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TWIN-TO-TWIN TRANSFUSION SYNDROME: AN UPDATE

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The twin birth rate has risen steadily since 1980. This increase is due to advancing maternal age at conception and the increased use of assisted reproductive technologies. Twins are generally monozygotic or dizygotic. In monozygotic twins, the majority of monochorionic twins have placental vascular anastomoses. When this shared circulation of blood becomes imbalanced, twin-to-twin transfusion syndrome (TTTS) can develop. TTTS is a serious complication in 10-20% of monozygous pregnancies. TTTS can occur at any time in these gestations, but is particularly associated with significant morbidity (abnormal neurodevelopment) and mortality (up to 90%) in untreated cases when it develops before viability.

PATHOPHYSIOLOGY

TTTS is a complex, dynamic, unpredictable and, in general, progressive clinical condition. The unequal placental sharing due to intertwin vascular anastomoses has been reported to cause a cascade of fetal humoral, biochemical and hemodynamic changes that appear to be responsible for the progression and ultimate outcome of TTTS.

These vascular anastomoses can be either superficial (between the umbilical cord vessels on the chorionic plate surface) or deep wherein the arterial vessel from one twin's cord pierces the chorionic plate to supply a placental cotyledon drained by the venous system of its co-twin or both. The type of vascular anastomoses may be artery-to-artery (AA), vein-to-vein (VV), artery-to-vein (AV), and vein-to-artery (VA). AA and VV anastomoses are superficial anastomoses with bidirectional flow. On the contrary, AV and VA anastomoses are deep anastomoses with unidirectional flow from one twin to the other. TTTS is thought to develop when there is a paucity of bidirectional AA and VV anastomoses that protect against blood flow imbalances. Recent evidence suggests that vascular diameter, intrinsic placental vascular resistance, cord insertion and placental sharing may be as important as the number and type of anastomoses in development, timing and severity of TTTS.

If the imbalance in blood volume brought about by the presence of vascular anatomoses becomes significant, one of the twins (the donor) becomes hypovolemic and oliguric while the other (recipient) twin becomes hypervolemic and polyuric. The donor's hypovolemia causes a decrease in renal perfusion which results in activation of the renin-angiotensin-aldosterone system. The effect is to increase tubular reabsorption and the production of angiotensin II, aldosterone and antidiuretic hormone as an adaptive mechanism to maintain euvolemia. This ultimately results in hypertension in the donor which has the paradoxical effect of decreasing renal and placental perfusion leading to increased vascular tone of the placental bed, worsening oliguria, oligohydramnios and growth restriction.

In contrast, recipient fetuses demonstrate renal downregulation of the renin-angiotension-aldosterone system. This increases the glomerular filtration rate and decreases tubular reabsorption in the kidney. In addition to these vasoactive substances, the recipient has increased production of natriuretic peptides, an endogenous group of hormones released by the heart in response myocardial stretch, volume overload, hypoxia and vasoconstrictors, such as angiotensin II. These peptides, mainly atrial natriuretic peptide, regulate blood pressure and body fluids through their diuretic, natriuretic, vasodilating and antihypertensive effects. Cardiovascular findings in the recipient twin, such as ventricular hypertrophy, atrioventricular valve regurgitation, and an increase in pulmonary and aortic outflow velocities are apparently attributed to not only volume overload, but also to increased cardiac afterload secondary to the development of systemic hypertension mediated by potent vasoactive substances transferred from the donor to the recipient through placental anastomoses and/or produced by the recipient's placenta itself.

DIAGNOSIS

The diagnosis of TTTS is one of exclusion and based upon a spectrum of ultrasound findings. The following features are suggestive of the diagnosis: (1) monochorionicity that includes a single placenta, a thin intertwin membrane and concordant fetal gender; (2) discrepancy in the amount of amniotic fluid between the amniotic sacs with polyhydramnios in the sac of the recipient twin (deepest vertical pocket > 8cm before 20 weeks and > 10cm after 20 weeks), and oligohydramnios in the sac of the donor twin (deepest vertical pocket < 2cm); and (3) discordance in size between the twins (≥ 20%).

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The differential diagnosis of TTTS include selective intrauterine growth restriction due to uteroplacental insufficiency, intrauterine infections and inter-twin discrepancy for structural or chromosomal abnormalities, growth discordance due to abnormal cord insertions and preterm premature rupture of membranes of one twin. Quintero proposed five stages of TTTS:

Stage 1 Polyhydramnios (deepest vertical pocket > 8cm in the recipient sac. Oligohydramnios (deepest vertical pocket < 2cm in the donor sac.

Stage 2 Donor bladder not visible.

Stage 3 Doppler abnormalities (absent/reversed umbilical artery (UA) end-diastolic flow, reversed atrial contraction component in ductus venosus (DV), pulsatile flow in umbilical vein).

Stage 4 Hydrops.

Stage 5 Intrauterine demise of one or both twins.

Besides the Quintero staging system, there are currently three other staging systems available: the Cincinnati staging system (a modification of the Quintero system that incorporates fetal echocardiographic findings), the cardiovascular profile scoring system (CVPS), and the Children's Hospital of Philadelphia (CHOP) system.The CVPS and the CHOP systems are based on echocardiographic findings of both twins.

Although the Quintero staging system provides a formidable framework for choosing between different management strategies and for comparison of treatment results among centers, it assumes that the natural history of TTTS follows an orderly progression over time. This system is also limited in its ability to predict outcome or progression of disease; is heavily weighted toward findings in the donor twin and does not take into account cardiovascular changes in the recipient twin. Based on echocardiographic assessment, significant degrees of cardiovascular compromise have been found in twin pairs assigned to early Quintero stages.

Prediction of which monochorionic twin pregnancies will be at risk of developing TTTS have been attempted by using sonographic features based on the premise that the underlying changes of the condition may be present much earlier in gestation. These have included nuchal translucency (NT) measurement (NT > 95th percentile for gestational age in at least one of the fetuses or NT discrepancy between the co-twins of equal or greater than 0.5mm), combining increased NT with abnormal blood flow in the ductus venosus (reversal of the A-wave during atrial contraction), folding of the intertwin membrane seen on ultrasounds performed serially from week 10 to week 21 and placental mapping for the presence of AA anastomoses by color flow Doppler. A recent study of multifactorial screening using multivariate regression revealed that the only factors that predicted TTTS were differences in the crown-rump and discordance in the amniotic fluid volume in the first trimester. It is therefore suggested that the best method for early diagnosis is early and regular ultrasound evaluations of at-risk monochorionic pregnancies combined with patient reporting of symptoms of polyhydramnios.

TREATMENT

Laser photocoagulation of communicating anastomoses on the chorionic plate is currently the optimal therapy for TTTS that develops between 16- 26 weeks. Results of the Eurofetus (randomized trial that compared amnioreduction with laser photocoagulation) revealed that the group that underwent laser therapy had a significantly higher gestational age at delivery (33 vs. 29 weeks), along with higher survival of at least one fetus to 28 days of age (76% vs. 56%), improved neurologic outcomes with decreased risk of periventricular leukomalacia (6% vs. 14%) and a higher likelihood of being free of neurologic complications at six months of age (52% vs. 31%).

Amnioreduction still has a role in the management of TTTS under certain conditions. It may be a useful procedure to allow a patient to be transported to a center where more definitive therapy may be offered. It may be beneficial to decompress the uterus in cases where there is 1) evidence of cervical shortening to allow a cervical cerclage to be placed before laser therapy; 2) to manage symptomatic polyhydramnios when TTTS develops outside the gestational age where laser therapy can be performed; or 3) where laser therapy is technically not possible. It also may be useful in the management of stage 1 TTTS.

A number of early stage TTTS cases do not progress and remain at stage 1 or may even regress. The rate of progression of stage 1 patients has been known to range from 10% to 45%, with most studies reporting a 30% rate. The treatment of stage 1 TTTS is therefore controversial; whether the best therapy is observation, amnioreduction or laser photocoagulation remains to be determined. There is a randomized European trial underway for the management of stage 1 TTTS.

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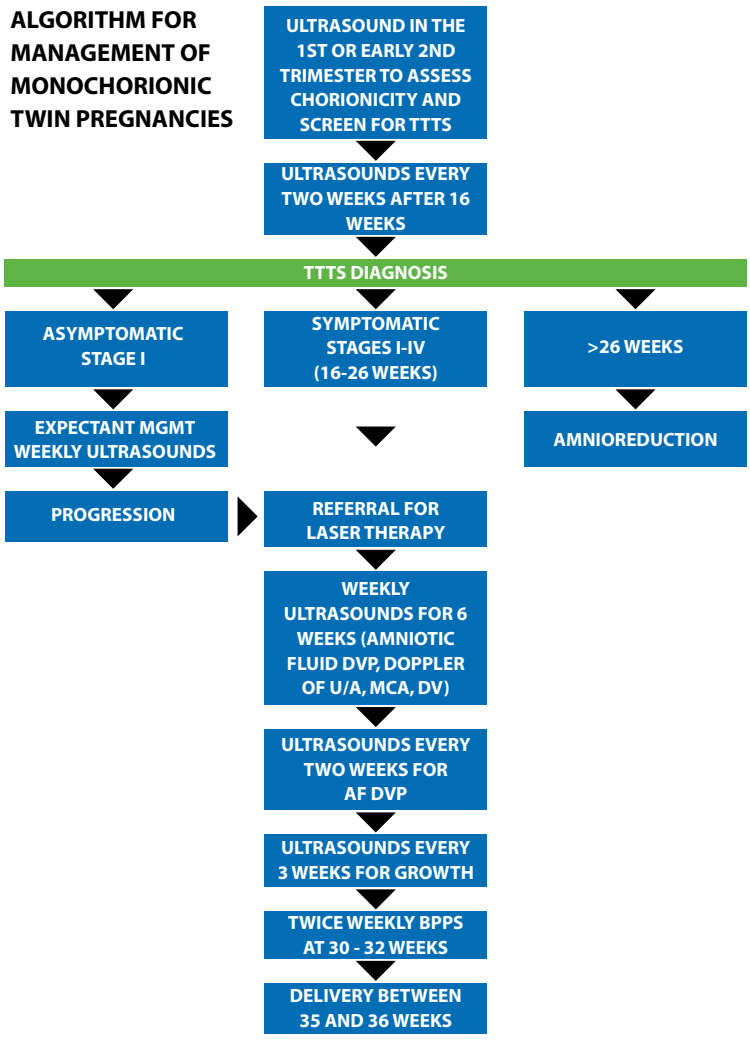
Twin-to-twin transfusion syndrome continued...



Selective termination of one fetus by bipolar cord coagulation or radiofrequency ablation is reserved for cases where there are discordant anomalies, pre-existing injury or imminent demise of one twin.

OUTCOME

The overall reported survival rate from centers specializing in laser therapy is approximately 85%. The survival of at least one fetus is 94% and of both, 77%. The mean gestational age at delivery in successfully treated cases is still less that that seen in similar cohorts without TTTS. The Eurofetus trial reported that 52% of surviving infants from the laser group at six months of age were free of major neurologic sequelae compared to 31% in the amnioreduction group. The largest series reporting on the long-term outcomes of infants followed to a mean gestational age of more than three years from pregnancies that underwent laser therapy before 26 weeks showed that 86.8% of infants developed normally, 7.2% had minor neurologic abnormalities and 6% severe neurologic abnormalities.

CONCLUSION

Twin-to-twin transfusion syndrome is a complex and progressive clinical condition affecting specifically monochorionic twin pregnancies. Identifying chorionicity early in pregnancy and close surveillance of monochorionic twins cannot be overemphasized. Given the recent advances in treatment, early identification of TTTS allows referral to experienced centers with laser therapy capabilities and improved pregnancy outcomes.

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Dr. Martinez-Poyer was born and raised in Venezuela. He received his medical degree from Luis Razetti, M.D. Medical School at the Central University of Venezuela. He completed his residency in obstetrics and gynecology and fellowship in maternal-fetal medicine at Wayne State University School of Medicine.

Dr. Martinez-Poyer's clinical interests include prenatal diagnosis, fetal therapy and multiple gestations. He has been involved in research in the areas of obstetric ultrasound and has received awards for his research work on fetal left cardiac function. He has published articles in the *Journal of Ultrasound in Medicine*, *Radiology*, the *American Journal of Obstetrics & Gynecology*, and the *New England Journal of Medicine*. Dr. Martinez-Poyer is board certified in obstetrics and gynecology and maternal-fetal medicine.

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