SIMPOSIO CIRUGÍA FETAL EN AMÉRICA LATINA

SYMPOSIUM FETAL SURGERY IN LATIN AMERICA

# Fetoscopic laser surgery for twin to twin transfusion syndrome

## Cirugía láser fetoscópica en el síndrome de transfusión feto fetal

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**ABSTRACT**

Twin to twin transfusion syndrome (TTTS) is a complication of circa 10% of all monochorionic pregnancies (MC). A predominantly unidirectional, net intertwin blood flow through placental vascular anastomoses triggers a variety of complex renal and cardiovascular disturbances in both fetuses. Left untreated, severe TTTS leads to a mortality rate above 80% and 15-50% morbidity in the survivors. Fetoscopic laser coagulation (FLC) of the placental anastomoses is the first line treatment for severe cases before 27 weeks and it has been shown to improve perinatal outcomes. The risk of preterm premature rupture of membranes (PPROM) and prematurity associated with FLC has to be balanced with the risk of adopting expectant management in every particular case. Since there is no accurate way to predict the evolution of the disease, and no effective method to prevent post-procedure PPROM has been described, the indication of FLC is as challenging as the procedure itself.

Key words: Fetal therapies, Feto-fetal transfusion, Fetoscopy, Laser coagulation, Twin pregnancy.

**RESUMEN**

El síndrome de transfusión de gemelo a gemelo (TTTS) complica alrededor del 10% de todos los embarazos monocoriónicos (MC). Un flujo sanguíneo intergemelar neto, predominantemente unidireccional, a través de anastomosis vasculares placentarias, desencadena una variedad de alteraciones renales y cardiovasculares complejas en ambos fetos. Sin tratamiento, el TTTS grave conduce a una mortalidad superior al 80% y una morbilidad del 15 a 50% en los sobrevivientes. La coagulación láser fetoscópica (CLF) de las anastomosis placentarias es el tratamiento de elección para casos graves antes de las 27 semanas y ha demostrado mejorar los resultados perinatales. El riesgo de rotura prematura de membranas (RPM) y de prematuridad asociada a CLF se debe sopesar con el riesgo de la conducta expectante en cada caso particular. Dado que no hay una manera precisa de predecir la evolución de la enfermedad, y no se ha descrito aun ningún método eficaz para prevenir la RPM posterior al procedimiento, la indicación de la CLF es tan desafiante como el procedimiento en sí mismo.

Palabras clave. Embarazo gemelar, Transfusión feto-fetal, Coagulación con láser, Terapias fetales.

## Introduction

Monochorionic (MC) twin pregnancy occurs in 1 of every 250 pregnancies and represents 20% of all twin pregnancies[1]. Perinatal mortality and morbidity are significantly higher in MC than in dichorionic twin pregnancies since the circulation of both fetuses is interconnected through vascular anastomoses in the common placenta. Therefore, the wellbeing of each fetus is both cause and consequence of that of the other[2,3]. In the unfortunate event of the demise of one of the twins, there is a significant risk of death or handicap in the co-twin due to acute blood loss through the placental anastomoses towards the death fetus[4,5].

Establishing chorionicity in every twin pregnancy during early gestation or at the time of the 11 to 13 weeks scan is crucial. A close follow up every fortnight from 16 weeks onwards to detect early signs of complications is needed for MC twins[6].

One of the most common complications in MC twins is twin to twin transfusion syndrome (TTTS), a complex condition in which an unbalanced blood flow exchange through placental anastomoses causes hypovolemia in one twin (donor) and hypervolemia in the other (recipient). This triggers a cascade of hormone-mediated renal and cardiovascular disturbances in both twins. Left untreated, severe TTTS leads to 80-100% perinatal mortality and 15-50% neurological morbidity in the survivors[7].

Although vascular anastomoses are just the anatomical component of a complex condition, its elimination via fetoscopic laser ablation can resolve de syndrome and significantly improve survival[8]. Considering the risk of premature rupture of membranes and preterm delivery added by an invasive procedure, the dilemma relies on the decision of the need and timing for the intervention.

## Vascular anastomoses

In MC twin pregnancies, where both cords insert and branch over a common placenta, 3 types of anastomosis can connect the circulation of both fetuses: 1) arterio-arterial (AA), 2) veno-venous (VV), and 3) arterio-venous (AV) anastomoses.

AA and VV anastomoses are superficial, presenting on the placental surface, where macroscopic vessels from the two cords can fuse in a true end-to-end connection. On the contrary, AV anastomosis are deep, presenting at capillary level, via a functional anastomosis in a shared cotyledon, arterially perfused by one of the twins, but drained into the venous circulation of the other. AV anastomosis have a constant unidirectional flow, whereas superficial anastomoses (AA or VV) can allow flow in both directions depending on the hemodynamic interaction between both circulations. In particular, AA anastomoses may act as protective compensatory shunts preventing the development of TTTS[9].

Postnatal placental studies confirm that almost all (95%) MC pregnancies have vascular interconnections at placental level. However, only 10 to 20% of monochorionic pregnancies will develop TTTS due to a predominantly unidirectional net blood flow from one twin to the other. This seems to be caused by the presence of at least one AV anastomosis (shared cotyledon) and the absence or scarcity of compensatory AA anastomoses. The role of VV anastomoses is controversial; they are rarer and there is evidence suggesting that its presence could contribute to the development of TTTS, especially in the absence of AA anastomosis[9,10].

## Diagnosis of TTTS

TTTS is diagnosed by ultrasound by the presence of polyhydramnios in one twin (DVP >8 cm before 20 weeks and >10 after 20 weeks) and oligohydramnios in the other (DVP <2 cm).

A new cut-off of a DVP >6 cm to define polyhydramnios in the recipient before 18 weeks, has recently been proposed to account for the gestational age dependent difference of the 90th centile in the normal DVP distribution[11].

## Concomitant selective fetal growth restriction (sFGR)

Placental anastomoses are not the only factor complicating MC pregnancies. The distribution of the placental mass is usually unequal in MC twins. When this discrepancy is excessive and one of the twins has a very small placental mass, its growth can be compromised.

sFGR is diagnosed when one of the fetuses has an abdominal circumference <5th centile before 22 weeks or an estimated fetal weight (EFW) <5th centile after 22 weeks together with a discrepancy in size with the cotwin >25%[1,12]. This complication has its own classification and management depending on the characteristics of the umbilical artery Doppler of the restricted fetus[12]. TTTS is superimposed in around 70% of MC twin pregnancies affected with sFGR[13].

## Natural history of TTTS

The donor twin suffers from hypovolemia and oliguria with progressive decrease in the amount of amniotic fluid, leading to anhydramnios and a persistent empty bladder. In the most severe cases there is absent end diastolic flow in the umbilical artery. On the contrary, the recipient twin is hypervolemic and polyuric presenting a large polyhydramnios. Volume overload may cause absent or reversed wave in the ductus venosus, pulsatile flow in the umbilical vein, tricuspid regurgitation and fetal hydrops in the most severe cases[7]. Hypertrophic cardiomyopathy suggesting systemic hypertension can also be seen in the recipient leading to right ventricular outflow tract obstruction (RVOTO) in 3% of the cases[14,15].

All these cardiovascular and renal disturbances described for both twins cannot be explained only by a blood volume depletion or overload. There is evidence to conclude that, in response to hypovolemia, activation of the renin-angiotensin system (RAS) in the donor and the placenta, aiming to increase vascular resistance, can have a negative paradoxical effect in both twins[16]. Also, upregulation of endothelin and vasoactive peptides may be involved[17].

The course of the disease in severe cases can lead to intrauterine demise of either twin. Consequently, exsanguination of the surviving co-twin into the fetoplacental territory of the death fetus can cause double fetal demise in up to 50% of the cases[18]. In those surviving after the demise of a co-twin, abnormal cranial imaging is found in up to 35% of the cases[19,20].

## Evaluation of severity

Some of the sonographic findings described have been used by Quintero et al in 1999 to establish a staging system for TTTS (QS) [Table 1][21]. This widespread classification is useful to describe, to some extent, the severity of the condition at the time of the examination, but its ability to predict the evolution of any particular case is limited. Some cases will progress, some will remain unchanged during the whole pregnancy and some others will even regress[22]. So far, no effective method to predict evolution has been described.

Although important prognostic factors such as specific cardiac findings in recipients, cervical length, EFW discrepancy and gestational age have been introduced in an attempt to produce new staging systems, QS in its simplicity remains broadly used[23,24]. This is probably because to some extent, in daily practice, MC twin pregnancies are being followed up in institutions were FLC is not available, therefore their duty is to differentiate mild from severe cases, or in other words, those cases needing expectant management from those needing urgent referral for active management and QS can do that.

## Management

Mild cases (QS I) will be followed expectantly. Active management is reserved for severe cases (QS II-IV) where surgical treatment or elective delivery by caesarean section will be needed depending on gestational age.

Fetoscopic laser coagulation (FLC) of the placental anastomoses is the first line treatment between 16 and 27 weeks. It eliminates the etiological cause of TTTS resulting in double survival in 70% of the cases and a least one fetus surviving in 85% of the cases[25].

Performing any invasive procedure before 16 weeks carries an increased risk for adverse pregnancy outcomes. Although early severe cases

Table 1. Staging of twin-twin transfusion syndrome (from Quintero et al 1999)[21].

| Quintero Stage | Findings |
|---|---|
| I | Oligohydramnios / Polyhydramnios sequence |
| II | Not visible bladder in the donor twin |
| III | Abnormal Doppler: A/REDF-UA, RaW-DV, pulsatile flow in the UV (one or both twins) |
| IV | Fetal hydrops (one or both twins) |
| V | Fetal death (one or both twins) |

*A/REDF-UA: Absent / reversed end diastolic flow in the umbilical artery; RaW-DV: Reversed a wave in the ductus venosus; UV: Umbilical vein.*

are rare, FLC before 16 weeks should be considered specially for QS IV or when imminent fetal demise is suspected[26].

The upper limit of 27 weeks is related to the technical difficulties found during fetoscopy. Visibility and space for maneuvering with the fetoscope are reduced due to bigger fetal size. How far this limit can be pushed is debatable. Intrauterine treatment can significantly reduce neonatal morbidity and mortality by decreasing prematurity and allowing time for the fetuses to recover in-utero from the cardiac and renal insult. In general terms, if severe TTTS is diagnosed after 27-28 weeks, elective caesarean delivery after lung maturation may be preferred for QS III-IV weeks. Amnioreductions should be considered for QS II with elective caesarean section in case of progression[26,27].

## Active management in mild cases

### Short cervix

Considering that polyhydramnios is the first manifestation of the syndrome, cervical length becomes a very important prognostic factor for adverse outcome related to miscarriage, preterm delivery and prematurity in twin pregnancies affected with TTTS. Cervical cerclage for CL <15 mm, immediately after FLC with amniodrainage may improve gestational age at delivery and survival in severe cases[28]. Therefore, the same management can be considered for QS I cases with a CL <15 mm, especially when they present early in gestation. FLC would eliminate the cause of the polyhydramnios and avoid repeated amniodrainage.

In cases of short cervix presenting after 28 weeks, serial amniodrainage could prolong the pregnancy and elective delivery would be indicated in case of progression of the syndrome.

### Reversal of TTTS

A reversal of TTTS is a rare situation. Ultrasonographic findings suggest an inversion of the phenotype, with the donor becoming recipient and vice versa. Its diagnosis is challenging, and prognosis is very poor with double demise occurring before the criteria for TTTS is fulfilled. It is an indication for immediate active management according to gestational age[29].

### Selective fetal growth restriction (sFGR)

A growth restricted MC twin has a higher risk for intrauterine demise (IUD) and therefore the risk of demise or handicap is increased for the cotwin. Mild TTTS in the context of sFGR has high incidence of adverse outcome and it may be considered an indication for active management [25,30].

## Fetoscopic laser coagulation technique

FLC is a minimally invasive procedure performed usually under local or regional anesthesia. Using Seldinger technique, a 10 fr (3 mm) vascular introducer is placed into the amniotic cavity of the recipient through the maternal abdomen. A thorough ultrasonographic examination is needed to decide the best position for the trocar. While the recipient can move freely in the polyhydramnios cavity, the donor is pushed against the uterine wall and the placenta, trapped by its own amniotic sac and the intertwin membrane (stuck twin). The exact location and boundaries of the placenta and the stuck twin should be defined. Both cord insertions must be identified to estimate the vascular equator, were the anastomosis are expected to be present. Velamentous cord insertion is not uncommon specially when TTTS and sFGR coexist[31].

The trocar has to be placed perpendicular to the long axis of the stuck twin and away from it. Perforating the intertwin membrane would cause an accidental septostomy allowing transfer of the recipient´s amniotic fluid into the donor´s sac, adding technical difficulties to the procedure and risk of pseudo-amniotic bands syndrome[32]. Ideally, the introduction of the trocar should also be away from the placental edge, aiming perpendicularly to the vascular equator. These basic principles are true regardless of placental position but entering away from the placental edge and perpendicular to the vascular equator in anterior placentas is not always possible, regardless of the shape of the fetoscope (straight or curved).

Once the trocar has been placed, the introduction of the fetoscope in the amniotic cavity will allow visualization of the placental vessels, identification of the vascular equator and localization of the anastomoses. A 400 or 600 µm laser fiber can be passed through the working channel of the fetoscope. A diode or NdYag laser machine

with a wave length of 980 nm is used to produce a 40W laser beam to coagulate the vascular connections under direct vision.

Correct individualization of every anastomosis and selective coagulation of these specific areas, preserving the rest of the placenta, has been broadly used but it is being abandoned since it may miss small anastomoses leading to incomplete treatment. Coagulating the placental plate from edge to edge with a continuous line joining the vascular anastomoses (Solomon technique), has been proven to be superior in achieving successful dichorionization, with a fivefold reduction of the incidence of postoperative complications derived from incomplete lasering[33,34].

Coagulation in a sequential manner, depending on the type and flow direction of the anastomoses, could contribute to intraoperative balancing of the circulation and may improve double survival[35,36].

Once the laser coagulation has finished, amniodrainage is performed through the introducer aiming for a DVP of 5 or 6 cm.

## Post-operative complications

### Preterm premature rupture of membranes (PPROM)

Post procedure PPROM <34 weeks has an overall rate close to 40%. Median procedure-to-PPROM interval is 46 days. Thus, PPROM is particularly deleterious when it follows FLC performed before viability, leading to miscarriage or extreme preterm birth[37]. Chorioamniotic separation and membrane tearing at the entry site may be responsible for these complications. Due to the inability of the amniotic membranes to heal, and since no effective method to seal the defect caused by the trocar has been found, fetoscopy is performed when the potential benefits of the surgery outweigh the risks related to PPROM (miscarriage or preterm delivery). Assuming these risks in severe cases (QS II-IV) is justified. Considering that survival is influenced directly by the severity of the condition at the time of the FLC[38], and since there is no accurate method for predicting progression, preventive FLC for QS I may be justified, but assuming the risk of PPROM, especially in pre-viable cases, is controversial.

### Recurrent TTTS

Recurrent TTTS can be diagnosed in around 3% and 7% of the cases at any time following selective FLC or Solomon technique respectively[39]. A persistent unidirectional blood flow from the donor to the recipient together with an upregulated RAS, could possibly explain why, even though most of the anastomosis were eliminated, the full spectrum of the syndrome can reappear. Early diagnosis is challenging specially if unintentional septostomy was caused by laser coagulation during the procedure, leading to a milder oligo-polyhydramnios sequence. Non-normalization of donor´s urination and/or Doppler parameters may help in the diagnosis.

### Post-operative twin anemia-polycythaemia sequence (TAPS)

Primary TAPS affects up to 5% of MC twins. It is a complication derived from predominant unidirectional blood flow through small and scarce placental anastomoses. The amount of blood exchange is insufficient to produce a TTTS but, in the long run, this chronic transfusion will result in anemia in one twin and polycythemia in the other[9]. Its classification and management depend on severity [Table 2][40].

An incomplete FLC can lead to postoperative TAPS in 1% and 16% of the cases treated with selective coagulation or Solomon technique respectively[39]. Usually the ex-recipient twin is the one presenting anemia. This could indicate that in these cases the anastomoses left untreated allows mainly unidirectional blood flow from the ex-recipient to the ex-donor.

Table 2. Antenatal TAPS classification (from Tollenaar et al 2016)[40].

| Antenatal stage | Findings at Doppler ultrasound examination |
|---|---|
| Stage 1 | MCA-PSV donor >1.5 MoM and MCA-PSV recipient < 1.0 MoM, without other signs of fetal compromise. |
| Stage 2 | MCA-PSV donor >1.7 and MCA-PSV recipient < 0.8 MoM, without other signs of fetal compromise. |
| Stage 3 | As stage 1 or 2, with cardiac compromise of the donor, defined as critically abnormal flow. |
| Stage 4 | Hydrops of donor. |
| Stage 5 | Intrauterine demise of one or both fetuses preceded by TAPS. |

*MCA-PSV: middle cerebral artery peak systolic velocity.*

## Pseudo amniotic band syndrome (PABS)

PABS can affect 2% of MC twin pregnancies treated with FLC. Unintentional septostomy during surgery, chorioamniotic membrane separation and PPROM following FLC are risk factors for PABS, and close surveillance of fetal limbs during follow up is needed. If any of the limbs is affected and its blood supply compromised, fetoscopic release of the amniotic band can be attempted[32,41].

## Repeated fetal laser coagulation

Repeated FLC should be attempt if the recurrent TTTS or severe TAPS are seen before 28 weeks. A free-floating intertwin membrane due to unintentional septostomy during FLC usually adds technical difficulties in the identification of untreated anastomoses[32]. In some cases, blood stained amniotic fluid can also affect visualization. Due to the complexity of the procedure and further iatrogenic damage to the amniotic membrane, the overall survival following repeated FLC is around 40%[42].

After 27 weeks, elective delivery after lung maturation is preferred for post-operative severe TTTS or TAPS. In order to prolong pregnancy, expectant management and amnioreduction or blood transfusion can be considered for mild TTTS and TAPS respectively.

## Long term outcome following FLC

In general terms, the rate of severe neurodevelopmental impairment in twin pregnancies treated with FLC for TTTS is around 10%, with cerebral palsy as the most frequent condition (40%) and no difference between donors and recipients[43]. Lower birth weight seems to be an independent factor associated with neurodevelopmental impairment (OR 1.33 for each week, 95% CI 1.05-1.67, P=.02)[44].

## Conclusion

The indication for FLC using Solomon technique for severe TTTS presenting before 28 weeks is clear. Mild cases in the context of sFGR, reversal of TTTS or short cervix are also candidates for surgery.

Cervical cerclage after FLC should be considered for a CL <15 mm at any stage. Survival and long-term outcomes are directly influenced by the severity of TTTS; therefore, FLC for mild cases has been proposed. If a method to significantly decrease the risk of postoperative PPROM and preterm delivery is found, every MC twin pregnancy presenting with the oligohydramnios / polyhydramnios sequence will be treated. Two relevant randomized control trial are being held: 1) Immediate treatment vs. delayed intervention upon progression for QS I cases (ClinicalTrials.gov Identifier: NCT01220011); and, 2) Prophylactic use of Arabin cervical pessary after FLC for TTTS vs. FLC alone (ClinicalTrials.gov Identifier: NCT01334489).

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