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## **Fetoscopic interventions in complicated monochorionic twin pregnancies**

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**Residual anastomoses after  
fetoscopic laser surgery in twin-to-  
twin transfusion syndrome:  
frequency, associated risks and  
outcome**

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## **Abstract**

*Objective:* To study the incidence and clinical implications of residual anastomoses in twin-to-twin transfusion syndrome treated with fetoscopic laser surgery

*Methods:* We examined all placentas treated with fetoscopic laser surgery and delivered at our centre between June 2002 and December 2005 with vascular injection using coloured dyes. Presence of residual anastomoses was studied in association with adverse outcome and inter-twin haemoglobin difference at birth. Adverse outcome was defined as fetal demise, neonatal death or severe cerebral injury. The relation between residual anastomoses and placental localization (anterior or posterior uterine wall) was evaluated.

*Results:* A total of 52 laser-treated placentas were studied. Residual anastomoses were detected in 33% (17/52) of placentas. Adverse outcome was similar in the groups with and without residual anastomoses, 18% (6/34) and 29% (20/70) respectively ( $p = 0.23$ ). Large inter-twin haemoglobin differences ( $> 5$  g/dL) were found in 65% (11/17) of cases with residual anastomoses and 20% (7/35) of cases without residual anastomoses ( $p < 0.01$ ). Anterior placental localization was not associated with a more frequent presence of residual anastomoses.

*Conclusions:* Residual anastomoses at our institution are seen in one third of monochorionic placentas treated with fetoscopic laser surgery. Although residual anastomoses in our study were not associated with adverse outcome, they were often associated with neonatal haematological complications.

## Introduction

Twin-to-twin transfusion syndrome (TTTS) presenting as oligo/polyhydramnios sequence is a major complication of monochorionic twin pregnancies and is due to inter-twin blood transfusion via placental vascular anastomoses.

Fetoscopic laser coagulation of placental vascular anastomoses is nowadays considered to be the treatment of choice in severe second trimester TTTS.

Fetoscopic laser surgery in TTTS is a causative treatment and is associated with significantly improved outcome compared to serial amniodrainage.<sup>1</sup>

The aim of laser coagulation of vascular anastomoses is to completely separate the inter-twin placental circulation. Careful examination of the placenta after birth through injection studies is required to determine whether all vascular connections have been adequately coagulated or whether residual anastomoses (RA) are still present.

Although the first report of fetoscopic laser surgery was published more than 15 years ago<sup>2</sup>, only few studies have since reported on the placental findings and incidence of RA after laser surgery.<sup>3-6</sup> Most importantly, the results of these studies are highly discordant and the incidence of RA varied from 0% to 75%.<sup>3-6</sup>

The objective of our study was to determine the incidence and clinical implications of RA in a large series of placentas treated with fetoscopic laser surgery. We hypothesized that the presence of RA may lead to a higher incidence of adverse outcome and larger inter-twin haemoglobin difference at birth. Furthermore, we tested the hypothesis that RA may be found more frequently in anterior placentas due to the more complex approach in these cases.

## **Material and methods**

All consecutive placentas of monochorionic twin pregnancies with TTTS treated with fetoscopic laser surgery and delivered at our centre between June 2002 and December 2005 were included in the study. The Leiden University Medical Centre is the national referral centre for laser treatment for TTTS in the Netherlands. TTTS was diagnosed using standard antenatal ultrasound criteria.<sup>7</sup> The fetoscopic laser surgery technique used was described in detail previously and is similar to the method reported by Hecher *et al* and Senat *et al*.<sup>1;8;9</sup> After birth, presence of RA was studied by placental coloured dye injection. The umbilical vessels of both cords were injected with different-coloured dyes (blue or green for arteries and orange or yellow for veins). Injection was continued until dye was seen to flow through the distal end of the vascular tree and into the placental substance. Placentas were then photographed in a plane view, and the picture was saved in a computerized data base. Placentas were divided in two groups, a group with RA and a group without RA. Placentas of TTTS pregnancies with single or double intrauterine fetal demise were excluded when placental maceration prohibited accurate evaluation of RA. Adverse outcome was defined as intrauterine fetal demise, neonatal death or severe cerebral injury on neonatal ultrasound examination. The criteria used for determining severe cerebral injury were published in a previous study.<sup>10</sup> Haemoglobin was measured at birth from cord blood. Anaemia and polycythemia at birth were defined as previously described.<sup>11</sup> Results of categorical variables were compared using Chi-squared test. Continuous variables were analysed with the Independent Samples T- test. A p-value < 0.05 was considered to indicate a statistical significance. Statistical analysis was performed with SPSS version 11.0 (SPSS, Inc., Chicago, Illinois, USA).

## Results

A total of 61 monochorionic placentas of TTTS pregnancies treated with laser were examined at our centre during the study period. Overall perinatal mortality was 21% (26/122: intrauterine fetal demise, n = 18; neonatal death, n = 8). The data required for this study could not be recorded completely for nine placentas due to maceration caused by single intrauterine fetal demise (n = 8) or placental fragmentation (n = 1). These nine cases were excluded from further analysis. Fifty-two placentas were thus included in the study. RA were found in 33% (17/52) of laser treated placentas. A total of 39 RA were detected, with an average of 2.3 ( $\pm 1.7$ ) RA per placenta. The type of RA detected were arterio-venous anastomoses from donor to recipient (n = 16), arterio-venous anastomoses from recipient to donor (n = 16), arterio-arterial anastomoses (n = 4) and veno-venous anastomoses (n = 3). Some placentas with RA (5/17) had multiple types of anastomoses. Twenty-five of the 39 (64%) RA were very small (< 1 mm diameter) (example shown in Figure 1 and 2). Superficial arterio-arterial or veno-venous anastomoses were found in 35% (6/17) of placentas with RA. Adverse outcome occurred in 8% (1/12) of infants with superficial RA compared to 23% (5/22) in infants with only deep arterio-venous RA (p = 0.39). Further details on placentas, vascular anastomoses and clinical outcomes in the RA group and no-RA group are presented in Table 1. The ten cases of intrauterine fetal demise in the no-RA group were all double demises: 4 pairs of twins died within 2 weeks of laser surgery and one pair of twins died 6 weeks after laser surgery.

In two of the 17 (12%) cases in the RA group, the presence of RA had already been predicted by the fetoscopic operator. In the first case a large arterio-arterial anastomosis was detected during fetoscopy but could not be coagulated due to its size. In the second case, surgery was complicated by intra-amniotic haemorrhage impeding further intervention due to blood-stained amniotic fluid. In two other cases (12%), presence of RA was suspected during the weeks following intervention because of fetal Doppler measurements (high middle cerebral artery peak systolic velocity (MCA-PSV) in one fetus). In the first case there was persistence of feto-fetal transfusion, in the second case there

**Table 1** Characteristics of TTTS pregnancies with and without residual anastomoses

	RA <sup>e</sup> group (n = 17 twin pairs)	no-RA <sup>e</sup> group (n = 35 twin pairs)	p-value
Gestational age at laser surgery – weeks <sup>a</sup>	19.9 ± 4.1	20.6 ± 3.2	0.51
Anterior placenta <sup>b</sup>	5 (29%)	11 (31%)	0.83
Number of anastomoses coagulated per placenta <sup>a</sup>	7.2 ± 4.5	6.0 ± 2.6	0.23
Gestational age at birth – weeks <sup>a</sup>	31.8 ± 3.2	31.1 ± 5.2	0.61
Birth weight – g <sup>a,c</sup>	1718 ± 608	1633 ± 855	0.60
Inter-twin birth weight difference > 20% <sup>b</sup>	7 (41%)	11 (31%)	0.49
Intrauterine fetal demise <sup>b,c</sup>	0 (0%)	10 (14%)	0.02
Neonatal death <sup>b,c</sup>	1 (3%)	6 (9%)	0.28
Severe cerebral injury <sup>b,c</sup>	6 (18%)	7 (10%)	0.27
Adverse outcome <sup>b,c,d</sup>	6 (18%)	20 (29%)	0.23

<sup>a</sup> Value given as mean ± SD

<sup>b</sup> Percentages are between brackets

<sup>c</sup> Refers to single infants instead of twin pair

<sup>d</sup> Adverse outcome was defined as intrauterine fetal demise, neonatal death or severe cerebral injury

<sup>e</sup> RA: residual anastomoses

**Table 2** Haemoglobin values at birth in TTTS pregnancies with and without residual anastomoses

	RA <sup>c</sup> group (n = 17 twin pairs)	no-RA <sup>c</sup> group (n = 35 twin pairs)	p-value
Haemoglobin – g/dL <sup>a</sup>	15.4 ± 5.6	16.0 ± 3.8	0.60
Anaemia in one twin <sup>b</sup>	9 (26%)	8 (11%)	0.06
Polycythaemia in one twin <sup>b</sup>	4 (12%)	2 (3%)	0.07
Inter-twin haemoglobin difference > 5 g/dL <sup>b</sup>	11 (65%)	7 (20%)	< 0.01
Twin pairs with anaemia or polycythaemia <sup>b</sup>	10 (59%)	8 (23%)	0.01

<sup>a</sup> Value given as mean ± SD

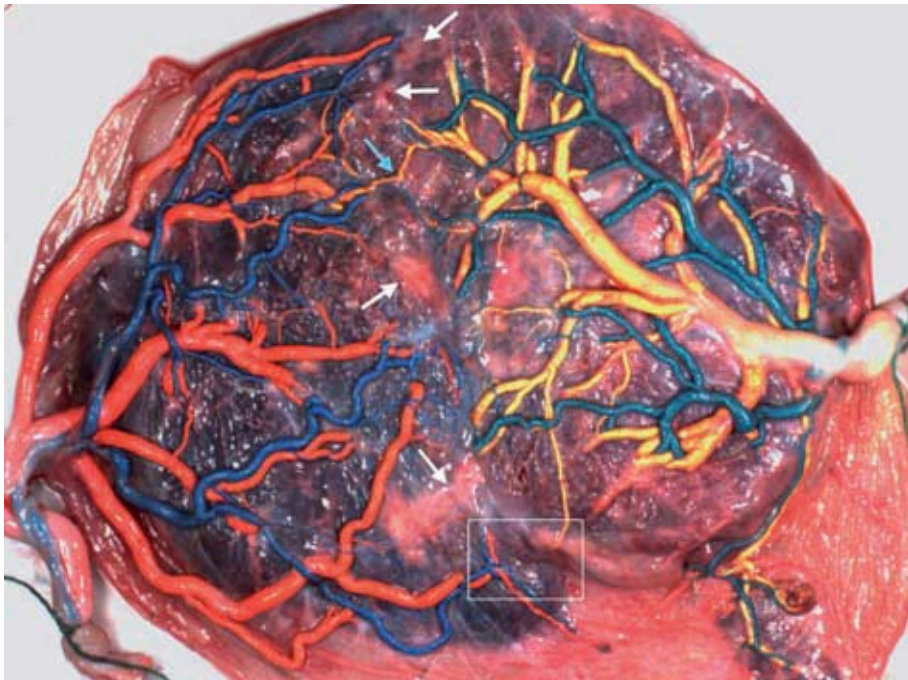
<sup>b</sup> Percentages are between brackets

<sup>c</sup> RA: residual anastomoses



was a reversal of feto-fetal transfusion. In the remaining 13 cases (76%), RA had not been suspected antenatally.

The results of haematological values at birth are presented in Table 2.



**Figure 1** Placenta of TTTS-pregnancy treated with laser at 17 week's gestation, followed by spontaneous delivery of 2 healthy girls at 38 weeks. The placental share of the ex-donor (birth weight 3055 gr) is on the left-side of the picture (arteries are blue, veins are orange). The placental share of the ex-recipient (birth weight 2915 gr) is on the right-side (arteries are green, veins are yellow). Haemoglobin level in the ex-donor and ex-recipient were 13.2 g/dL and 19.2 g/dL respectively. The white arrows indicate the successfully coagulated anastomoses. The light blue arrow indicates a residual veno-venous anastomosis. A very small residual arterio-venous anastomosis from the ex-donor to the ex-recipient is in the white square that is enlarged in Figure 2.



**Figure 2** Detail of the very small residual anastomosis (diameter < 1 mm) between an artery (blue) from the ex-donor and a vein (yellow) from the ex-recipient.

## Discussion

This study is the first large single centre study reporting on the frequency and clinical implications of RA after fetoscopic laser surgery. We found that RA are present in one third of laser treated placentas. In a small study, De Paepe *et al* found a much higher incidence of RA in laser treated placentas, namely 75%.<sup>3</sup> Quintero *et al*, on the other hand, described a much lower incidence of RA, ranging from 0% to 5%.<sup>4-6</sup> Such an extreme discrepancy between the various studies can be due to several factors, namely (1) number of placentas studied, (2) differences in laser technique and surgical results and (3) differences in placental injection techniques. Obviously, no reliable conclusions on incidence of RA can be drawn if the number of studied placentas is too small. De Paepe *et al*, for example, were able to study only 8 placentas.<sup>3</sup> The second factor, adequate identification and successful coagulation of vascular anastomosis, probably depends on the ability of each fetal surgeon. Hecher *et al* reported an association between improved outcome and growing experience in the laser technique, possibly attributable to an improved efficiency in laser surgery.<sup>9</sup> However, the relation between RA and inter-individual or inter-centre variation in fetoscopic laser surgery has not been studied. Nevertheless, we have

previously shown that the overall outcome after laser surgery in our centre is similar to that in other large centers.<sup>8</sup> Finally, the third factor, differences in placental injection technique, may influence the results on the incidence of RA. Discordant opinions on the sensitivity of various injection methods have recently resulted in a fierce debate in the literature.<sup>12</sup> Quintero *et al* performed placental injection studies with air and claimed that this method has similar sensitivity compared to other methods.<sup>6;13</sup> Most other authors, as well as our group, advocate placental injection with coloured dye.<sup>3;14-19</sup> Which of the two methods (air injection or coloured dye injection) is superior in detecting RA is not known. However, in our experience, the vast majority of RA are very small (with diameters < 1 mm) and therefore difficult to detect without accurate injection with coloured dye.

Several reasons can be envisaged to explain the occurrence of RA, namely (1) anastomoses (particularly the minuscule ones) were not detected during fetoscopy, (2) anastomoses were not coagulated because surgery was too selective in order to spare cotyledons, (3) placental vessels of the donor were collapsed due to hypovolemia and vasoconstriction preventing adequate detection, (4) insufficient coagulation led to temporary anastomotic flow obstruction, but revascularization occurred later, and (5) anastomoses were detected during fetoscopy, but were considered too large to tackle. These reasonings may have consequences for the laser surgery technique. If (1), (2) or (3) are true, RA can be avoided using a technique of complete coagulation (with a 5 mm width) of the entire vascular equator. If (4) is true, then RA can be avoided by creating sufficient placental damage using a technique of deeper, longer-lasting and more frequent coagulation.

This study shows that, despite the fact that laser surgery in anterior placentas is technically more complex, anterior placentas are not associated with increased incidence of RA. Furthermore, the overall outcome of TTTS pregnancies with RA in our study was similar to those in TTTS pregnancies without RA. Both hypotheses, that RA could be associated with anterior placentas and adverse outcome, were thus not confirmed in our study. Lack of association between RA and adverse outcome may partly be due to the frequent presence (35%) of residual superficial anastomoses. Superficial arterio-

arterial anastomoses are known to protect against TTTS.<sup>20</sup>

An important (but inevitable) bias in our study may have been introduced by the exclusion of nine cases in which placental fragmentation or post-mortem placental changes prohibited the injection and demonstration of the vessels on the placental surface. Adverse outcome in the nine excluded pregnancies was 50% (9/18; intrauterine fetal demise: n = 8, severe cerebral injury: n = 1). If adverse outcome in these pregnancies would have been caused by RA, then the incidence of adverse outcome in the RA group would have increased from 18% (6/34) to 29% (15/52). This is still similar to the incidence of adverse outcome in the no-RA group (29%) ( $p = 0.97$ ). Therefore, it seems reasonable to deduce that RA in our study were not associated with adverse outcome.

We have shown in this study that large inter-twin haemoglobin differences ( $> 5$  g/dL) were significantly more frequent in the presence of RA compared to the group without RA. Therefore, the hypothesis related to the association between RA and larger inter-twin haemoglobin difference seems legitimate. RA were also associated with a higher incidence of anaemia or polycythemia at birth. Overall, RA were associated with isolated haemoglobin discordance at birth or recurrent TTTS in 11 of the 52 (21%) TTTS pregnancies treated with laser surgery. Our findings are in agreement with recent reports suggesting that incomplete coagulation results in isolated haemoglobin discordance or recurrent TTTS in up to 27% of double survivors after laser surgery.<sup>21-23</sup> Routine serial ultrasound examination with MCA-PSV measurement after laser surgery proved invaluable in the early detection of severe fetal haematological disorders and is nowadays strongly recommended.<sup>21-23</sup> Similarly, we also strongly recommend routine placental injection study in TTTS treated with laser because it may give equally invaluable information to perinatologists to understand the etiology of severe haematological disorders. Finally, placental injection studies are an important feedback source to individual fetoscopic surgeons.

In conclusion, clinicians involved in the care for monochorionic twins should be aware that RA occur frequently after fetoscopic laser surgery in TTTS. Although RA are not clearly associated with adverse outcome, these anastomoses may be associated with severe haematological disorders in fetuses and neonates. Routine Doppler measurements after laser surgery and accurate placental

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injection studies after birth can help in detecting and understanding fetal and neonatal haematological complications.

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