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## Teaching and quality control in fetoscopic surgery

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## Chapter 6

# Monochorionic triplets complicated by fetofetal transfusion syndrome: A case series and review of the literature

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## ABSTRACT

**Objective** To compare perinatal outcome in monochorionic (MC) triplets with twin-to-twin transfusion syndrome (TTTS) versus dichorionic (DC) triplets with TTTS.

**Study Design** Retrospective analysis of all triplets with TTTS treated at our center and all cases reported in the literature between 1990 and 2010. Survival and gestational age at birth of MC and DC triplets were compared and stratified by type of intervention. We excluded triplets with one or more fetal deaths <16 weeks' gestation and those with one or more fetuses with congenital anomalies.

**Results** MC triplets were affected by TTTS in a total of 27 cases, and overall survival was 51% (38/75 fetuses) compared to 105 DC triplets with a survival of 76% (220/291 fetuses) ( $p < 0.05$ ). Mean gestational age at birth in MC triplets was 28 weeks, compared to 31 weeks in DC triplets ( $p < 0.05$ ). Perinatal survival of at least one fetus in MC triplet and DC triplet pregnancies was 70% (19/27) and 91% (96/105) ( $p < 0.05$ ). In DC triplets, survival after laser therapy was significantly improved compared to expectant management, amniodrainage or selective feticide ( $p < 0.05$ ).

**Conclusion** MC triplets with TTTS are at a considerably higher risk for perinatal mortality and preterm birth than DC triplets. The optimal strategy to manage MC triplets with TTTS, including the role of selective feticide and laser therapy of all anastomoses, is still to be established.

## INTRODUCTION

Twin-to-twin transfusion syndrome (TTTS) is a serious complication of monochorionic (MC) twin gestations and is the result of an unbalanced exchange of blood due to vascular anastomoses that connect the circulations. If untreated, this condition is associated with high perinatal mortality and morbidity rates. Survival is improved with fetoscopic laser coagulation of the placental anastomoses.<sup>1</sup> TTTS is not only seen in MC twins, but can also occur in MC and dichorionic (DC) triplet gestations.

Spontaneous triplets occur in about 1 in 7,000 deliveries, but incidences have increased over the past decades, mainly because of assisted reproductive technologies.<sup>2</sup> Depending on the type of placentation, triplet pregnancies can be trichorionic triplets (i.e. 3 fetuses with separate placentas and amniotic cavities), DC triplets (i.e. monochorionic twins and a singleton with a separate placenta) and MC triplets (i.e. 3 fetuses with one shared placenta and three amniotic cavities). Only a few cases of MC (triamniotic) triplets have been reported, with estimated incidences of 1–1.6 in 100,000 deliveries.<sup>3,4</sup> Since trichorionic triplets have no placental vascular anastomoses, TTTS may only occur in MC and DC triplets. The incidence of TTTS in MC twins is approximately 9% of all cases<sup>5</sup>, and this is probably similar for DC triplets. However, the incidence of TTTS in MC triplets, in which all 3 fetuses shared a common circulation, is not well known.

Management options and survival of triplets with TTTS are frequently discussed in the literature.<sup>2,6-9</sup> Because an MC twin pair can also be part of any other high-order multiple pregnancy, survival rates of MC triplets are often confused with DC triplets, with one pair of MC twins affected by TTTS and one singleton. The prognosis of TTTS for MC triplets is considered to be different from that for DC triplets and has been reported to be severe, with higher rates of mortality and preterm birth, despite interventions.<sup>7, 10</sup> However, the literature on triplets and higher-order multiple births with TTTS consists mainly of case reports and small series, most of which fail to discuss placentation.<sup>3,11-19</sup> In this study, we aim to compare the perinatal outcomes of all the MC and DC triplets with TTTS treated at our center and reported in the literature in the last two decades.

## METHODS

At the Leiden University Medical Center (LUMC), the national tertiary referral center for invasive fetal therapy, fetoscopic laser surgery has been the preferred treatment modality for all pregnancies complicated by TTTS Quintero stage II or higher, and for

selected cases with Quintero stage I with symptomatic polyhydramnios since August 2000.<sup>20</sup>

### *Cases in LUMC*

We performed a retrospective analysis of prospectively collected data on perinatal outcome and management of all MC and DC triplet pregnancies with TTTS treated at our center. An MC triplet pregnancy was diagnosed when the 3 fetuses shared the same MC placenta, and a DC triplet pregnancy was determined when 2 fetuses shared one MC placenta, whereas the third fetus had an independent single placenta.

Detailed sonographic examination was performed in all fetuses at the referral center and continued on a weekly or biweekly basis at our center. Chorionicity and amnionity were established by sonographic examination in the first trimester of pregnancy. The diagnostic (established) criteria for TTTS in triplets were similar to that for twins. Details on sonographic criteria and details on procedures for fetoscopic laser surgery and umbilical-cord coagulation have been described previously.<sup>20</sup> Once the diagnosis of TTTS was established, parents were counseled regarding the outcome and offered the options of expectant treatment, termination of the whole pregnancy, serial amniodrainage, selective termination of (one of) the MC twins in cases of DC triplets, or one of the fetuses in the case of lethal prognosis or fetoscopic coagulation of the communicating vascular anastomoses. After written informed consent was obtained from the parents, the procedure was performed by one of the four operators, specialized in fetoscopic surgery, as previously reported<sup>20</sup>, using a fetoscope (2 mm; Storz, Vianen, the Netherlands) for percutaneous introduction through a 3.3-millimeter shaft into the amniotic sac of the recipient(s). Coagulation of the anastomoses or umbilical cord was performed using a diode laser (Diomed Limited, Cambridge, UK) or Nd:YAG laser (Dornier Medizin Technik, Germering, Germany) with an output of 15–70 W. If there were two recipients in MC triplets, the fetoscope was introduced into both cavities via two different uterine entries, but if there were two donors, only the vascular anastomoses between the recipient and both donor fetuses were coagulated.

After the procedure, patients remained in the hospital for 12–48 h. Complications including vaginal blood loss, hypotension, bleeding from uterine vessels, prelabor premature rupture of membranes (PPROM) and maternal fever were recorded. Ultrasound examination was performed within 24 h after surgery and then on a weekly or biweekly basis. The data on obstetric and neonatal outcomes were derived from medical charts. In cases where the delivery did not take place in our center, data were provided by outcome reports from the referring obstetricians and pediatricians.

### *Meta-analysis of cases reported in the literature*

An electronic literature search using MEDLINE, EMBASE and the Cochrane Database was performed to find all relevant articles reporting perinatal outcome and management in MC and DC triplet pregnancies with TTTS. A search in PubMed was performed to find relevant articles reporting outcomes of MC and DC triplet pregnancies complicated by TTTS using the following keywords ‘fetofetal transfusion’ AND ‘triplet’, ‘survival rate’, ‘monochorionic’ AND ‘laser therapy’ OR ‘intervention’. No language restrictions were applied. We accepted original articles, short communications, letters to the editor and case reports. In addition, a search was performed from the reference list of all identified articles. When needed, we contacted authors for additional, unpublished information. Articles were included irrespective of their primary objective. We included all reported cases of MC and DC triplet pregnancies assessed by 1st-trimester ultrasound and complicated by TTTS. TTTS was diagnosed with standard criteria (polyhydramnios >8 cm in the recipient(s) sac(s) and oligohydramnios <2 cm in the donor sac). Exclusion criteria were one or more fetal deaths <16 weeks’ gestation and pregnancies with 1 or more fetuses with congenital anomalies. Cases in which artificial termination of the whole pregnancy was performed were not included.

Two of the authors (S.H.P.P. and D.O.) initially screened all the titles and abstracts of papers, identified by the review search strategy, for their relevance. Only studies that were obviously irrelevant were excluded at this stage; they independently assessed all other studies independently (on the basis of their full text) for inclusion or exclusion, using the above criteria. Discrepancies were to be resolved by discussion with a third reviewer, but this proved unnecessary.

Data extracted from each article included survival, gestational age at birth, intervention, and, if reported, long-term perinatal outcomes in donors and recipients. A  $p$  value  $\leq 0.05$  was considered to indicate statistical significance. A  $\chi^2$  test and an independent Student  $t$  test were used to compare survival and gestational age between triplets. Statistical analysis was performed with SPSS version 18.0 (SPSS, Inc., Chicago, Ill., USA).

## RESULTS

### *Cases in LUMC*

During the 10-year study period from 2000 to 2010, 10 fetoscopic procedures in 2 MC and 8 DC triplet pregnancies were performed in our center. All triplet pregnancies were triamniotic.

A total number of 340 laser surgeries were performed for all twin and triplet pregnancies affected by TTTS during this 10-year period. Details on gestational age at procedure, type of intervention and outcome in triplet pregnancies are described in table 1.

Fetoscopic laser coagulation was performed in 9 cases, including 1 case of MC triplets with percutaneous entry into two amniotic sacs. In 1 case of MC triplets, umbilical cord coagulation with selective reduction of the recipient was carried out. The procedure was performed at a median gestational age of 18 weeks (range 14–26 weeks). Three cases were classified as Quintero stage II and 7 cases Quintero stage III. Fetal demise occurred in 9 of 30 fetuses (30%) (including 2 cases of selective feticide) and neonatal demise in 1 neonate (3%). Overall perinatal survival was 70% (20/30). In the DC triplets, perinatal survival of both children involved in the monochorionic twin pair was 50% (4/8). Median gestational age at delivery was 31 weeks' gestation (range 21–36 weeks). Median birth weight in live-born neonates was 1,661 g (range 845–2,780 g).

A procedure-related complication occurred in 1 case (table 1, case No. 3) where laser coagulation of a DC triplet was performed. During uterine entry, an umbilical artery of the donor was perforated and massive bleeding occurred, with the result of intrauterine fetal demise of the donor. The recipient twin and the singleton were born at 34 weeks' gestation. No maternal complications occurred.

In one of the DC triplets (table 1, case No. 7) treated with laser surgery at 20 weeks' gestation, intrauterine fetal demise of the donor was assessed at 22 weeks. PPRM occurred at 27 weeks' gestation and corticosteroids, antibiotics and atosiban were administered to prevent preterm labor. Nevertheless, the patient went into spontaneous labor at 29 weeks and 6 days. The MC twin in this pregnancy was delivered at 30 weeks' gestation, including the stillborn donor, but the recipient died 4 days after birth due to intracranial hemorrhage grade IIb and sepsis due to group B streptococcus. The delivery of the third child took place on the same day and it was alive and well at discharge.

In 1 case of DC triplets (table 1, case No. 9) fetoscopic laser coagulation was performed with intentional perforation of the intertwin membrane because of the presence of vascular anastomoses in the other amniotic cavity, thereby creating a monoamniotic twin and one singleton. Unfortunately MRI scans that were performed during follow-up of the pregnancy showed severe brain damage with ventriculomegaly and ischemic lesions of the former recipient. A reintervention was performed and selective feticide of the recipient twin was carried out. The donor and the singleton were born healthy at 35 weeks' gestational age.



From 1990 to 2010, 22 articles met the inclusion criteria and we identified 25 MC and 97 DC triplet pregnancies with TTTS.<sup>2,3,6-19,21-25</sup> Quintero stage, in the reported cases including the cases in this study, was stage I in 7% (2/27) stage II in 15% (4/27), stage III in 45% (12/27) and stage IV in 33% (9/27) of the MC triplets. In the DC triplets, Quintero stage I was classified in 2% (2/105), stage II in 23% (24/105), stage III in 68% (72/105) and stage IV in 7% (7/105).

Survival rates of all triplet pregnancies complicated by TTTS reported in the literature (including the cases in our center) – classified according to chorionicity – are presented in table 2. Perinatal survival of at least 1 fetus in MC and DC triplet pregnancies was 70% (19/27) and 91% (96/105), respectively ( $p = 0.004$ ). Overall perinatal survival of MC and DC triplets was 51% (38/75) and 76% (220/291), respectively ( $p = 0.018$ ). Median gestational age at delivery was 28 weeks (range 18–40 weeks) for the MC triplets, compared to 31 weeks (range 20–39 weeks) in the DC triplets ( $p = 0.016$ ). In DC triplets, survival after laser therapy was significantly improved compared to expectant management, amniodrainage or selective feticide ( $p = 0.007$ ). Neonatal death within 4 weeks after birth occurred in 8% (6/75) of MC cases and in 8% (24/291) of DC cases ( $p = \text{NS}$ ). In 1 case of MC triplets, a neonate died on the 75th day after birth.

Case	Chorionicity	Intervention	Quin- tero stage	Placenta location	GA at diagnosis (wks)	GA at inter- vention (wks)	GA at birth (wks)	Fetuses	Outcome	Birth weight	Follow up
1	MC	selective fetocide	3	ant	17	22	22	donor recipient asymptomatic	stillbirth at 22+3 wks select fetocide at 22 wks* stillbirth at 22+3 wks	330 g 340 g 430 g	
2	DC	laser	2	post	17	17	30	donor recipient dichorionic	Live birth at 30+4 wks Live birth at 30+4 wks Live birth at 30+4 wks	1180 g 1490 g 1455 g	Alive and well Alive and well Alive and well
3	DC	laser	2	post	14	17	34	donor recipient dichorionic	IUFD at 17 wks Live birth at 34+3 wks Live birth at 34+3 wks	50 g 845 g 1120 g	Due to damage chorial vessel during intervention Alive and well Alive and well
4	DC	laser	3	post	25	25	30	donor recipient dichorionic	Live birth at 30 wks Live birth at 30 wks Live birth at 30 wks	1180 g 1350 g 1195 g	Alive and well Alive and well Alive and well
5	DC	laser	3	ant	16	16	28	donor recipient dichorionic	IUFD 18 wks Live birth at 28+4 wks Live birth at 28+4 wks	1050 g 1130 g	Alive and well Alive and well
6	DC	laser	3	post	18	19	36	donor recipient dichorionic	Live birth at 35+6 wks Live birth at 35+6 wks	2300 g 2600 g	Alive and well Severe congenital cardiac disorder
7	DC	laser	3	ant	12	20	30	donor recipient dichorionic	Live birth at 35+6 wks IUFD 22 wks Live birth at 29+6 wks	2780 g 1440 g	Alive and well Neonatal death 4 days intracranial hemorrhage and sepsis**
								dichorionic	Live birth at 29+6 wks	1600 g	Alive and well

8	DC	laser	2	post	15	15	32	donor recipient dichorionic	Live birth at 32+4 wks Live birth at 32+4 wks Live birth at 32+4 wks	1950 g 1743 g 2030 g	Alive and well Alive and well Alive and well
9	DC	laser reintervention selective fetocide	2	ant	15	15	35	donor recipient dichorionic	Live birth at 35+1 wks selective fetocide at 21 wks *** Live birth at 35+1 wks	2310 g 2435 g	Alive and well Alive and well Alive and well
10	MC	laser	3	post	14	15	30	donor recipient donor	IUFD at 22 wks IUFD at 16 wks Live birth at 30+5 wks	1640 g	Alive and well

MC: monochorionic, DC: dichorionic, IUFD: intra uterine fetal demise, ant: anterior placenta, post: posterior placenta

\* Laser coagulation impossible due to decreased visibility because of bleeding in uterine wall converted to selective fetocide

\*\* PPROM occurred at GA 27 weeks.

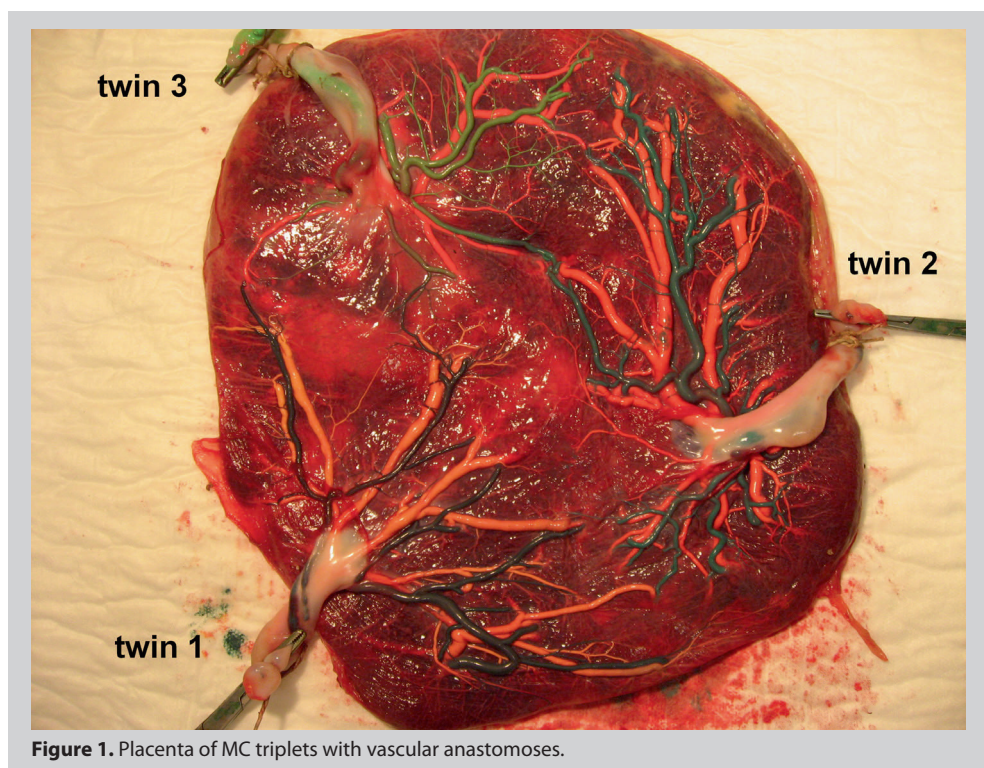
\*\*\* Iatrogenic monoamnioticity. Severe hypoperfusion damage was diagnosed after laser procedure.

**Table 1.** Our center experience: pregnancy outcome after endoscopic laser coagulation and selective fetocide in triplet pregnancies complicated by TTTS

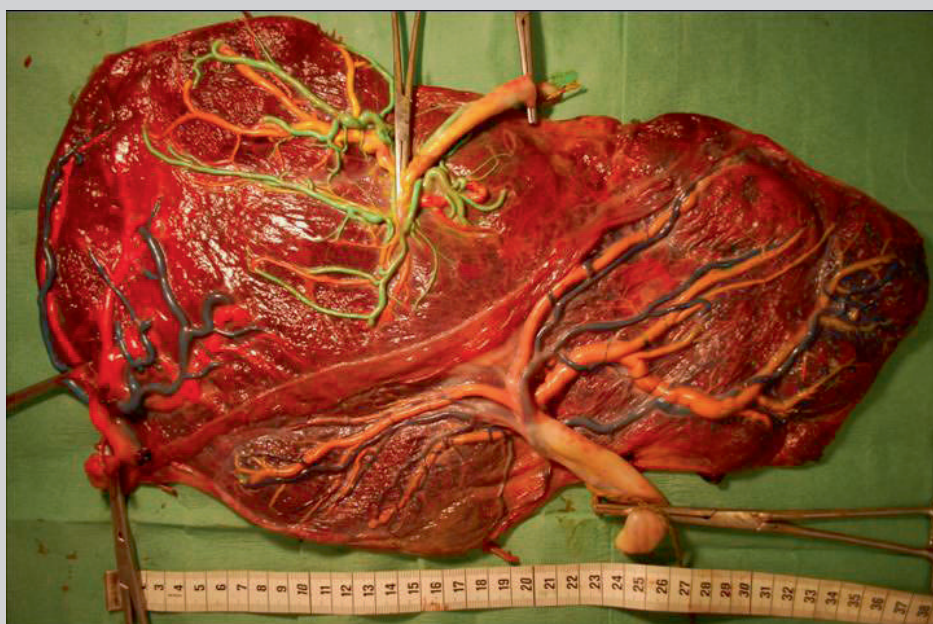
Intervention	MC triplets	Survival (fetuses)		n	GA at birth wks (range)	
		n	DC triplets		MC triplets	DC triplets
Laser	26/48 (54%)	16	184/237 (78%)	79	28 (18-34)	31 (20-36)
Selective feticide	1/6 (17%)	2	11/24 (46%)	8	31 (22-40)	32 (25-37)
Amniodrainage	4/9 (44%)	3	20/39 (51%)	13	26 (23-27)	29 (24-39)
Expectant	7/18 (39%)	6	5/15 (33%)	5	28 (23-35)	26 (23-29)
Total	38/81 (47%)	27	220/315 (70%)	105	28 (18-40)	31 (20-39)

**Table 2.** Survival rates and gestational age at birth of MC and DC triplet pregnancies according to type of intervention

Figures 1 and 2 demonstrate the difference between a triplet pregnancy with an MC placenta with vascular anastomoses and a DC placenta of an MC twin (and one singleton) complicated by TTTS and treated with laser coagulation.



**Figure 1.** Placenta of MC triplets with vascular anastomoses.



**Figure 2.** Placenta of DC triplet with MC twin complicated by TTTS and treated with laser surgery and one singleton. As is common in dichorionic placentas, the placenta of the singleton is fused together with the monochorionic twin placenta. The thick intertwin membrane indicates dichorionicity.

## DISCUSSION

This study shows that perinatal morbidity and mortality in MC triplets with TTTS is higher than in DC triplets. Of the 81 fetuses involved in fetofetofetal transfusion, only 38 (51%) survived. In addition, median gestational age at delivery in MC triplet pregnancies is significantly shorter than in DC triplets (28 vs. 31 weeks' gestation). This outcome could be due to the technical difficulties of interventions in MC triplets because all three circulations are connected, therefore making fetoscopic treatment much more challenging.

The data in this study also demonstrate that fetoscopic laser coagulation of communicating vascular anastomoses in DC triplet pregnancies complicated by TTTS is a feasible treatment option with increasing survival rates and more advanced gestational age at birth. Perinatal survival rates of at least one survivor (91%) appear comparable to MC twins (around 90%).<sup>26,27</sup> Although treatment appears to be associated with an improved perinatal outcome for DC triplets, survival rates are still limited for MC triplets.

Various therapeutic measures have been proposed for triplets with TTTS. Amnioreduction, to decrease the pressure of the amniotic cavity with polyhydramnios, is not a permanent solution and is associated with a high risk of mortality and morbidity to the cotriplets due to the presence of vascular anastomoses in the case of intrauterine fetal demise. Serial amnioreduction is therefore considered, at best, a temporary treatment and does not correct the underlying problem.

Fetoscopic laser coagulation is the only causative treatment option because, provided that all anastomoses can be visualized on the chorionic surface, this operation will separate the fetal circulations.<sup>28</sup> This technique potentially avoids perinatal mortality and the high morbidity rate attributed to vascular accidents mainly after intrauterine death of one of the multiplets.<sup>7</sup> Loss of cotyledons following laser ablation could either cause or exacerbate placental insufficiency in the normal triplets; however, according to Chmait et al.<sup>29</sup>, twin weight discordance and donor fetus intrauterine growth restriction appear to improve after laser therapy. In DC triplet pregnancies with severe TTTS, the technique for fetoscopic laser coagulation is the same as in MC twins with this condition. Comparable to Sepulveda et al.<sup>7</sup>, survival rates appear similar to that of MC twins when a successful procedure was performed. Conversely, in MC triplet pregnancies the outcome was poor. In 6 cases of MC <sup>3,6,9,11,15,22</sup> and 5 cases of DC <sup>6,23,24</sup> triplets complicated by TTTS, only 12/33 (36%) survived with expectant management. Although based on small numbers, these results strongly suggest that laser coagulation is preferable to expectant management or amniodrainage.<sup>17</sup> Five successful cases of MC triplet gestations (with 3 survivors) treated with laser coagulation were reported (including the cases in our study),<sup>2,7-10,21</sup> but 11 other cases were not successful.

Most likely, this is due to the technical difficulties of the fetoscopic treatment because of the identification and coagulation of vascular anastomoses between all 3 fetuses. To reach the appropriate location of the interfetal communicating vessels, it is necessary to have two uterine entries with the fetoscope into two different sacs. In addition, complete ablation of the intercommunications can be technically impossible to achieve because of placental location, the presence of multiple fetal parts that hamper visualization of the placental anastomoses and oligohydramnios in the sac of the donor. Incomplete separation could result in the intrauterine death or severe morbidity of the remaining fetus(es) after the procedure, because of retrograde hemorrhage of the live fetuses into the dead placental tissue.

Selective feticide of the affected triplets [i.e. the MC pair in a DC triplet or a compromised triplet(s)] offers the potential advantages of interrupting the circulatory imbalance with a single procedure and provides a maximal placental volume for the remaining fetus.

Umbilical cord coagulation has proven beneficial in conditions such as twin-reversed arterial perfusion or MC twins discordant for a major anomaly, with survival of 78% of co-twins and an excellent long-term outcome; therefore, it may also be used in triplets with these kinds of conditions.<sup>30</sup> Furthermore, some parents could consider selective reduction of 1 or more healthy fetuses, to improve the survival and long-term follow-up of the remaining children.

Care should be taken when interpreting these results due to the limited data on perinatal outcome in triplets with TTTS, particularly MC triplets. Only 27 cases of MC triplet pregnancies with TTTS have been reported in the literature. The actual number of MC and DC triplets with TTTS may be higher due to underreporting/publication bias. Several cases in which the pregnancy was terminated or fetal demise occurred spontaneously have probably not been reported. Irrespective of zygosity, triplets are high-risk pregnancies due to the high incidence of preterm delivery, intrauterine growth restriction and congenital anomalies.<sup>31</sup> Only 1 case of fetofetal transfusion syndrome in MC quadruplets has ever been reported. Laser ablation of vascular anastomoses between one donor and two recipients was carried out at 20 weeks' gestation and fetal demise of one quadruplet occurred shortly after procedure. Delivery occurred at 25 weeks after the recurrence of TTTS. Only the sole survivor, not affected by transfusion, was born alive.<sup>32</sup>

In conclusion, this case series and review of the literature demonstrates that, although technically more challenging, fetoscopic surgery is feasible in triplets. In cases of MC triplets where fetoscopic laser coagulation is technically impossible, parents should be counseled on the increased likelihood of unfavorable outcome. However, the rarity of these conditions, the required operator and prenatal diagnostic skills, the variety of management options and the requirement of in-depth counseling of patients currently limit the availability of such interventions to referral centers for fetal medicine. Further experience will be required in order to evaluate the risks and efficacy of this therapy in triplet cases.



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