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Perinatal outcome of monochorionic triamniotic triplet pregnancy: multicenter cohort study

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KEYWORDS: growth restriction; miscarriage; multiple; outcome; pregnancy; TAPS; triamniotic; triplet; TTTS

CONTRIBUTION

What are the novel findings of this work?

Of our cohort of 153 monochorionic triamniotic (MCTA) triplet pregnancies, 93% were managed expectantly. The incidence of fetal structural abnormalities was 14%, that of twin reversed arterial perfusion sequence was 5%, that of twin-to-twin transfusion syndrome was 28% and that of selective fetal growth restriction was 16%. No antenatal complication was recorded in 49% of the pregnancies. Survival was affected by the development of complications.

What are the clinical implications of this work?

Monochorionicity-related complications overall may occur in up to half of MCTA triplet pregnancies and impact negatively the perinatal outcome. Surveillance and management protocols of MCTA should be established and shared through an international prospective registry, together with standardized long-term follow-up of these infants.

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ABSTRACT

Objective *Monochorionic (MC) triplet pregnancies are extremely rare and information on these pregnancies and their complications is limited. We aimed to investigate the risk of early and late pregnancy complications, perinatal outcome and the timing and methods of fetal intervention in these pregnancies.*

Methods *This was a multicenter retrospective cohort study of MC triamniotic (TA) triplet pregnancies managed in 21 participating centers around the world from 2007 onwards. Data on maternal age, mode of conception, diagnosis of major fetal structural anomalies or aneuploidy, gestational age (GA) at diagnosis of anomalies, twin-to-twin transfusion syndrome (TTTS), twin anemia–polycythemia sequence (TAPS), twin reversed arterial perfusion (TRAP) sequence and or selective fetal growth restriction (sFGR) were retrieved from patient records. Data on antenatal interventions were collected, including data on selective fetal reduction (three to two or three to one), laser surgery and any other active fetal intervention (including amniodrainage). Data on perinatal outcome were collected, including numbers of live birth, intrauterine demise, neonatal death, perinatal death and termination of fetus or pregnancy (TOP). Neonatal data such as GA at birth, birth weight, admission to neonatal intensive care unit and neonatal morbidity were also collected. Perinatal outcomes were assessed according to whether the pregnancy was managed expectantly or underwent fetal intervention.*

Results *Of an initial cohort of 174 MCTA triplet pregnancies, 11 underwent early TOP, three had an early miscarriage, six were lost to follow-up and one was ongoing at the time of writing. Thus, the study cohort included 153 pregnancies, of which the majority (92.8%) were managed expectantly. The incidence of pregnancy affected by one or more fetal structural abnormality was 13.7% (21/153) and that of TRAP sequence was 5.2% (8/153). The most common antenatal complication related to chorionicity was TTTS, which affected just over one quarter (27.6%; 42/152, after removing a pregnancy with TOP < 24 weeks for fetal anomalies) of the pregnancies, followed by sFGR (16.4%; 25/152), while TAPS (spontaneous or post TTTS with or without laser treatment) occurred in only 4.6% (7/152) of pregnancies. No monochorionicity-related antenatal complication was recorded in 49.3% (75/152) of pregnancies. Survival was apparently associated largely with the development of these complications: there was at least one survivor beyond the neonatal period in 85.1% (57/67) of pregnancies without antenatal complications, in 100% (25/25) of those complicated by sFGR and in 47.6% (20/42) of those complicated by TTTS. The overall rate of preterm birth prior to 28 weeks was 14.5% (18/124) and that prior to 32 weeks' gestation was 49.2% (61/124).*

Conclusion *Monochorionicity-related complications, which can impact adversely perinatal outcome, occur in almost half of MCTA triplet pregnancies, creating a challenge with regard to counseling, surveillance and management.* © *2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Monochorionic (MC) triplet pregnancies are extremely rare, with an estimated prevalence of 1 in 100 000 pregnancies[1]. Due to the increasing use of assisted reproductive technologies, the incidence of multiple pregnancy has increased in recent years[2]. As well as the well-recognized risks of triplet pregnancy, such as preterm birth (PTB) and increased perinatal morbidity and mortality, together with maternal risks such as pre-eclampsia and postpartum hemorrhage, they also have the additional risk of MC-specific complications, such as twin-to-twin transfusion syndrome (TTTS), twin anemia–polycythemia sequence (TAPS) and twin reversed arterial perfusion (TRAP) sequence[2]. The risk of stillbirth and low birth weight (BW) in these pregnancies is also increased[3].

Due to the known risks of higher-order multiple pregnancy, it is now recommended to offer routinely the option of selective fetal reduction[4]. However, in MC pregnancy, selective reduction is complicated and carries a high risk of demise of the cotwin, miscarriage or PTB, and there is no evidence in the literature to guide the optimal mode and timing of such intervention.

Few studies have investigated the perinatal outcome of triplets, and reported numbers of MC triplets have been small. The largest cohort of MC triamniotic (TA) triplets ($n = 50$) was reported by Kawaguchi *et al.*[5], who identified and compared perinatal outcome with that of trichorionic (TC) and dichorionic (DC) triplets. They noted that the risk of neonatal death (NND) was 2.6 times higher in MCTA triplets than in TCTA triplets, and the rate of TTTS was 8.0% in MC *vs* 5.6% in DC triplets[5]. However, this cohort included only triplet pregnancies that survived beyond 22 weeks' gestation and did not focus on those that miscarried earlier in the pregnancy or those that underwent selective fetal reduction, or on the methods and timing of selective reduction.

We aimed to investigate, in a multicenter retrospective cohort study of MCTA triplet pregnancy, the risk of early and late pregnancy complications, perinatal outcome and the timing and methods of fetal intervention.

METHODS

Study design and objectives

This was a retrospective multicenter cohort study; a list of participating centers is given in Table S1. The primary objective was to describe the fetal and perinatal outcome of MCTA triplet pregnancies. Secondary objectives were: to explore outcomes such as the risk of miscarriage,

stillbirth or PTB following fetal reduction in these pregnancies; to describe the nature and severity of monochorionicity-related complications, such as TTTS and selective fetal growth restriction (sFGR); and to determine the optimal mode and timing of fetal reduction or active fetal intervention in complicated pregnancies.

Study population

Included were MCTA triplet pregnancies managed in 21 participating centers from 2007 onwards. We excluded twin pregnancies and multiple pregnancies of higher order than triplets, and DC or TC triplet pregnancies. Chorionicity was confirmed by ultrasound examination at 11–14 weeks of gestation. Monochorionicity was determined by the presence of thin intertwin membranes at the site of insertion in the placenta or the T-sign on transabdominal or transvaginal ultrasound examination at 11–14 weeks. Gestational age (GA) was determined by the crown–rump length of the largest fetus in pregnancies conceived spontaneously, and by the date of oocyte retrieval or embryonic age from fertilization in pregnancies conceived via *in-vitro* fertilization. The patients had at least 2-weekly scans from 16 weeks' gestation onwards. At each of these scans, estimated fetal weight (EFW) and the deepest vertical pocket of amniotic fluid were assessed for each fetus. Screening for aneuploidy, detailed anatomy ultrasound scans and monitoring for monochorionicity-related complications were performed as per local or international guidelines[6]. Data on the placental pathological examination were not evaluated in this study. However, most of the participating centers included in their protocol routine assessment of chorionicity on placental pathological examination and none of the included cases had any discrepancy between these findings and the chorionicity determined prenatally using ultrasound.

A diagnosis of TTTS was made if there was polyhydramnios–oligohydramnios sequence affecting two or all three fetuses, and a diagnosis of TAPS was made when there was evidence of discordance in the middle cerebral artery peak systolic velocity[6]. Size discordance was assessed using the formulae[6]: (EFW or BW of largest fetus – EFW or BW of smallest fetus) ÷ (EFW or BW of largest fetus) and (EFW or BW of largest fetus – EFW or BW of middle fetus) ÷ (EFW or BW of largest fetus), and sFGR was diagnosed when the EFW or BW discordance was 25% or more. TRAP sequence was diagnosed by the presence of a TRAP or acardiac mass perfused by an apparently normal (pump) twin in a retrograde fashion.

Study outcomes and data collection

From patient records we retrieved data on maternal age, mode of conception, diagnosis of major fetal structural anomalies or aneuploidy, GA at diagnosis of anomalies, TTTS, TAPS, TRAP and sFGR. Data on antenatal intervention, including selective fetal reduction (three fetuses to two, or three fetuses to one), laser surgery or any other active fetal intervention (including amniodrainage) were also collected. If selective reduction or other intervention was performed, data on the indication, GA and technique used were recorded. Perinatal outcome, including live birth, intrauterine fetal demise (IUD), NND in the first week, NND after the first week, perinatal death, defined as IUD occurring beyond 22 weeks' gestation or NND, and termination of fetus or pregnancy (TOP) were documented. Data on the GA at birth, BW and mode of delivery (vaginal or Cesarean section), admission to the neonatal intensive care unit (NICU) and neonatal morbidity (respiratory distress syndrome, necrotizing enterocolitis, retinopathy of prematurity or brain abnormality), were also collected. Composite neonatal morbidity was defined as the presence of at least one of these neonatal morbidities.

A standardized Excel spreadsheet (Microsoft Corp., Redmond, WA, USA) was used to record data for each triplet separately. A search was performed of each hospital's secure database, and the retrieved data were anonymized and recorded. Pregnancy outcomes were obtained from the maternity database and neonatal records. The anonymized data were transferred securely to the study coordinator, who analyzed the final outcomes and stored them on an encrypted hospital hard-drive.

Statistical analysis

Continuous variables are presented as either median and interquartile range (IQR) or mean and SD, depending on the distribution characteristics (i.e. for non-normally and normally distributed data, respectively). Normality assumptions were tested with the Shapiro–Wilk test. Continuous variables were compared using the *t*-test or Wilcoxon rank-sum test, depending on the distribution characteristics. Categorical variables were compared by chi-square test or Fisher's exact test as appropriate. For comparison of fetus-level data, generalized estimating equations were used to account for intertriplet dependency. *P*-values < 0.05 were considered statistically significant. All statistical analyses were performed using R for statistical computing software (version 4.2.2 GUI 1.79 Big Sur ARM build) and using the Geepack package (geepack_(1.3.9.tgz)).

RESULTS

We identified 174 women with a MCTA triplet pregnancy managed at one of the 21 participating centers during the study period who were eligible for inclusion. Of these, 11 (6.3%) opted for early (prior to 12 weeks' gestation) TOP of the entire pregnancy, three (1.7%) pregnancies resulted in early miscarriage, six (3.4%) were lost to follow-up and one (0.6%) was ongoing at the time of analysis. After counseling, of the remaining 153 women (459 fetuses), 142 (92.8%) opted for expectant management and had known outcome, and 11 (7.2%) opted for selective reduction (10 from three fetuses to

two, and one from three fetuses to one). Table 1 presents the general characteristics and pregnancy outcomes of the cohort, stratified according to whether the pregnancy was managed expectantly or underwent selective reduction. The mode of conception was spontaneous in 85.0% of the study cohort (83.8% of those who opted for expectant management and all of those who underwent selective reduction).

The incidence of second-trimester miscarriage (triple IUD prior to 22 weeks or spontaneous labor resulting in delivery prior to 22 weeks) was 12.4% (18.2% of those who underwent selective reduction and 12.0% of those who opted to continue the pregnancy as triplets). Fetal structural abnormalities (not including TRAP as an anomaly) were detected in 21 (13.7%) pregnancies. TRAP sequence occurred in 5.2% of pregnancies. The incidence of isolated (i.e. not complicated further) monochorionicity-related complications was 16.3% for TTTS, 15.0% for sFGR and 1.3% for TAPS. The median GA at birth was 32.0 (IQR, 29.6–33.8) weeks. The incidence of PTB prior to 28 weeks' gestation was 14.5%, and that prior to 32 weeks' gestation 49.2% (Table 1).

Tables 2 and 3 present survival and GA at birth according to pregnancy complications. Among the 67 MCTA pregnancies without fetal anomalies that did not develop an antenatal chorionicity-related complication, in 74.6% ($n = 50$), all three infants survived beyond the neonatal period, 6% ($n = 4$) had two survivors, 4.5% ($n = 3$) had one survivor and, in 10 (14.9%) cases, there were no survivors (Table 2). Table 4 shows the incidence of NND, admission to the NICU and composite neonatal morbidity per fetus according to pregnancy complications.

Incidence and outcomes of pregnancies complicated by TRAP sequence

The incidence of TRAP sequence was 5.2% (8/153): 12.5% (1/8) miscarried before any treatment and the remaining 87.5% (7/8) underwent active prenatal intervention. Of those undergoing intervention, 42.9% (3/7) were treated with intrafetal interstitial laser, 42.9% (3/7) with radiofrequency ablation and 14.3% (1/7) with cord occlusion of the acardiac mass. Three TRAP pregnancies had an additional anomaly in one fetus. One TRAP pregnancy was complicated by TTTS and resulted in no survivors (2 NND). Overall, 50% (4/8) of pregnancies complicated by TRAP sequence had two survivors, 25% (2/8) had one survivor (1 TOP and 1 NND) and 25% (2/8) had no survivors (Figure 1).

Table 1 General characteristics and outcomes of study cohort of 153 monochorionic triamniotic triplet pregnancies, according to management

Characteristic/outcome	*Total* (n = *153*)	*Expectant management* (n = *142*)	*Selective reduction* (n = *11*)
Maternal age (years)	30.5 (26–35)	30 (26–35)	35 (32.5–38)
Spontaneous conception	130 (85.0)	119 (83.8)	11 (100)
Second-trimester miscarriage*	19 (12.4)	17 (12.0)	2 (18.2)
Selective fetal reduction (three to two)	10 (6.5)	N/A	10 (90.9)
Selective fetal reduction (three to one)	1 (0.7)	N/A	1 (9.1)
Fetal structural anomaly	21 (13.7)	21 (14.8)	N/A
Affecting one fetus	16 (10.5)	16 (11.3)	N/A
Affecting two fetuses	4 (2.6)	4 (2.8)	N/A
Affecting three fetuses	1 (0.7)	1 (0.7)	N/A
TRAP sequence only	4 (2.6)	4 (2.8)	N/A
TTTS only	25 (16.3)	25 (17.6)	1 (9.1)
TAPS only	2 (1.3)	2 (1.4)	0 (0)
sFGR only	23 (15.0)	22 (15.5)	1 (9.1)
GA at birth (weeks)†	32.0 (29.6–33.8)	31.7 (29.6–33.3)	34.7 (34.1–36.3)
Birth weight (g)‡	1500 (1111.5–1800)	1480 (1087.5–1765)	2110 (1900–2340)
PTB < 28 weeks†	18/124 (14.5)	18/114 (15.8)	0/10 (0)
PTB < 32 weeks†	61/124 (49.2)	60/114 (52.6)	1/10 (10.0)
PTB at 32 to < 34 weeks†	32/124 (25.8)	32/114 (28.1)	0/10 (0)
PTB at 34–37 weeks†	29/124 (23.4)	22/114 (19.3)	7/10 (70.0)
Term delivery > 37 weeks†	2/124 (1.6)	1/114 (0.9)	1/10 (10.0)
Intrauterine demise > 20 weeks§¶	34/430 (7.9)	31/409 (7.6)	3/21 (14.3)
Live birth§**	320/404 (79.2)	304/383 (79.4)	16/21 (76.2)
Neonatal death§††	28/320 (8.8)	28/304 (9.2)	0/16 (0)
Perinatal death§‡‡	55/404 (13.6)	54/383 (14.1)	1/21 (4.8)
Admission to neonatal unit§**	277/320 (86.6)	266/304 (87.5)	11/16 (68.8)

Data are given as median (interquartile range), *n* (%) or *n*/*N* (%). *Intrauterine death of all three triplets prior to 22 weeks or spontaneous labor resulting in delivery prior to 22 weeks. †In pregnancies with at least one live birth and including neonatal deaths, $n = 124$. ‡In liveborn fetuses with data available, $n = 318$ fetuses. §Expressed per fetus. ¶All terminations performed before 20 weeks excluded from denominator. **All terminations excluded from denominator. ††Denominator includes only liveborn fetuses. ‡‡Numerator includes intrauterine demise >22 weeks and neonatal deaths; all terminations excluded from denominator. GA, gestational age; N/A, not applicable; PTB, preterm birth; sFGR, selective fetal growth restriction; TAPS, twin anemia–polycythemia sequence; TRAP, twins reversed arterial perfusion sequence; TTTS, twin-to-twin transfusion syndrome.

Incidence and outcomes of pregnancies complicated by fetal structural anomalies

The incidence of fetal structural abnormalities was 13.7% (21/153 pregnancies). In the majority of these (76.2% (16/21)), there was one affected fetus, in 19.0% (4/21), two fetuses were affected and, in 4.8% (1/21), all three fetuses were affected. The parents of the pregnancy with three affected fetuses opted for TOP and this pregnancy was then removed from the analysis, reducing the cohort to 152 pregnancies. The most common fetal abnormality was cardiac defect (5/27 (18.5%) fetuses). Two pregnancies had conjoined twins. Three pregnancies had one acardiac twin (TRAP sequence), one fetus with an anomaly and one fetus with no anomalies. The parents opted for TOP of the affected fetus in 48.1% (13/27) of cases. Data on additional monochorionicity-related complications (i.e. TTTS, sFGR, TAPS or TRAP sequence) and survival are shown in Figures 2 and 3.

Incidence and outcomes of pregnancies complicated by TTTS

TTTS developed in 42/152 (27.6%) pregnancies, including those with structural abnormalities (in all cases affecting one fetus), or TRAP sequence and those

Table 2 Survival* rates in 153 monochorionic triamniotic triplet pregnancies according to whether pregnancy was complicated or underwent fetal reduction

Type of complication or management	*No survivors*	*One survivor*	*Two survivors*	*Three survivors*
Fetal structural anomaly affecting one fetus ($n=16$)†	4 (25.0)	2 (12.5)	5 (31.3)	5 (31.3)
Fetal structural anomaly affecting two fetuses ($n=4$)†	4 (100)	0 (0)	0 (0)	0 (0)
Fetal structural anomaly affecting three fetuses ($n=1$)	1 (100)	0 (0)	0 (0)	0 (0)
TRAP sequence ($n=8$)	2 (25.0)	2 (25.0)	4 (50.0)	N/A
TTTS ($n=42$)‡	22 (52.4)	6 (14.3)	9 (21.4)	5 (11.9)
TTTS, treated with laser surgery ($n=24$)	10 (41.6)	5 (20.8)	8 (33.3)	1 (4.2)
TTTS, no laser surgery ($n=18$)	12 (66.7)	1 (5.6)	1 (5.6)	4 (22.2)
Spontaneous TAPS ($n=2$)	0	0	1 (50.0)	1 (50.0)
Post-laser TAPS ($n=3$)	1 (33.3)	1 (33.3)	1 (33.3)	0 (0)
TAPS after TTTS treated with amniodrainage ($n=2$)	1 (50.0)	1 (50.0)	0	0 (0)
sFGR ($n=25$)‡	0 (0)	3 (12.0)	5 (20.0)	17 (68.0)
No antenatal chorionicity-related complications (including fetal anomalies), expectant management ($n=67$)	10 (14.9)	3 (4.5)	4 (6.0)	50 (74.6)
Selective fetal reduction (three to two) ($n=10$)	2 (20.0)	1 (10.0)	7 (70.0)	N/A
Selective fetal reduction (three to one) ($n=1$)	0 (0)	1 (100)	N/A	N/A

Data are presented as *n* (%). *Survival beyond neonatal period. †Including pregnancies which developed further complications (twin-to-twin transfusion syndrome (TTTS), selective fetal growth restriction (sFGR), twin anemia–polycythemia sequence (TAPS), twin reversed arterial perfusion (TRAP) sequence). ‡Including pregnancies with fetal anomaly and/or which developed further monochorionicity-related complications (TTTS, sFGR, TAPS, TRAP sequence). N/A, not applicable.

Table 3 Incidence of preterm birth (PTB) at different gestational-age cut-offs in 124 monochorionic triamniotic triplet pregnancies with at least one live birth, according to whether pregnancy was complicated or underwent fetal reduction

	PTB at:				
Type of complication or management	*< 28 weeks*	*28 to < 32 weeks*	*32 to < 34 weeks*	*34–37 weeks*	*Delivery > 37 weeks*
Fetal structural anomaly affecting one fetus ($n=13$)*	1 (7.7)	3 (23.1)	6 (46.2)	3 (23.1)	0 (0)
TRAP sequence ($n=7$)†	2 (28.6)	1 (14.3)	3 (42.9)	1 (14.3)	0 (0)
TTTS ($n=24$)†	8 (33.3)	10 (41.7)	4 (16.7)	2 (8.3)	0 (0)
TTTS, treated with laser surgery ($n=18$)	6 (33.3)	8 (44.4)	2 (11.1)	2 (11.1)	0 (0)
TTTS, no laser surgery ($n=6$)‡	2 (33.3)	2 (33.3)	2 (33.3)	0	0 (0)
Spontaneous TAPS ($n=2$)	0	1 (50.0)	1 (50.0)	0	0 (0)
Post-laser TAPS ($n=3$)	1 (33.3)	1 (33.3)	1 (33.3)	0	0 (0)
TAPS after TTTS treated with amniodrainage ($n=1$)	0	0	0	0	1 (100)
sFGR ($n=25$)†	5 (20.0)	9 (36.0)	6 (24.0)	5 (20.0)	0 (0)
No antenatal chorionicity-related complications (including fetal anomalies and selective reduction) ($n=65$)	3 (4.6)	22 (33.8)	19 (29.2)	20 (30.8)	1 (1.5)
Selective fetal reduction (three to two) ($n=8$)	0 (0)	1 (12.5)	0 (0)	7 (87.5)	0 (0)
Selective fetal reduction (three to one) ($n=1$)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)

Data are presented as *n* (%). Only pregnancies with information available on gestational age at birth were included in this analysis. Neonatal deaths were included. *Including pregnancies which developed further complications (twin-to-twin transfusion syndrome (TTTS), selective fetal growth restriction (sFGR), twin anemia–polycythemia sequence (TAPS), twin reversed arterial perfusion (TRAP) sequence). †Including pregnancies with fetal anomaly and/or which developed further monochorionicity-related complications (TTTS, sFGR, TAPS, TRAP sequence). ‡Six of seven cases reported because in one case with live birth, gestational age at delivery was unknown.

undergoing selective reduction from three fetuses to two. The incidence in pregnancies that continued as MCTA triplets beyond 16 weeks' gestation was 27.3% (35/128).

Of the pregnancies complicated by TTTS, 57.1% (24/42) were treated with fetoscopic laser photocoagulation of the placental anastomoses. Of these, 62.5% (15/24) did not develop further monochorionicity-related complications, but two of these 15 pregnancies were complicated by a miscarriage (delivery prior to 22 weeks' gestation) after the laser surgery. Additional monochorionicity-related complications, namely sFGR and sFGR with TAPS, complicated 25% (6/24) and 12.5% (3/24) of these pregnancies, respectively. Overall, of this group of TTTS pregnancies treated with laser, 41.7% (10/24) resulted in no survivors, 20.8% (5/24) had one survivor, 33.3% (8/24) had two survivors and the remaining 4.2% (1/24) had three survivors.

Among the 42.9% (18/42) of pregnancies complicated by TTTS but not treated with laser surgery, 38.9% (7/18) were treated with amniodrainage; in one of these cases, this followed a failed laser procedure (due to failure to visualize the vascular equator). In 16.7% (3/18) of the pregnancies, a miscarriage occurred without active fetal intervention, while, in 11.1% (2/18), it was decided to perform TOP of the whole pregnancy. Selective TOP of the twin pair affected by TTTS using cord occlusion was performed in one (5.6%) of the 18 cases; this pregnancy was complicated by miscarriage (with no survivors). No active fetal intervention was performed in the remaining 27.8% (5/18) of these cases: two of these five pregnancies (40%) had no survivors (three IUDs and three NNDs), two (40%) pregnancies had three survivors (one of these pregnancies was also complicated by sFGR) and one (20%, 1/5) pregnancy was lost to follow-up after two IUDs.

Table 4 Incidence (per liveborn fetus) of neonatal death, admission to neonatal unit (NNU) and composite neonatal morbidity in 124 monochorionic triamniotic triplet pregnancies with at least one live birth, according to whether pregnancy was complicated or underwent fetal reduction

Type of complication or management	*Live birth*	*Neonatal death*	*NNU admission**	*Composite neonatal morbidity**
Fetal structural anomaly affecting one fetus ($n=13$)†	29	4/29 (13.8)	28/29 (96.5)	15/29 (51.7)
TRAP sequence ($n=7$)‡	13	3/13 (23.1)	7/11 (63.6)	2/11 (18.2)
TTTS ($n=25$)‡	51	12/51 (23.5)	45/48 (93.8)	27/48 (56.3)
TTTS, treated with laser surgery ($n=18$)	33	9/33 (27.3)	28/31 (90.3)	14/31 (45.2)
TTTS, no laser surgery ($n=7$)	18	3/18 (16.7)	17/17 (100)	13/17 (76.5)
Spontaneous TAPS ($n=2$)	6	1/6 (16.7)	6/6 (100)	4/6 (66.7)
Post-laser TAPS ($n=3$)	6	3/6 (50.0)	5/6 (83.3)	0/6 (0)
TAPS after TTTS treated with amniodrainage ($n=1$)	1	0/1 (0)	Data missing	Data missing
sFGR ($n=25$)‡	69	5/69 (7.2)	56/69 (81.2)	36/69 (52.2)
No antenatal chorionicity-related complications (including fetal anomalies and selective reduction) ($n=65$)	182	9/182 (4.9)	163/182 (89.6)	87/172 (50.6)
Selective fetal reduction (three to two) ($n=8$)	15	0/15 (0)	11/15 (73.3)	5/15 (33.3)
Selective fetal reduction (three to one) ($n=1$)	1	0/1 (0)	0 (0)	0 (0)

Data are expressed as *n* or *n*/*N* (%). *n* values in first column are number of pregnancies. Denominator varies among outcome groups because only pregnancies with available information on particular outcome were included in analysis. *Including only liveborn with available information, as specified in denominator. †Including pregnancies which developed further complications (twin-to-twin transfusion syndrome (TTTS), selective fetal growth restriction (sFGR), twin anemia–polycythemia sequence (TAPS), twin reversed arterial perfusion (TRAP) sequence). ‡Including pregnancies with fetal anomaly and/or which developed further monochorionicity-related complications (TTTS, sFGR, TAPS, TRAP sequence).

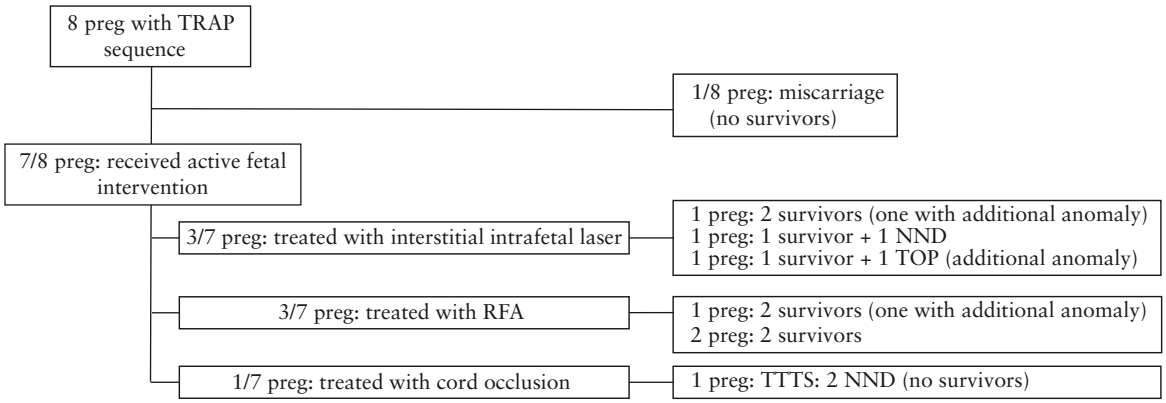

Figure 1 Flowchart summarizing outcome of monochorionic triplet pregnancies complicated by twin reversed arterial perfusion (TRAP) sequence. NND, neonatal death; preg, pregnancy/pregnancies; RFA, radiofrequency ablation; TOP, termination of pregnancy or of individual fetus; TTTS, twin-to-twin transfusion syndrome.

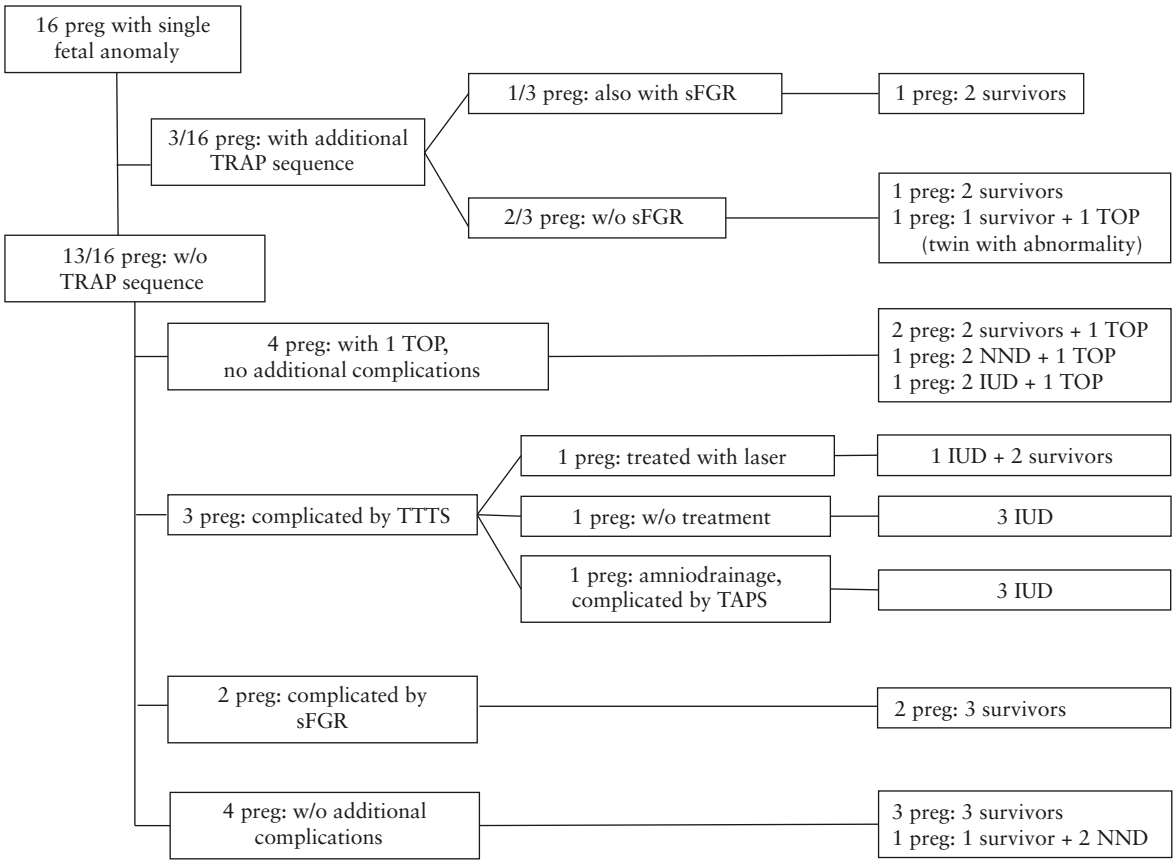

Figure 2 Flowchart summarizing outcome of monochorionic triplet pregnancies with one fetus with structural anomaly. IUD, intrauterine fetal death; NND, neonatal death; preg, pregnancy/pregnancies; sFGR, selective fetal growth restriction; TAPS, twin anemia–polycythemia sequence; TOP, termination of pregnancy; TRAP, twin reversed arterial perfusion; TTTS, twin-to-twin transfusion syndrome; w/o, without.

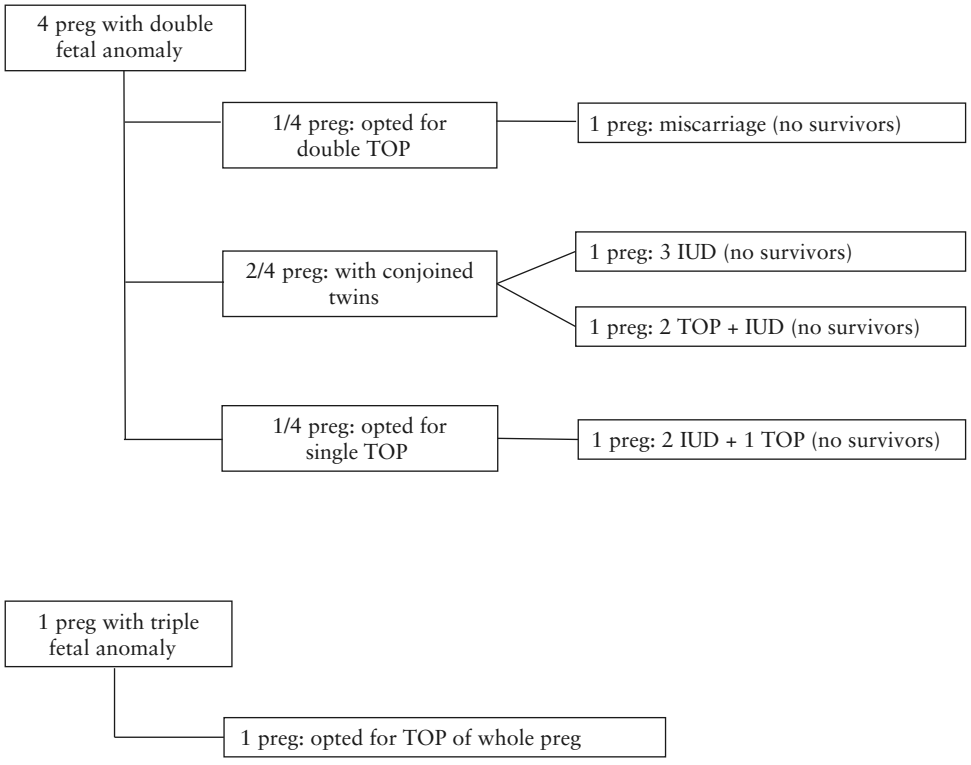

Figure 3 Flowcharts summarizing outcome of monochorionic triplet pregnancies with two or three fetuses with structural anomaly. IUD, intrauterine fetal death; preg, pregnancy/pregnancies; TOP, termination of pregnancy or of individual fetus.

Among the pregnancies complicated by TTTS that did not undergo laser surgery, 11.1% (2/18) developed sFGR and 11.1% (2/18) developed TAPS. Overall in this group, 66.7% (12/18) pregnancies had no survivors, 5.6% (1/18) had one survivor, 5.6% (1/18) had two survivors and 22.2% (4/18) had three survivors. Further details are presented in Figures 2 and 4.

Incidence and outcomes of pregnancies complicated by sFGR

sFGR complicated 16.4% (25/152) of pregnancies (including those with structural abnormalities and those undergoing fetal reduction from three fetuses to two). The incidence of sFGR in those continuing as MCTA triplets beyond 16 weeks' gestation and without structural abnormalities was 20.2% (22/109). Of the pregnancies complicated by sFGR, 84.0% (21/25) did not receive any active fetal intervention (no active treatment), 12.0% (3/25) had selective TOP of the smaller fetus and 4.0% (1/25) were treated using fetoscopic laser surgery. In the cohort of sFGR pregnancies, 68.0% (17/25) resulted in three survivors, 20.0% (5/25) resulted in two survivors and 12.0% (3/25) had one survivor. Figure 5 outlines the outcomes of these pregnancies according to the management options.

Incidence and outcomes of pregnancies complicated by TAPS

Spontaneous TAPS complicated 1.3% (2/152) of the MCTA pregnancies, in 1.3% (2/152) of cases, TAPS developed after TTTS treated with amniodrainage only and post-laser TAPS complicated 2.0% (3/152) (including those with structural abnormalities and those undergoing selective fetal reduction from three fetuses to two). The incidence of TAPS overall in those continuing as MC triplets beyond 16 weeks' gestation was 5.5% (7/128).

In the spontaneous TAPS group, one case was treated with fetoscopic laser surgery and resulted in three survivors. The other was treated with intrauterine transfusion and had two survivors and one NND. In the

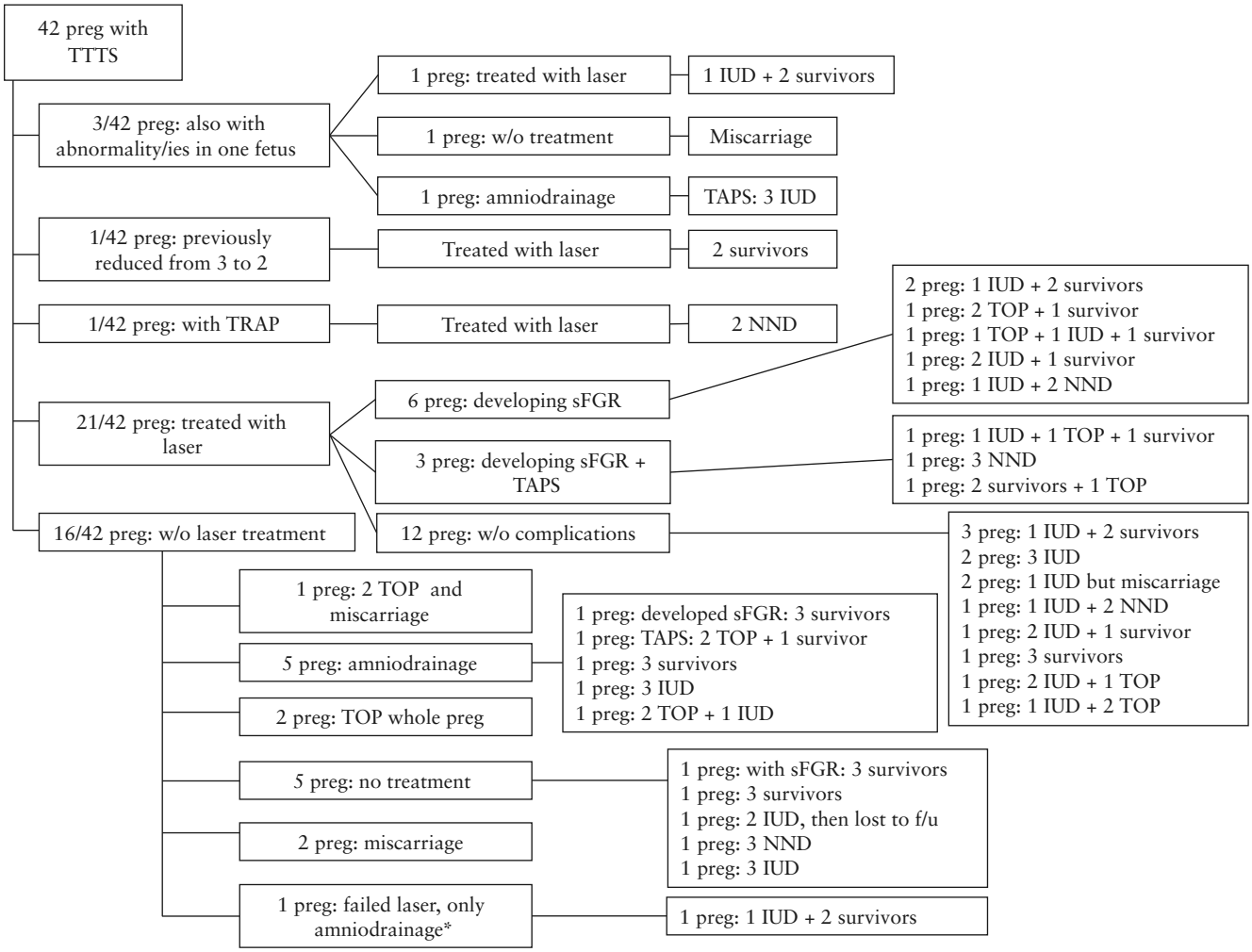

Figure 4 Flowchart summarizing outcome of monochorionic triplet pregnancies complicated by twin-to-twin transfusion syndrome (TTTS). *Laser procedure initiated (with fetoscope) but photocoagulation of anastomoses was not performed for technical reasons; only removal of some amniotic fluid was achieved. f/u, follow-up; IUD, intrauterine fetal death; NND, neonatal death; preg, pregnancy/pregnancies; sFGR, selective fetal growth restriction; TAPS, twin anemia–polycythemia sequence; TOP, termination of pregnancy or of individual fetus; TRAP, twin reversed arterial perfusion sequence; w/o, without.

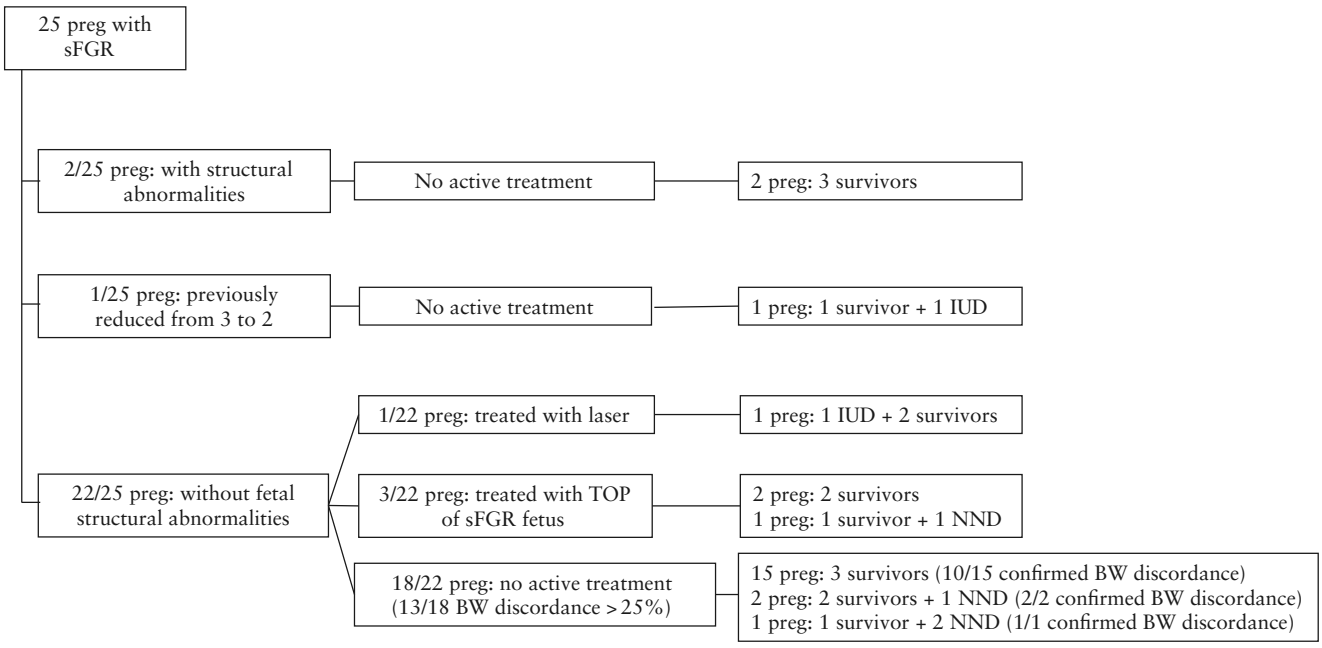

Figure 5 Flowchart summarizing outcome of monochorionic triplet pregnancies complicated by selective fetal growth restriction (sFGR) without twin-to-twin transfusion syndrome or twin anemia–polycythemia sequence. BW, birth weight; IUD, intrauterine fetal death; NND, neonatal death; preg, pregnancy/pregnancies; TOP, termination of pregnancy or of individual fetus.

group which developed TAPS following laser treatment for TTTS ($n = 3$), one pregnancy had two survivors, one pregnancy had one survivor and one pregnancy had no survivors. In the group with TAPS developing after TTTS treated with amniodrainage ($n = 2$), one pregnancy had one survivor and the other had no survivors.

Outcome of MCTA pregnancies without antenatal complications

In 49.3% (75/152) of the pregnancies (including those with structural abnormalities and those undergoing selective reduction from three fetuses to two and excluding the pregnancy reduced to one fetus), no monochorionicity-related complications (i.e. TTTS, sFGR, TAPS or TRAP) were recorded. Eight of these pregnancies had one fetus with structural anomaly and four pregnancies had two such fetuses. In this group, 66.7% (50/75) of pregnancies had three survivors, 13.3% (10/75) had two survivors, 4% (3/75) had one survivor and 16% (12/75) had no survivors.

Sixty-five of these pregnancies had information available on the GA at birth and at least one livebirth. The incidence of PTB prior to 28 weeks' gestation in this group was 4.6% (3/65) and that of PTB from 28 weeks to prior to 32 weeks' gestation was 33.8% (22/65) (Table 3).

Selective fetal reduction

In 11 pregnancies without fetal structural abnormalities or TRAP sequence, the parents opted for selective fetal reduction: reduction from three fetuses to two in 10 pregnancies and reduction from three fetuses to one in one pregnancy (Figure 6). Of the pregnancies reduced to two fetuses, the procedure was performed in six using intrafetal laser, in two using ultrasound-guided cord coagulation, in one using fetoscopic cord coagulation and in one using radiofrequency ablation. Their median GA at selective reduction was 13.1 (IQR, 12.3–14.8) weeks. Of these pregnancies, TTTS and sFGR developed in 10% (1/10), and sFGR alone was diagnosed in one (10%). There were no additional complications in the remaining 80% (8/10). In this group, 70% (7/10) of the pregnancies had two survivors, 10% (1/10) had one survivor and 20% (2/10) had no survivors. The pregnancy undergoing selective reduction with intrafetal laser from three to one at 13 + 6 weeks' gestation resulted in a livebirth at 39 weeks without further antenatal complications.

DISCUSSION

Key findings

Of our cohort of 153 MCTA triplet pregnancies, the majority (92.8%) were managed expectantly. The incidence of TRAP sequence was 5.2% and that of fetal structural abnormalities was 13.7%. Of the latter, one pregnancy underwent TOP because all fetuses were affected, and this pregnancy was removed from the cohort. TTTS complicated just over a quarter (27.6%) of the 152 pregnancies, followed by sFGR (16.4%), while TAPS (both spontaneous and post-laser) occurred in only 3.3% of pregnancies. No monochorionicity-related antenatal complication was recorded in 49.3% of pregnancies. Survival was associated largely with the development of these complications: there was at least one survivor in 85.1% of pregnancies without antenatal complications, in 100% of pregnancies complicated by sFGR and in 47.6%

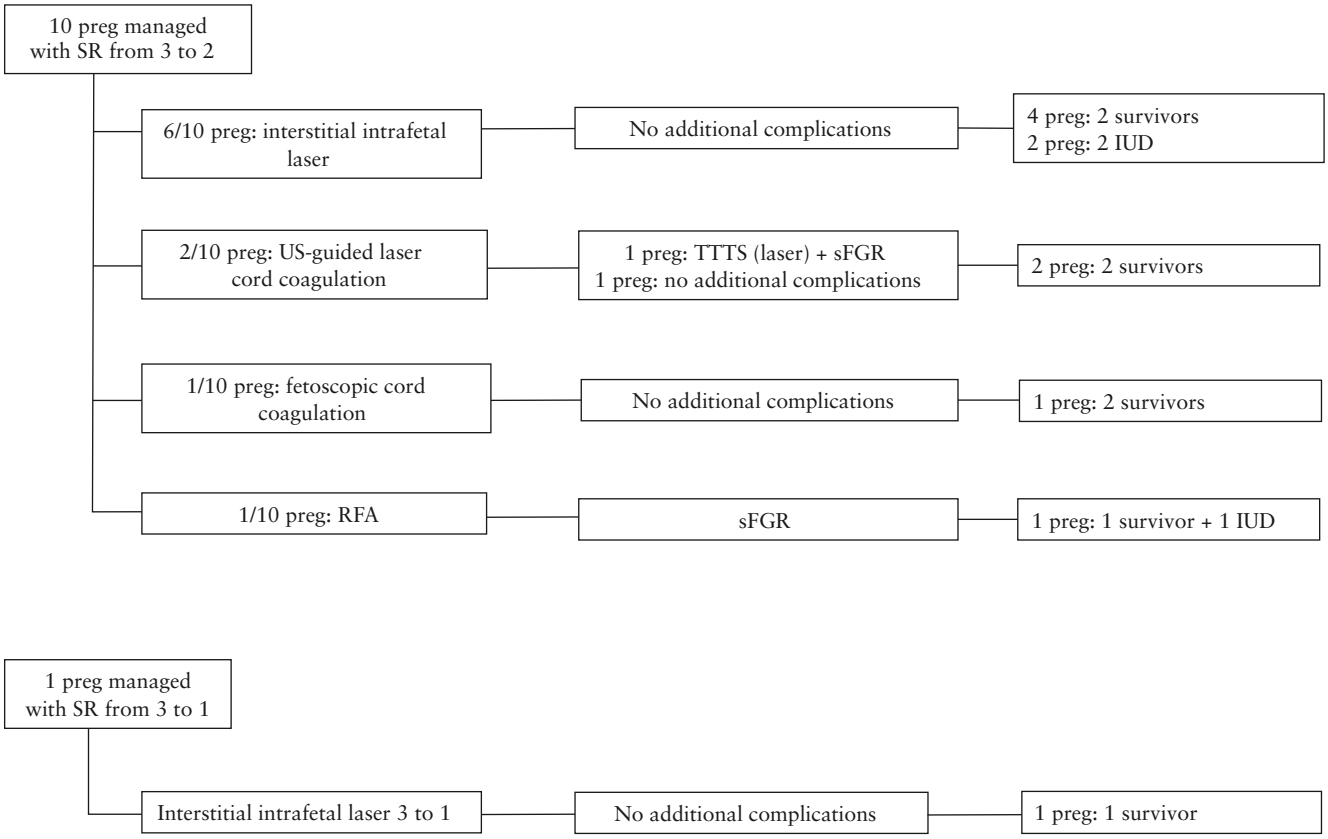

Figure 6 Flowchart summarizing outcome of monochorionic triplet pregnancies undergoing selective reduction (SR). IUD, intrauterine fetal death; preg, pregnancy/pregnancies; RFA, radiofrequency ablation; sFGR, selective fetal growth restriction; TTTS, twin-to-twin transfusion syndrome; US, ultrasound.

of those complicated by TTTS. The overall rate of PTB prior to 28 weeks was 14.5% and that prior to 32 weeks' gestation was 49.2%.

Interpretation of study findings and comparison with published literature

This study collates data on 174 MCTA triplet pregnancies from 21 centers across the world and describes the management and outcome of 153 of these pregnancies. This is the largest cohort of MCTA triplet pregnancies reported to date detailing the incidence of antenatal chorionicity-related complications such as TRAP sequence, TTTS, TAPS and sFGR. Kawaguchi *et al.*[5], in their cohort of 50 MCTA triplet pregnancies, reported an incidence of TTTS of 8%, without providing information on the incidence of sFGR or TAPS. The incidence of TTTS in our cohort was higher, possibly because Kawaguchi *et al.*[5] included only triplet births beyond 22 weeks' gestation, thereby excluding all IUDs, miscarriages and TOPs occurring at an earlier GA. Furthermore, we also included TTTS occurring in pregnancies complicated by fetal anomalies or with superimposed sFGR.

Mustafa *et al.*[7] recently reviewed perinatal outcome of triplets with TTTS undergoing laser treatment, reporting that fetal survival overall was 74% (95% CI, 52–92%) and 99% of pregnancies had at least one survivor, compared to 59% in our cohort. However, unlike in their study, we also included cases with additional complications, fetal anomalies or TOP, while no information on TOP could be retrieved from other papers[5,7].

Few studies have reported data on sFGR in triplets[8,9]. In the NorSTAMP and STORK multiple pregnancy cohort[9] the incidence of intertriplet growth discordance in DCTA/MCTA triplets was between 33% and 39%. In our cohort, sFGR complicated 16% of the pregnancies, increasing to 20% of those continuing as MCTA pregnancies beyond 16 weeks' gestation.

The majority (84%; 21/25) of pregnancies complicated by sFGR were managed expectantly in our cohort and all pregnancies had at least one survivor.

Most published cases on TAPS in triplets are anecdotal and involve mainly DCTA pregnancies[10–12]. We recorded two cases of spontaneous and three cases of post-laser TAPS. Despite this being the largest published cohort to date, the low number of these cases prevents any conclusion from being drawn regarding the best management option for TAPS in MCTA triplet pregnancy.

PTB is one of the most common complications of multiple gestation. We found an overall rate of PTB < 28 weeks' gestation of 14.5% in our cohort, but, in pregnancies without antenatal complications, the rate of PTB was 5% compared with around 30% in complicated pregnancies. Kawaguchi *et al.*[5] reported a rate of PTB < 28 weeks of 7.1%, but with only 4/50 cases

of TTTS in MCTA pregnancies. In the NorSTAMP and STORK cohort[9], the rate of PTB < 30 weeks' gestation was 23.4% of triplets with a MC unit, i.e. including both DCTA and MCTA.

PTB and antenatal monochorionicity-related complications are likely to represent the main determinants of long-term outcome in these MCTA triplet pregnancies. Management options in triplets, therefore, include the possibility of embryo reduction to twins or a singleton. Selective reduction through intrafetal laser ablation is particularly complex with a MC placenta. In fact, despite the lower rates of miscarriage and early PTB, around half of the pregnancies resulted in the delivery of one rather than two liveborn infants in the case series described by Chaveeva *et al.*[13], in which DC triplet pregnancies were reduced to DC twins by reducing one twin of a MC pair. Intrafetal laser ablation was the most commonly used technique for reduction in our cohort. It seems that fetal reduction reduces the risk of severe prematurity compared with expectant management, but the small number of cases limits our ability to draw any firm conclusion.

Strengths and limitations

The main strength of this study is the large number of MCTA triplet pregnancies included from 21 fetal medicine units across 16 different countries from all continents, making it truly representative of the management of these pregnancies in referral centers worldwide. Several limitations should be acknowledged. Despite being the largest cohort described so far, the number of MCTA pregnancies was relatively small. The retrospective nature of the study has an inherent risk of bias and not all information could be retrieved reliably, such as which fetuses were involved in TTTS or the laser therapy strategy used in some cases. Moreover, data from pathological examination of the placenta were not included in this study. Furthermore, each center had its own local protocol for both surveillance and treatment, if needed, of antenatal complications in these pregnancies. Additionally, the fact that fetal therapy is performed in almost all of the centers included in the study might have introduced the risk of selection bias towards more complicated cases. Moreover, the small number of pregnancies which underwent selective fetal reduction prevented any statistical comparison with those managed expectantly. Finally, no data on the long-term outcome of these pregnancies and their infants were included.

Implications for clinical practice and research

MCTA triplet pregnancies are rare and therefore their optimal management has not yet been established. Despite several studies[13–16] evaluating the impact of fetal reduction in triplet pregnancies on the risk of miscarriage and PTB, its timing and optimal method have not yet been determined. Accurate comparison with expectant management could only be provided by randomized trials, which are very unlikely to be performed. Optimal surveillance protocols have not been established in these pregnancies; in fact, prenatal evaluation usually follows the surveillance protocols used in MC twin pregnancies with respect to frequency and timing.

Fetal therapy has been used to treat TTTS in triplet pregnancy. However, in MCTA pregnancies it is possible that there are anastomoses among the three connected fetal circulations, making the technique even more challenging than that in MC diamniotic or DCTA pregnancy. Indeed, the perinatal outcome following laser therapy for TTTS in our cohort was relatively poor compared with that of laser therapy in MC twins with TTTS[17].

An international prospective registry of MCTA triplet pregnancies should be established to share common protocols for their surveillance and for management of the complications of these pregnancies, as well as to standardize the long-term follow up of these infants.

Conclusion

MCTA triplet pregnancy represents a challenge in counseling, surveillance and management since monochorionicity-related complications may occur in almost half of these pregnancies and impact adversely the perinatal outcome.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 List of centers participating in study