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WHAT IS TWIN-TO-TWIN TRANSFUSION SYNDROME?*

Twin-to-twin transfusion occurs in a monochorionic pregnancy (i.e., identical twins who share a single placenta) when blood from one fetus circulates to the other twin. In general, identical twins normally exchange some blood during gestation; this exchange is usually balanced, so that one twin will act as the 'blood donor' one moment, and as the 'recipient' the next. The twin-to-twin transfusion syndrome occurs when one twin always 'donates' blood to the other, because the communication between the two is unbalanced.

*Underlined terms are explained in the glossary at the end

Twin-to-twin transfusion syndrome does not occur in non-identical twin fetuses, where each fetus has its own placenta. It is also much less likely to occur if both twins are not only identical, but share a common amniotic space (so-called mono-amniotic twins). The latter is the least common form of twin pregnancies, but is associated with other potentially life-threatening problems.

In the twin-to-twin transfusion syndrome, one twin (donor) will have to pump blood, not only for himself, but also to transfuse the recipient twin. The donor has to do more work, thereby having less energy to grow; he will show signs of intrauterine growth retardation, will produce less amniotic fluid (oligohydramnios), and eventually become almost wrapped in its amniotic membranes: there is now so little fluid surrounding him that he is 'stuck.' Hence, twin-to-twin transfusion syndrome is sometimes referred to as 'stuck twin' syndrome.

The recipient twin, on the other hand, ends up with too much blood and fluids, which forces him to eliminate it through the urine: a recipient twin will therefore often be seen with a full bladder. The excess fluid causes polyhydramnios, the excess accumulation of amniotic fluid in this fetus's amniotic space. The fetus himself will tend to swell (become edematous), and may go into heart failure, or 'hydrops'. The combination of polyhydramnios in the recipient and oligohydramnios in the donor is also referred to as 'poly-oli' syndrome, another term for twin-to-twin transfusion syndrome.

Figure 1 illustrates a normal situation, where blood flows in either direction. Figure 2A illustrates the onset of twin-to-twin transfusion syndrome, where blood preferentially flows from one fetus (the donor) to the other (the recipient). In figure 2B, the full-blown syndrome ("stuck twin") develops.

HOW COMMON IS TWIN-TO-TWIN TRANSFUSION SYNDROME?

It happens in 5 to 15% of all identical twins, and puts about 6,000 babies at risk in the United States each year.* It can happen anytime during the pregnancy. It can also affect triplet and higher order pregnancies.

WHAT IS THE RISK TO THE TWINS?

If twin-to-twin transfusion syndrome occurs late in gestation, the risks are usually minimal; if one fetus is threatening to develop hydrops or failure, delivery of the babies might be the best option. If this occurs earlier, before the babies are mature enough to survive out of the womb, the options are fewer and the risks greater.

Preterm, premature rupture of the membranes (PPROM) and premature labor are often a threat to the twin pregnancy, possibly due to increased pressure and increased amounts of amniotic fluid (polyhydramnios in the 'recipient' fetus). If the babies are born prematurely, they may be at a higher risk of suffering serious complications, or even dying in infancy.

One or the other twin is at a high risk of suffering severe heart- or brain problems (due to insufficient or inappropriate blood flow caused by the transfusion). The donor twin is usually the sickest; he will often be anemic (not enough red blood cells), and is the one at highest risk of dying in utero.

The recipient twin may suffer as well, and develop hydrops (heart failure) due to fluid and blood overload. In addition, chronic transfusion may make the recipient's blood thicker (more viscous). This, in combination with somewhat sluggish blood flow because of heart failure, may place the recipient at risk for "vascular accidents" whereby a blood vessel becomes blocked. This may theoretically affect any organ, or an entire limb, causing necrosis. As a result, the organ may be damaged or even absent. Examples of this are an absent kidney, an interruption in the intestinal tract or a severely abnormal leg.

Once a fetus dies, the remaining twin is at a very high risk of dying within days. If he survives, he is very likely to develop very severe heart or brain damage.

If twin-to-twin transfusion syndrome develops early in pregnancy (before 20 weeks) and nothing is done, there is a very high likelihood that both twins will die.

ARE ALL CASES OF TTTS THE SAME?

No, some cases of TTTS are extremely severe and rapid in onset, while others have a less aggressive course. There are several ways doctors can describe and classify the severity of the syndrome, but the most commonly used is the one devised by Dr. Ruben Quintero. The Quintero classification (or its modifications) uses ultrasound findings to estimate the severity of TTTS:

In **stage I**, there is severe polyhydramnios around the recipient and severe oligohydramnios around the donor, but the donor is still able to produce enough urine to fill his bladder (which is visible on ultrasound).

In **stage II**, the degree of transfusion and dehydration of the donor is such, that he is no longer able to fill his bladder - the bladder is now no longer visible on ultrasound.

In **stage III**, additional signs of fetal stress are seen: there may be pulsatile (rather than uniform) flow through the umbilical vein (usually of the recipient), absent or even reversed end-diastolic flow in the umbilical artery (usually of the donor) or other signs of cardiovascular stress, such as a leaky heart valve (tricuspid regurgitation, or TR). As a group, these signs are called "critical dopplers," because they are usually diagnosed by using doppler ultrasound (a feature of the ultrasound machine).

In **stage IV**, there are now overt signs of heart failure in one or both twins: fluid starts to accumulate around the heart (pericardial effusion), around the lungs (pleural effusions), in the abdomen (ascites) or under the skin (edema, or thickened nuchal fold).

Clearly, stages III and IV are more severe than stages I and II. In general, surgical intervention (such as laser) is not recommended in lesser stages, and most centers will only offer aggressive treatment for stages II, III or IV. The main reason for this is that the prognosis is better for stage I than for higher stages (provided that the twins remain in stage I and do not progress to a higher stage).

Unfortunately, it is very difficult, at this time, to predict *how* a particular case will progress: some twins have been seen to remain in stage I for many weeks, or even improve on their own; while others have progressed very rapidly to a higher stage, sometimes even skipping one or more stage. Much of the current research in TTTS is now directed at understanding why some twins develop the syndrome and others don't, and why some progress more rapidly than others.

WHAT ARE THE TREATMENT OPTIONS?

1. Observation and bedrest.

If twin-to-twin transfusion syndrome occurs after 25 to 28 weeks, conservative measures (bedrest, single amnioreduction) and early delivery are usually recommended. Amnioreduction means the removal, through a fine needle, of the excess amniotic fluid from the recipient twin with polyhydramnios (see below). As the pregnancy comes closer to term, it may be best to 'wait and see,' and to plan early delivery if either twin shows signs of distress. In this situation, the risks associated with (mild to moderate) prematurity may be smaller than the risk of an intervention in the womb (such as the ones described below).

2. Amnioreduction.

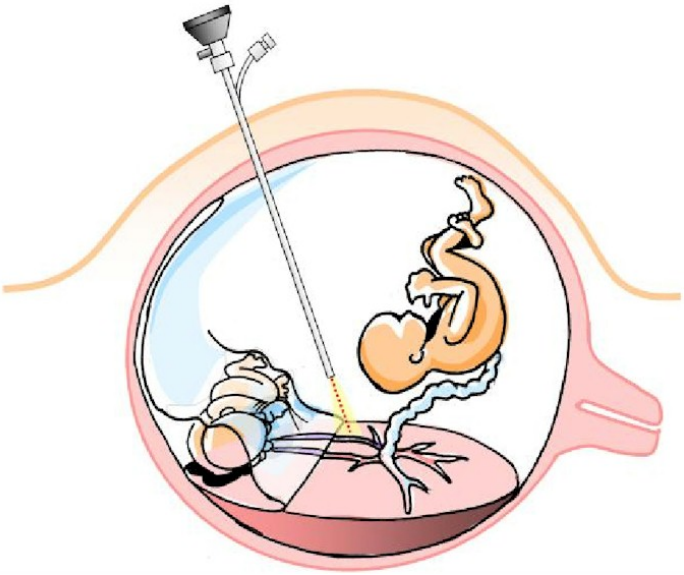
Removal of excess amniotic fluid from the recipient twin has been, until recently, the best available treatment for twin-to-twin transfusion syndrome. The reason for its effectiveness is not completely clear, but removing the excess amniotic fluid may help decrease the risk of rupture of the membranes (PPROM) and premature labor. It may also be beneficial by relieving the pressure on the umbilical cord of the twin with excess fluid, and thus improve blood flow between the fetus and the placenta.

Amnioreduction does not, however, treat the cause of twin-to-twin transfusion syndrome, only one of its effects. Since the fluid is likely to accumulate again (usually within a few days to a week or two), the procedure will have to be repeated. With each amnioreduction, the risk of bleeding or infection increases, as does the risk of injury to the membranes.

The results of repeated amnioreduction depend on how often this has to be done, and how rapidly fluid accumulates again. In general, the earlier in gestation the syndrome develops and the quicker polyhydramnios recurs after amnioreduction, the worse the outcome. Whereas survival of either twin in twin-to-twin transfusion syndrome is very low if the condition develops early (before 20 weeks of gestation), repeated amnioreduction can improve survival of at least one twin to 50-60%. Unfortunately, the risks of severe complications in the surviving twins may be as high as 20 to 35%, and includes severe heart or brain anomalies.

3. Laser coagulation of the communicating placental vessels.

This technique, a form of fetal surgery, was originally described in 1995 by Dr. Julian DeLia, and is now being performed in several centers world-wide, including our own. This is the only known form of treatment for twin-to-twin transfusion syndrome where the likely cause of the condition is addressed. In essence, a laser fiber is used, through a very small endoscope (a long telescopic lens) inserted into the uterus, to block all vessels that run from one twin to the other (see figure 3)



Fetal surgery is done under epidural or general anesthesia. A small incision is made on the mother's abdomen and, under ultrasound guidance, a long and thin instrument (less than 1/8 " in diameter) is introduced into the amniotic cavity. This instrument contains an endoscope, which allows the surgeon to directly look into the uterus; and a laser fiber to coagulate, or block, the blood vessels that are seen to cross from one twin to the other. All other blood vessels, that connect the fetus to its own side of the placenta, are left alone.

The procedure has been performed hundreds of times since it was first described. It was initially developed in the United States, but the majority of cases have been performed in Europe. Today, several centers in the U.S. are offering this technique.

The results of laser fetal surgery appear to be better than those of other techniques, when patients are properly selected. Survival of at least one twin has been reported to be 70-80%, and survival of both twins is seen in 30-40% of the pregnancies. Also, the complication rate appears to be much lower. There are much fewer cases of severe heart and brain damage, and the overall complication rate (including a few instances of infection and damage to the membranes) is less than 10%, not including PPROM.

Preterm, premature rupture of the membranes (PPROM) usually leads to premature delivery; it is common in twin gestations (5-15%), particularly if TTTS is present. While decreasing the polyhydramnios (see under Amnioreduction) reduces that risk, it may still occur as a result of the invasive procedure itself. After laser coagulation, the incidence of PPROM may be as high as 15%, particularly if multiple procedures (such as repeated amnioreductions) preceded the endoscopic operation.

Since its first description, the technique has undergone many improvements. For example, the use of special endoscopes that can be custom-curved now allows the treatment of patients with an anterior placenta. The use of magnetic resonance imaging (MRI) and computerized three-dimensional reconstruction allows the surgeons to plan the procedures on a virtual reality model, before the uterus is even entered (figure 5).

It is important to note that this is a form of fetal surgery and the most aggressive of the treatment options for TTTS, and that risks, although reduced to a minimum, exist for the mother and the fetuses. While the procedure aims at separating the two blood circulations, communications may still persist after the operation. As a result, one fetus's demise could theoretically still affect the other (although that risk is clearly much reduced compared with any of the other treatment options). Complications of TTTS, such as fetal death, brain damage, limb necrosis and others have been

reported even when laser therapy was performed. It is our belief that most of these represented previously undiagnosed abnormalities (undiagnosed, perhaps, because of limitations on the ability of ultrasound to detect evolving problems in their early stages); nevertheless, the possibility also exists that the treatment may not be successful and the TTTS may progress.

Until recently, it had not yet been demonstrated in a scientific way that endoscopic laser ablation of placental vessels was clearly superior to amnioreduction. **Therefore, our center participated in a randomized, controlled trial involving many institutions throughout several continents, and administered by Eurofoetus.** Patients who qualify were offered to enroll in the study, which aimed to compare serial amnioreduction with endoscopic laser surgery. The study showed that laser ablation was superior to amnioreduction for advanced stage TTTS. This is the first time a randomized controlled study has been performed for fetal treatment of TTTS. It is also the first study to demonstrate that laser surgery is superior to amnioreduction.

For more information regarding the recently completed Eurofoetus study, please contact us or go to the Eurofoetus web site, where a full description of the trial protocol is available. The complete results of the study were published in 2004 in the New England Journal of Medicine.

SUMMARY: OUTCOME OF SEVERE TTTS WITH AND WITHOUT TREATMENT

[1] Risk increases with increasing number of amnioreductions

	Untreated	Amnioreduction	Laser
Survival of both twins	0-10%	26%	35%
Survival of at least 1 twin	0-30%	51%	76%
Maternal complications			
	PPROM (5-15%)	PPROM (5-15%) [1]	PPROM (5-15%)
		Infection [1]	Infection
		Bleeding	Bleeding
Fetal complications:			
Neurologic/Cardiac damage	20-35%	20-35%	<5%
Limb necrosis	described	described	described
Organ damage/absence	described	described	described

Glossary:
Explanation of Medical Terms

Absent end-diastolic flow: Normally, the blood flow through the umbilical artery (and in all other arteries) is forward; as the heart pumps the blood forward, the flow through the arteries is more rapid right after each heartbeat, and slows down a little in between heartbeats. In some disease states (such as severe TTTS), the blood flow in the umbilical artery comes to a stop in between heartbeats: there is absent flow at the end of diastole (the phase in between heartbeats, as opposed to systole, or heartbeat). In very severe cases, the blood flow in diastole is even reversed (blood flows backward, *toward* the heart): this is termed reversed end diastolic flow in the umbilical artery.

Amnioreduction: refers to the removal of excess amniotic fluid. Under ultrasound guidance, and after numbing of the mother's abdominal wall, a long, very fine needle is introduced into the uterus and into the amniotic cavity. While the fetus is being monitored with ultrasound, excess fluid from the amniotic cavity is aspirated. It is similar to amniocentesis, where a small amount of amniotic fluid is aspirated for diagnostic reasons. With amnioreduction, the purpose is to aspirate large amounts of fluid, in order to correct polyhydramnios.

Amniotic membrane: the fetus is surrounded by amniotic fluid, and both fetus and fluid are surrounded by a number of layers. Closest to the fetus is the amniotic membrane. The amniotic membrane itself is surrounded by the chorionic membrane, which is contained within the muscle layer of the uterus (the myometrium). In twin pregnancies, fetuses can share a common amniotic membrane (monoamniotic twins), or each fetus and its amniotic sac can be contained by a common chorionic membrane (monochorionic, diamniotic twins). In this case, they still share a common placenta. Non-identical twins have separate amniotic and chorionic membranes: they are dichorionic twins.

Amniotic space: in the womb, a fetus 'floats around' in amniotic fluid, which is contained within an amniotic sac, or amniotic membranes. This defines the fetus's amniotic space.

Anemia: condition where there are too few red blood cells in the blood. Because of that, the heart has to work faster, to be able to pump the same amount of red blood cells. This may lead to heart failure and hydrops.

Ascites: the presence of large amoounts of fluid in the abdomen. It can be due to a number of causes, depending on the type of fluid, associated conditions, etc. In TTTS, ascites is most often a sign of hydrops, as fluid accumulates outside the blood vessels. Other spaces where fluid can collect: around the heart (pericardial effusion), around the lungs (pleural effusion) and under the skin (edema).

Coagulation: closing a blood vessel through heat, such as with an electric current (electrocoagulation) or a laser. Using a laser in twin-to-twin transfusion syndrome allows reliable coagulation of the vessel only, without damage to surrounding tissues, all this within the amniotic fluid.

Doppler ultrasound: the Doppler phenomenon refers to the cange in wave length that occurs when a sound travels toward, or away from, the observer (think of the siren's pitch that changes when an ambulance drives past). The same occurs with ultrasounds, and a doppler allows one to measure the amount and direction of flow inside a blood vessel, by measuring the wave length reflected off the blood. In TTTS, "critical dopplers" refers to abnormal flow in the blood vessels or the heart: blood flow in the umbilical vein can be pulsatile, it can be absent in diastole in the umbilical artery; or blood can be seen to leak back through a heart valve (tricuspid regurgitation).

Edema: the accumulation of fluid under the skin, giving it a puffy appearance. In the fetus, it is often measured in the skin of the neck: the skin fold in the back of the neck (the nuchal fold) is then thickened.

Endoscope: a long, thin instrument that contains lenses, and can be introduced in a cavity. Through the lenses (and with adequate lighting through the instrument), one can look at the inside of that body cavity without the need for an incision. Endoscopes are used a lot in medicine, and can be utilized to look inside a joint (arthroscopy), the stomach (gastroscopy), the abdomen (laparoscopy) or the uterus (fetoscopy or amnioscopy).

Effusion: abnormal collection of fluid. a pericardial effusion (fluid around the heart) or pleural effusions (fluid around one or both lungs) can be signs of heart failure of the fetus (hydrops). Other signs of abnormal fluid accumulation are ascites and edema.

Hydrops: heart failure or fluid overload of the fetus, a condition that, if not rapidly corrected, will lead to fetal death. It is characterized by swelling (edema), thickened skin, fluid accumulation around the lungs and in the abdomen of the fetus.

Intrauterine growth retardation: is said of a fetus who does not grow as fast as he should, often because not enough nutrients or not enough blood (and oxygen) arrive to him, or because the fetus has to 'work' harder than usual. In twin-to-twin transfusion, it is often seen in the donor twin, who has to pump blood to himself and to the recipient twin. Intrauterine growth retardation can be seen by ultrasound, when the fetus appears smaller than expected for a given gestational age. At birth, this will lead to a baby who is 'small for gestational age.'

Monoamniotic twins: identical twins who not only share a common placenta, but a common amniotic space as well. This is a much rarer situation than identical twins who each have their own amniotic sac (so-called monochorionic, diamniotic twins).

Monochorionic twins: identical twins who share a common placenta. In addition, they can either have their own amniotic sac (they are then called monochorionic, diamniotic twins) or share a common amniotic sac (which is much less common, and is called a monochorionic, monamniotic twin pregnancy).

Nuchal fold: the skin fold in the back of the neck. Measuring its thickness can be used to decide whether there is edema, in which case that fold will be thicker.

Oligohydramnios: there should always be a sufficient amount of amniotic fluid around the fetus, to allow him to develop and move around. When there is too little fluid, it is called oligohydramnios. Anhydramnios refers to a situation where there is virtually no fluid left.

Polyhydramnios: too much amniotic fluid. Although the fetus can now freely move around, polyhydramnios can represent a danger because of an increased risk of premature rupture of the membranes (PPROM). It can also cause too much pressure on the umbilical cord. Polyhydramnios is often noted because the mother's abdomen is much larger than expected for the time of pregnancy.

Preterm Premature Rupture Of Membranes (PPROM): around the time of labor, the membranes rupture (or are ruptured by the obstetrician, if labor has to be induced). If membranes rupture before the fetus has reached term, it is called preterm premature rupture. This will often lead to the onset of labor, causing the baby to be born prematurely.

Pulsatile flow: blood flow in arteries is pulsatile: it is fastest with each heartbeat, and slows down a little in between beats. In contrast, blood flow in a vein is generally uniform: always at the same speed. In severe TTTS, the fetus may be so stressed that flow in the umbilical vein becomes pulsatile. This can be seen with a doppler ultrasound examination of the vein.

Randomized Controlled Trial (RCT)**:** A clinical research trial set up to evaluate a new form of treatment or a new drug, by comparing it to an existing one (the control group). In this, the most scientifically correct form of research, patients agree to be "randomized," or assigned to one or the

other form of treatment in a random fashion: neither the patient nor the treating physician can choose to which group the patient will belong. Thus, any possible bias is eliminated. In the case of Twin-to-twin Transfusion Syndrome, a randomized controlled trial is currently in progress. Our Fetal Treatment Center participates in the first such trial, sponsored by Eurofoetus

Tricuspid regurgitation: the tricuspid valve is the heart valve between the right atrium and the right ventricles (two of the heart chambers). Valves keep the blood flowing in one direction only (from the veins into the atrium, from the atrium into the ventricle, and from the ventricle into the arteries. If the heart is stressed and enlarged, the tricuscpid valve may be stretched too, and may not close properly anymore: blood can then be seen to leak backward, or regurgitate. This is best seen with doppler ultrasound.