Ultrasound studies in monochorionic twin pregnancies : results of TULIPS: Twins and ultrasound in pregnancy studies

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Chapter 5

Changes in fetal cerebral and renal blood flow after fetoscopic laser therapy for twin-to-twin transfusion syndrome

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Abstract

Objective To investigate fetal hemodynamics in monochorionic twins with twin-to-twin transfusion syndrome (TTTS) before and after fetoscopic laser therapy, focusing on the renal and cerebral blood flow.

Methods In a prospective study, we performed Doppler studies in monochorionic twin pregnancies with TTTS. The pulsatility index (PI) and end-diastolic flow (EDF) of the umbilical artery (UA) (recorded as present, absent or reversed); the PI and the peak systolic velocity of the middle cerebral artery (MCA PSV); the maximum flow velocity (V max) and flow pattern of the intrahepatic part of the umbilical vein (UV) (classified as pulsatile or non-pulsatile); the pulsatility index for veins (PIV) and A-wave of the ductus venosus (DV) (recorded as present, absent or reversed); and the PI and PSV of the renal artery (RA) were measured within 24 h before, 12 to 24 h and 4 to 10 days after laser therapy. At each examination, the presence or absence of tricuspid regurgitation (TR) and of hydropic signs (pleural effusion, ascites, pericardial effusion, or skin edema) was recorded. Hemoglobin values and reticulocyte counts were determined at birth. Long-term follow-up was assessed at the age of 2 years.

Results In donor twins (n=34), DV PIV increased significantly 12 to 24 h after laser therapy, however returned to pre-operative values within 4 to 10 days. A significant decrease in UA PI and increase in UV V max was detected after laser treatment. Twenty percent (6/30) showed signs of TR 12 to 24 h after laser therapy, which was resolved completely after 4 to 10 days. The MCA PI and RA PI were significantly decreased 12 to 24 h after laser treatment, however returned to pre-operative values within 4 to 10 days. MCA and RA PSV values were unchanged by fetoscopic laser therapy.

In recipient twins (n=32), DV PIV decreased significantly 4 to 10 days after laser therapy. The RA PI increased non-significantly after laser treatment; RA PSV values were unchanged. MCA PI and MCA PSV values increased significantly after laser therapy.

After birth, mean hemoglobin values of donors (17.3 ± 4.9 g/dL) and recipients (16.1 ± 4.2 g/dL) were comparable (p=0.43). At the age of 2 years, neurodevelopmental impairment was diagnosed in 15% (4/26) of donors and in 10% (2/21) of recipients and was not related to abnormal MCA flow. None of the children suffered from chronic renal failure.

Conclusion Fetoscopic laser ablation of the placental anastomoses in TTTS affects the fetal and fetoplacental circulation in various ways, such as transient volume overload in donors and improvement of cardiac function in recipients. Cerebral and renal flow changes occur after laser therapy. Whether these are permanent or temporarily fetal adaptations needs further investigation with prolonged follow-up. In our study, the changes found were not associated with long-term neurological or renal sequelae.

Introduction

Twin-to-twin transfusion syndrome (TTTS) is a severe complication that occurs in about 15% of monochorionic diamniotic twin pregnancies during the second trimester[1]. TTTS originates from unbalanced blood transfusion through placental vascular anastomoses from one twin (donor) to the other (recipient) and is diagnosed sonographically by signs of anuria in the donor, and polyuria in the recipient, resulting in the characteristic oligo/polyhydramnios sequence[2]. If left untreated, TTTS is associated with extremely high mortality and morbidity rates[3-5]. Nowadays, fetoscopic laser coagulation of vascular anastomoses is the treatment of choice in severe second-trimester TTTS, although many cases are still managed with serial amniodrainage[6,7]. Perinatal survival rates however, even after laser therapy, are still less than 70% in most series[6,8-11]. Neurological damage is found in 15 to 26% of survivors after treatment with amniodrainage[12-15] and in 6 to 17% after laser surgery[16-19]. In addition, in TTTS treated conservatively, up to 30% of donors suffer from renal failure and/or renal tubular dysgenesis due to chronic volume depletion and renal hypoperfusion *in utero*[15,20-22]. In order to improve these relatively poor outcomes, more insight is needed in the pathophysiology of the disease and the effects of treatment on these hemodynamic changes. Several studies have evaluated the effect of TTTS and its treatment on fetal cardiac and placental blood flow[23-28]. With the increased use of laser ablation as first-line treatment for TTTS, there is an urgent need for more research on the effects both of the disease itself and laser therapy on other vulnerable and vital fetal organs, especially the brain and the kidneys.

The aim of our study was to investigate fetal hemodynamics in monochorionic twins with TTTS by performing Doppler studies in donor and recipient fetuses before and after fetoscopic laser therapy, focusing on the renal and cerebral blood flow.

Methods

Population

The Leiden University Medical Center (LUMC) is the national referral center for fetoscopic laser treatment in the Netherlands. During a two-year period (September 2002 to September 2004), a consecutive cohort of monochorionic diamniotic twin pregnancies with TTTS underwent sequential detailed ultrasound examinations before and after laser treatment for TTTS. Monochorionicity was diagnosed by a first-trimester scan showing twins with absent lambda sign and thin dividing membrane and was confirmed by postpartum placental studies. Pregnancies with fetal congenital anomalies were excluded.

TTTS was diagnosed by the presence of oligo/polyhydramnios sequence in the absence of other causes between 15 and 26 weeks of gestation. Polyhydramnios and oligohydramnios

were defined as a deepest vertical pocket of amniotic fluid of >8 cm at ≤20 weeks (or >10 cm at >20 weeks) and <2 cm, respectively. TTTS severity was assessed according to Quintero's established criteria[2]. Pregnancies complicated by TTTS ≥ Quintero Stage 2 or Quintero Stage 1 with symptomatic polyhydramnios were treated using laser ablation of the communicating placental vessels combined with a single amniodrainage at the end of the laser procedure[6,11]. Patients with unreliable identification of former donor and recipient after laser treatment were excluded.

The hospital's institutional review board approved the study. All patients gave informed consent.

Ultrasound examination and Doppler studies

All patients underwent sonographic assessment of fetal morphology and biometry, amniotic fluid volume, placental location, umbilical cord insertions and Doppler studies within 24 h before laser therapy (T1). Twelve to 24 hours (T2) and 4 to 10 days after laser therapy (T3), the Doppler studies were repeated. Doppler examination included the pulsatility index (PI) and end-diastolic flow (EDF) of the umbilical artery (UA) (recorded as present, absent or reversed); the PI and the peak systolic velocity of the middle cerebral artery (MCA PSV); the maximum flow velocity (V max) and flow pattern of the intrahepatic part of the umbilical vein (UV) (classified as pulsatile or non-pulsatile); the pulsatility index for veins (PIV) and A-wave of the ductus venosus (DV) (recorded as present, absent or reversed); and the PI and PSV of the renal artery (RA). At each examination, the presence or absence of tricuspid regurgitation (TR) was recorded. TR was defined as 50% or more regurgitation of the right ventricle during systole. Presence or absence of hydropic signs (pleural effusion, ascites, pericardial effusion, or skin edema) was recorded at each examination.

Measurements were obtained in the absence of fetal breathing or movements by one of two experienced operators (MS, KAT) using an Acuson Sequoia (Acuson, Mountain View, CA) ultrasound machine with a 4.0 to 6.0 MHz probe.

Postnatal follow-up

Hemoglobin values and reticulocyte counts were determined at birth from umbilical cord blood in all neonates born at our hospital. Twin anemia-polycythemia sequence (TAPS) was diagnosed if, in the presence of residual anastomoses at placental examination, one twin was anemic with high reticulocyte counts, and the other twin polycythemic, in the absence of twin oligo/polyhydramnios sequence[29]. Long-term outcome concerning neurological and renal sequelae were assessed at the age of 2 years (corrected for prematurity). A composite outcome, termed neurodevelopmental impairment, was defined as any of the following: cerebral palsy, mental or psychomotor developmental indexes of less than 2 SD, bilateral blindness, or bilateral deafness

requiring amplification, as previously described[19]. Chronic renal failure was defined as permanent loss of kidney function requiring medical treatment, dialysis or kidney transplantation.

Statistical Analyses

Percentage of perinatal (fetal and early neonatal, until 7 days postpartum) survival was defined as 100x the number of live born children divided by the total number of fetuses in each group. Data were analyzed using the SPSS 12.0 statistical package (SPSS Inc., Chicago, IL, USA). Since Doppler measurements were not normally distributed, the Wilcoxon signed-rank test for matched pairs and the Mann-Whitney test for independent groups were used for statistical comparison. Accordingly, non-parametric descriptive statistics were used in tables. Qualitative variables were compared using the Mac Nemar test. Hemoglobin values were normally distributed. Student's T-test was used for statistical comparison. Findings with a p-value of <0.05 were considered statistically significant.

Results

Thirty-seven patients were recruited for this prospective study. One pregnancy was excluded due to a fetal congenital anomaly (necrotic right hand and forearm). In two other pregnancies, ultrasound identification of former donor and recipient after laser therapy was unreliable due to iatrogenic intertwin membrane perforation during laser treatment.

Median gestational age at laser treatment and delivery was 19.5 weeks (range, 15.6-24.7) and 33.7 weeks (range, 18.3-39.0), respectively. Quintero staging at laser treatment was as follows: Stage 1, 26.5% (n=9); Stage 2, 26.5% (n=9); Stage 3, 41.2% (n=14), and Stage 4, 5.9% (n=2). The overall perinatal survival rate was 72% (49/68); 79% (27/34) of donor twins and 65% (22/34) of recipient twins. Miscarriage occurred in 9% (3/34) of pregnancies. Intrauterine fetal death (IUFD) occurred in 9% (3/34) of donors and 24% (8/34) of recipients. Two recipients died within 24 h after laser therapy; two more recipients died before T3 measurements could be performed. Four donors died and two miscarriages occurred (with the loss of two donors and two recipients) after T2 and before T3 measurements could be performed. Therefore, a total of 34 donors and 32 recipients were available for analysis before and 12 to 24 h after laser therapy; a total of 30 donors and 28 recipients were available for analysis before and after 4 to 10 days after laser therapy. Neonatal death occurred in 3% (2/68) of fetuses. One recipient twin died at birth due to perinatal asphyxia. This case was previously described[30]. One donor twin died within 24 h after birth due to lung hypoplasia.

Doppler measurements of the fetal arteries and veins could successfully be obtained in 99% (UA), 98% (MCA), 98% (UV), 98% (DV), and 85% (RA) of TTTS cases. TR could be recorded in 87%.

Table 1 Doppler measurements in the donor fetus in pregnancies with twin-to-twin transfusion syndrome before and after fetoscopic laser therapy

	<24 h before laser therapy (T1)	12-24 h after laser therapy (T2)	4-10 days after laser therapy (T3)	p-value (T2 compared to T1)	p-value (T3 compared to T1)
UA PI*	1.57 (1.06-2.48)	1.23 (0.99-2.27)	1.46 (0.99-2.08)	0.001	0.007
UA EDF – absent or reversed°	27% (9/33)	18% (6/33)	15% (4/27)	0.45	0.45
MCA PI*	1.70 (1.04-3.05)	1.47 (0.96-2.56)	1.65 (1.23-2.57)	0.002	0.13
MCA PSV (cm/s)*	26 (16-70)	25 (12-40)	26 (12-41)	0.33	0.79
UV V max (cm/s)*	11 (4-34)	13 (6-32)	16 (7-34)	0.05	0.007
UV – pulsations°	9% (3/34)	24% (8/33)	17% (5/29)	0.13	0.63
DV PIV*	0.85 (0.41-1.64)	1.06 (0.42-2.70)	0.75 (0.51-1.54)	0.03	0.36
DV A-wave – absent or reversed°	6% (2/34)	18% (6/33)	7% (5/28)	0.22	1.0
RA PI*	2.29 (1.26-4.11)	1.70 (0.94-3.37)	2.10 (1.35-3.82)	0.02	0.20
RA PSV (cm/s)*	20 (8-61)	18 (7-43)	23 (14-47)	0.24	0.08
TR°	0%	20% (6/30)	0%	0.06	-
Hydropic signs°	3% (1/34)	9% (3/34)	7% (2/29)	0.50	1.0

*Results are expressed as medians (range); °results are expressed as percentages (number). Abbreviations: UA, umbilical artery; EDF, end-diastolic flow; MCA, middle cerebral artery; PI, pulsatility index; PSV, peak systolic flow; UV, umbilical vein; V max, maximum flow velocity; DV, ductus venosus; PIV, pulsatility index for veins; RA, renal artery; TR, tricuspid regurgitation.

Ultrasound and Doppler findings of donor twins before and after fetoscopic laser therapy are shown in Table 1. Donor DV PIV increased significantly 12 to 24 h after laser therapy, however returned to pre-operative values within 4 to 10 days. A significant decrease in UA PI and increase in UV V max was detected after laser therapy, both within 12-24 h and 4-10 days after treatment. Twenty percent (6/30) of donors showed signs of TR 12 to 24 h after laser therapy, which was resolved completely after 4 to 10 days. The MCA PI and RA PI were significantly decreased 12 to 24 h after laser therapy, however returned to pre-operative values within 4 to 10 days. MCA and RA PSV values were unchanged by laser therapy.

Ultrasound and Doppler findings of recipient twins before and after fetoscopic laser therapy are shown in Table 2. Recipient DV PIV decreased after laser therapy. This change was significant after 4 to 10 days. The RA PI increased non-significantly after laser treatment; RA PSV values were unchanged. MCA PI and MCA PSV values increased significantly after laser therapy.

The following ultrasound and Doppler measurements were significantly different between donor and recipient fetuses before laser therapy: UA PI, MCA PI, UV V max, UV pulsations, and RA PI; and 12 to 24 h after laser therapy: MCA PSV, UV V max, and RA PSV. Four to 10 days after laser therapy, no significant differences between donors and recipients could be detected anymore.

Median birth weight of donors and recipients was 1780 g (range, 755-3320) and 2193 g (range, 1170-3070), respectively. Postnatally, mean hemoglobin values were determined in 71% (20/28)

Table 2 Doppler measurements in the recipient fetus in pregnancies with twin-to-twin transfusion syndrome before and after fetoscopic laser therapy

	<24 h before laser therapy (T1)	12-24 h after laser therapy (T2)	4-10 days after laser therapy (T3)	p-value (T2 compared to T1)	p-value (T3 compared to T1)
UA PI*	1.34 (0.97-3.23)	1.25 (0.93-3.57)	1.33 (0.99-1.70)	0.21	0.07
UA EDF – absent or reversed°	15% (5/34)	9% (3/32)	4% (1/25)	0.50	0.50
MCA PI*	1.33 (0.84-2.48)	1.60 (1.04-2.63)	1.74 (1.17-3.26)	<0.001	<0.001
MCA PSV (cm/s)*	25 (15-58)	33 (19-57)	26 (16-62)	0.002	0.06
UV V max (cm/s)*	15 (7-30)	18 (7-40)	17 (7-30)	0.02	0.06
UV – pulsations°	47% (16/34)	41% (13/32)	13% (3/24)	0.69	0.07
DV PIV*	0.94 (0.38-1.86)	1.02 (0.22-1.80)	0.81 (0.46-1.40)	0.27	0.04
DV A-wave – absent or reversed°	12% (4/34)	16% (5/32)	4% (1/25)	1.0	0.25
RA PI*	1.71 (1.08-2.71)	2.02 (1.18-4.01)	1.92 (1.12-3.82)	0.07	0.90
RA PSV (cm/s)*	22 (10-37)	24 (14-33)	23 (14-47)	0.23	0.19
TR°	23% (7/31)	32% (9/28)	17% (4/23)	0.50	1.0
Hydropic signs°	3% (1/34)	0%	0%	1.0	1.0

*Results are expressed as medians (range); °results are expressed as percentages (number). Abbreviations: UA, umbilical artery; EDF, end-diastolic flow; MCA, middle cerebral artery; PI, pulsatility index; PSV, peak systolic flow; UV, umbilical vein; V max, maximum flow velocity; DV, ductus venosus; PIV, pulsatility index for veins; RA, renal artery; TR, tricuspid regurgitation.

of live born donors and in 78% (18/23) of live born recipients and were 17.3 ± 4.9 g/dL and 16.1 ± 4.2 g/dL (p=0.43), respectively. One twin pair was affected by TAPS (6%, 1/17). In this twin pair, MCA PSV was 20 cm/s in the donor twin and 22 cm/s in the recipient twin before laser therapy. Twelve to 24 h after laser, MCA PSV in the donor was 22 cm/s (1.0 MoM) and 43 cm/s (>1.50 MoM) in the recipient twin, with spontaneous normalization after 4 to 10 days.

Complete follow-up was available in 96% (47/49) of long-term survivors. The parents of one twin pair refused to participate in the follow-up study because of the long travel distance. Neurodevelopmental impairment was diagnosed in 15% (4/26) of donors and in 10% (2/21) of recipients. No relation was found between MCA PI and MCA PSV values and neurodevelopmental outcome. Long-term outcome of a part of this group has been previously reported[19]. None of the donors and none of the recipients suffered from chronic renal failure.

Discussion

The results of our Doppler examinations suggest that laser ablation of the placental anastomoses in TTTS affects the fetal and fetoplacental circulation in various ways, such as transient volume overload in donors and improvement of cardiac function in recipients. These findings confirm studies by others[25-28,31]. In addition, we found new and intriguing changes in cerebral and renal blood flow before and after laser therapy for TTTS, such as increased MCA PSV and RA

PSV in recipients compared to donors 12 to 24 h after laser therapy and increased MCA PI and MCA PSV values in recipients after laser therapy.

Fetal anemia can be detected noninvasively by Doppler measurement of the MCA PSV in Rhesus-D alloimmunized pregnancies[32]. In monochorionic twinning with single IUFD, the surviving fetus is put at risk for acute anemia. The measurement of MCA PSV has been found to be a reliable noninvasive diagnostic tool in this situation as well[33]. In monochorionic twins complicated by TTTS, we were unable to show significant differences in MCA PSV values between donors and recipients before laser therapy. This is in line with previous reports that have used cordocentesis to determine hemoglobin levels in monochorionic twin pairs with TTTS. Although it has been shown that the donor fetus may have lower hemoglobin levels, a hemoglobin discordance of $\geq$5 g/dl was only present in 25% of TTTS cases[34]. Other small studies also found that hemoglobin levels in donor twins are not necessarily lower than in recipients[35,36]. The Doppler findings in this study confirm that intertwin hemoglobin differences in TTTS before laser treatment are not pronounced.

After laser therapy, the MCA PSV in recipients was found to be increased, which suggests a decrease in hemoglobin levels. This could be caused by a reversal of TTTS or TAPS due to residual anastomoses[29]. Isolated intertwin hemoglobin differences without oligo/polyhydramnios sequence have been described to occur after laser therapy in up to 13% of treated cases[37,38] and is thought to be the result of chronic, unidirectional blood transfusion through patent, miniscule arteriovenous anastomoses[29]. TAPS may lead to severe fetal or neonatal hematological complications[29]. Ex-recipient twins with TAPS are typically described to present with fetal anemia and high reticulocyte counts, suggesting compensatory hematopoeisis. Only one pair of twins in this series fulfilled our criteria for TAPS. *In utero*, the ex-recipient showed a significant increase in MCA PSV within 12 to 24 h after laser therapy in that case; however, this was followed by a significant decrease in MCA PSV 4 to 10 days after laser therapy. In view of the chronic aspect of TAPS, it is unlikely that TAPS can already be diagnosed by high MCA PSV within 24 h after surgery. This topic needs further, prospective investigation in larger study groups and with a prolonged follow-up period.

The most likely cause of acute increased MCA PSV in recipients after laser treatment is a post-procedure hemodilution. The single amniodrainage procedure that is performed at the end of each laser operation leads to the transfer of fluid from the mother to the fetal circulation[39]. This is followed by an acute decrease in hemoglobin in the recipient due to hemodilution. Effects of this mechanism may be less pronounced if time after laser therapy increases, which could possibly explain the non-significant increase 4 to 10 days after therapy.

The MCA PI has been acknowledged for its significant decrease in intrauterine growth restriction (IUGR) due to increased placental resistance. Indeed, when UA PI is raised as a result of increased placental resistance, the MCA PI decreases in order to maintain cerebral perfusion. This phenomenon is referred to as “brainspairing”. We found significantly decreased MCA PI values in recipients compared to donors before laser therapy with a significant increase in

MCA PI in recipients until 4 to 10 days after treatment. Our findings are in agreement with the studies of Martinez *et al.*[27] and Hecher *et al.*[23,24]. Martinez *et al.*[27] speculated that chronic inter-twin transfusion and imbalanced hemodynamics may induce "brainsparing" as a compensating mechanism, however without the classical meaning and poor prognosis that has been reported in IUGR from placental insufficiency.

In our study, 6 cases of neurodevelopmental impairment (four donors and two recipients) were detected. A relation between abnormal MCA flow and postnatal neurological sequelae could not be shown by our data, probably due to the small size of the study population. In the literature, we only found that reduction in head circumference is especially cumbersome, since there is a clear association between small head size and poor intellectual and neurodevelopmental outcome in severely growth-restricted neonates[40]. Unfortunately, information on the presence or absence of abnormal MCA flow was not reported. Moreover, all infants with neurodevelopmental impairment in our study were born (extreme) prematurely, which is an important confounding factor[41].

Renal function impairment is an essential feature in donor twins. Before laser, donors suffer from hypovolemia, leading to decreased renal perfusion and oliguria. As a result, the fetal renin-angiotensin system has been shown to be upregulated in donors, subsequently leading to increased arterial resistance[42,43]. Previous reports have already shown increased UA PI in donors before laser therapy with a drop in PI afterwards[25,26]; a finding that is confirmed in our study. It is reasonable to hypothesize, that other fetal arteries and the RA in particular, would behave similarly. It has been well documented that RA PI in growth-restricted fetuses is significantly higher, particularly in the presence of reduced amniotic fluid[44-46]. RA PI has also been reported to decrease in anemic fetuses directly after intrauterine transfusion, with return to normal values after one day. It was suggested that renal blood flow was increased in order to eliminate excess fluid[47]. We only found one Russian article (abstract in English) that reported on the RA and TTTS[48]. They found a significantly lower RA PI in recipients as compared to donors before laser therapy, in agreement with our findings. We hypothesize that donor RA PI is raised in relation to the (relative) growth restriction of donor fetuses and their oligo/anhydramnios in TTTS. The lower RA PI values in the recipient may be associated with their hypervolemic state in TTTS. After laser therapy, RA PI became similar in ex-donors and ex-recipients.

The RA PSV was similar in donor and recipient twins before laser therapy. Twelve to 24 h after treatment, RA PSV became significantly higher in recipients compared to donors, however, values were similar after 4 to 10 days. Theoretically, this temporarily increase might be due to a higher cardiac output (CO) or it may be the result of redistribution and reduced aortic flow (and increased RA flow) in recipients after laser. In a not-yet published study on CO in monochorionic twins with and without TTTS, we have indeed shown that median CO/kg fetal weight was higher in recipients compared to donors after laser therapy. Another suggestion is that the RA PSV, like the MCA PSV, is a marker of decreased hemoglobin levels. To our knowledge, no studies have been performed to investigate this relation. RA PSV values have been reported to

be frequently below the fifth percentile in growth-restricted fetuses[49], however, no literature on increased RA PSV could be found.

In our population, none of the long-term survivors had chronic renal failure. This is in agreement with recent studies that show that renal disease does not occur in TTTS treated with laser[30,50]. An association between abnormal RA flow *in utero* and kidney disease after birth seems therefore not likely.

A major limitation of our study is the small sample size. Another potential bias is the variation in timing of the third measurement, namely 4 to 10 days. As laser ablation is a minimally invasive procedure, which is done within 24 h after presentation of the patient at our unit, we aim to discharge patients the day after therapy. A follow-up visit is then scheduled the following week. Ideally, all patients would therefore be scanned exactly 7 days later. However, in practice, with patients referred from all over the country, this cannot always be realized, which explains the interval of 4 to 10 days. Nonetheless, our data remain representative of the changes in fetal hemodynamics that are caused by laser treatment for TTTS.

In conclusion, our results concerning intrauterine Doppler flow measurements of the fetal cerebral and renal system provide new insights in the hemodynamic changes that are induced by laser therapy. It would be valuable to follow-up these Doppler studies for a more extended period after laser therapy, and to evaluate whether these are temporarily or permanent changes. In our study, changes in cerebral and renal blood flow were not associated with long-term neurological or renal sequelae.

Since the outcome of laser therapy for TTTS, even in the best series[6,8-11], is still associated with the loss of at least one baby in approximately 50% of affected pregnancies, further research is needed, preferably with a longer intrauterine follow-up, to determine whether this high rate of IUFD can be explained by the hemodynamic changes after laser therapy for TTTS.

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