention. Moderate TTTS has a 75% survival rate with therapy, and a 50% survival rate without therapy. Doppler velocimetry has documented a return of diastolic flow in the umbilical artery of the smaller twin.
after therapeutic amniocentesis of the polyhydramnic gestational sac. The International Amnio Reduction Registry evaluated 223 sets of twins who were diagnosed with TTTS before 28 weeks (i.e. moderate to severe TTTS); 78% of the twins were born alive; 60% were alive at 4 weeks after delivery. The interval between the last therapeutic amniocentesis and delivery varied between 0 and 138 days. Table IV outlines the antenatal/neonatal parameters associated with survival.

Table IV. Antenatal and neonatal parameters associated with survival rate after therapeutic amniocentesis for twin-to-twin transfusion syndrome (TTTS)

- Gestational age at diagnosis of TTTS
- Presence of diastolic blood flow in the umbilical artery
- Presence of hydrops
- Volume of amniotic fluid removed/week
- Gestational age at delivery
- Birth weight

An evaluation of the recipient’s cardiovascular function after single or serial amnio reduction indicates that diastolic dysfunction persists, and even progresses, after therapeutic amniocentesis.

ENDOSCOPIC LASER SURGERY

The goal of laser ablation is to prevent intertwin transfusion by cauterizing the anastomotic vessels. Before 26 weeks’ gestation a multi-institutional European study (Eurofetus) found laser coagulation of placental anastomoses to be a more effective treatment for severe TTTS than therapeutic amniocentesis. Since some cases of TTTS respond to a single therapeutic amniocentesis, Crombleholme and co-workers evaluated stage II-IV TTTS that failed to respond to this initial therapy. While this prospective randomized multicenter trial only recruited 42 patients, they did not find a difference in outcome between therapeutic amniocentesis and selective fetoscopic laser photocoagulation. As previously mentioned, cardiomyopathy was observed to progress in the recipient twin after amniocentesis reduction. In the selective laser photocoagulation group, a strong predictor of post-procedure recipient demise was cardiomyopathy. These findings suggest that treatment prior to recipient cardiomyopathy may improve outcome.

In a prospective study of fetoscopic laser therapy in 200 consecutive severe cases of TTTS, Huber et al reported a 59.5% survival of both twins; survival of at least one twin was 83.5%. These results are equivalent to the Eurofetus trial. Huber et al also found a significant trend with decreasing survival rate with increasing stage – 75.9% of pregnancies had survival of both fetuses in stage I versus 50% in stage IV.

The studies to date suggest that a stage-based treatment scheme for TTTS may be the most effective. Therapeutic amniocentesis for stage I and II TTTS and referral to a tertiary center for laser coagulation of placental anastomoses in stage III or before cardiovascular findings associated with diastolic dysfunction; i.e. abnormal E-wave to A-wave diastolic filling (Fig. 15); increased reversed "A" wave in the inferior vena cava; absent (Fig. 10) / reversed flow (Fig. 11) in the ductus venosus; or umbilical vein pulsations.
Approximately 40% of fetal deaths after laser ablation occur within the first 48 hours. Beyond the immediate post-operative period, the recipient twin has a 10% survival advantage over donors\textsuperscript{40}. With respect to the donor, when the percent of absent end-diastolic velocity in the umbilical artery is > 30% (Fig. 10), the risk of an intrauterine fetal demise is increased 4.3-fold\textsuperscript{41}. Improvement in cardiac function, reversal of diastolic dysfunction and resolution of hydrops occurs in recipients within days of placental laser therapy\textsuperscript{42}.

The laser approach to therapy is limited by placental positioning and peripheral anastomoses that cannot be identified laparoscopically. Approximately 50% of cases with residual anastomoses develop twin anemia – polycythemia sequence after placental laser ablation\textsuperscript{43}.

**NEUROLOGIC OUTCOME AFTER LASER ABLATION**

In a study of long-term outcome after placental laser ablation for TTTS, the incidence of neurodevelopmental impairment was 18%. As one would expect, lower gestational age at birth is the most significant factor associated with neurodevelopmental impairment. The incidence of antenatally acquired severe cerebral injury in TTTS is 6-fold higher than in a control group without TTTS\textsuperscript{44}. There was no difference in neurodevelopment between donor and recipient twins\textsuperscript{45}.

**LONG-TERM OUTCOME AFTER TWIN-TO-TWIN TRANSFUSION SYNDROME**

Cardiovascular adaptation in the donor twin to hypovolemia changes the physical properties of the arterial system. The resulting vascular remodeling increases cardiac afterload and may result in long-term cardiovascular health problems\textsuperscript{46}. Fetoscopic laser therapy alters, but does not completely abolish, this vascular remodeling\textsuperscript{47}.

**CORD OCCLUSION**

In severe cases of twin-to-twin transfusion syndrome, when the demise of one twin is likely, cord occlusion by bipolar diathermy permits the remaining twin to survive without neurologic sequelae\textsuperscript{48}.
REFERENCES