Pregnancy outcomes of dichorionic triamniotic triplet pregnancies after in vitro fertilization-embryo transfer: multifoetal pregnancy reduction versus expectant management

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Abstract

Background: Trichorionic triplet pregnancy reduction to twin pregnancy is associated with a lower risk of preterm delivery but not of miscarriage. However, reports on dichorionic triamniotic (DCTA) triplet pregnancy outcomes are few. This study aimed to compare the pregnancy outcomes of reducing DCTA triplets achieved via in vitro fertilization-embryo transfer (IVF-ET) to monochorionic (MC) singleton or monochorionic diamniotic (MCDA) twin pregnancies at 11-13+6 gestational weeks to the pregnancy outcomes of expectant management. Method: Two hundred and ninety-eight patients with DCTA triplets via IVF-ET from January 2012 to December 2016 were retrospectively analysed. All foetuses were alive until 11-13+6 gestational weeks. Eighty-four DCTA triplet pregnancies were reduced to MC singleton pregnancies (group A), 149 were reduced to MCDA pregnancies (group B), and 65 were managed expectantly (group C). Each multifoetal pregnancy reduction (MFPR) was performed at 11-13+6 gestational weeks. Pregnancy outcomes were compared among these 3 groups. Result(s): There were no significant differences in the miscarriage rates (4.8 vs. 2.7 vs. 6.2%, respectively) or live birth rates (90.5 vs. 87.2 vs. 86.2%, respectively) among groups A, B and C (P > 0.05). Group A had significantly lower preterm delivery (11.9 vs. 89.2%; odds ratio (OR) 0.016, 95% confidence interval (CI) 0.006-0.045) and low birth weight rates (LBW; 9.2 vs. 92.9%; OR 0.008, 95% CI 0.003-0.021) than group C (P < 0.001). Group B had significantly lower preterm delivery (51.7 vs. 89.2%; OR 0.129, 95% CI 0.055-0.301) and LBW rates (59.0 vs. 92.9%; OR 0.111, 95% CI 0.057-0.214) than group C (P < 0.001). Group A had significantly lower preterm delivery (11.9 vs. 51.7%; OR 0.126, 95% CI 0.061-0.263; P < 0.001), LBW (9.2 vs. 59.0%; OR 0.071, 95% CI 0.031-0.160; P < 0.001) and perinatal mortality rates (5.0 vs. 13.4%; OR 0.339, 95% CI 0.117-0.978; P = 0.037) than group B. Conclusion: The MFPR of DCTA triplet pregnancies to singleton or MCDA pregnancies was associated with better pregnancy outcomes than DCTA triplets managed expectantly. The perinatal outcomes of DCTA triplets reduced to singleton pregnancies were better than those of DCTA triplets reduced to MCDA pregnancies.

Background

Over the past few decades, due to advancing maternal age, the widespread application of assisted reproductive technology (ART) and the use of ovulation induction drugs, there has been a dramatic increase in the incidence of multifoetal pregnancies (MFPs) [1–3]. As a result of restrictions in the number of embryos transferred in women undergoing ART, a decline in MFPs has been observed in recent years [4, 5]. However, the splitting of one embryo into two embryos may lead to higher-order multiple pregnancies (HOMPs), including triplet pregnancies containing monochorionic (MC) twins [5–7].

Compared with singleton and twin pregnancies, HOMPs are associated with a higher risk of maternal-perinatal and long-term complications [8–10] and with increased hospital costs [11]. Compared with singleton and twin pregnancies, triplet pregnancies are at a higher risk of miscarriage (pregnancy loss < 24 gestational weeks) and preterm birth (delivery < 32 gestational weeks) [5, 12–16]. To reduce the risks associated with triplet pregnancies and HOMPs, multifoetal pregnancy reduction (MFPR) has been performed in recent years [17, 18], and several methods have been described [19, 20]. There is ample

evidence that reducing quadruplet-or-higher pregnancies to twins is associated with more favourable outcomes, including increased gestational age (GA) at delivery [13, 15, 21]. Previous study [16] has shown that a trichorionic triplet pregnancy reduction to a twin pregnancy is associated with a lower risk of preterm delivery, without a significantly increased miscarriage rate. However, until now, studies regarding the outcomes of women with dichorionic triamniotic (DCTA) triplet pregnancies conceived from in vitro fertilization-embryo transfer (IVF-ET) and options for their management have been infrequently reported.

The aim of this study was to investigate the pregnancy and obstetric outcomes of women with DCTA pregnancies conceived from IVF-ET that were reduced to singleton pregnancies (foetus with a separate placenta) or to monochorionic diamniotic (MCDA) twin pregnancies at 11–13^{+6} gestational weeks to those of DCTA pregnancies that were managed expectantly.

Methods

A retrospective analysis was conducted of infertile patients with DCTA pregnancies conceived via IVF-ET from January 2012 to December 2016 at the Reproductive and Genetic Hospital of CITIC-Xiangya (Changsha city, Hunan, China). This study was approved by the Ethics Committee of the Reproductive and Genetic Hospital of CITIC-Xiangya (LL-SC–2019–013). Written informed consent was obtained from each participant.

We identified 476 infertile patients who conceived a DCTA triplets via IVF-ET. The IVF procedure and ET were carried out as previously described [22]. Chorionicity was evaluated during the first trimester by ultrasound based on the number of placental sites; the presence of the “lambda sign” or “T sign” in the presence of a single placenta; and an evaluation of the interfoetal membranes by experienced radiologists [23]. Only those who underwent IVF-ET, ultrasound examinations and MFPR at our hospital were included in this study. Patients with spontaneous reductions (n = 119) or pregnancy loss (n = 57) before 11–13^{+6} gestational weeks, with selective reductions at other centres (n = 1) and who were lost to follow-up (n = 1) were excluded from this analysis. Finally, 298 patients with DCTA pregnancies with three viable foetuses until 11–13^{+6} gestational weeks were included for data analysis (Figure 1). When a foetal heartbeat was detected by ultrasound, the pregnancy was considered viable. GA was the date of embryo transfer (ET) plus 17 or 19 days for day–3 embryo or blastocyst transfers, respectively.

All patients were counselled regarding the risks of DCTA pregnancy and the different options for their management, either to undergo MFPR or to be managed expectantly. The reason for MFPR could be either a structural abnormality in one or two of the foetuses or patient preference. The procedure was performed transabdominally by ultrasound-guided intrathoracic injection of potassium chloride (10% KCl, 2 ml) using a 20 G spinal needle (15 cm in length). All reductions were performed by a highly skilled physician (Dr. Yan Shen). MFPRs were undertaken during 11–13^{+6} gestational weeks (58–80 days after ET) after a nuchal translucency (NT) scan. The selection of foetuses to be reduced was based on the NT scan exam and accessibility. If one or both of the MCDA twins of the DCTA pregnancy had an abnormal NT, both of them were reduced because of the presence of vascular connections between MC twins, and

if the MC singleton of the DCTA pregnancy had an abnormal NT, this foetus was reduced. If all foetuses had a normal NT, the reduction of the MC singleton or MCDA twins relied on patient preference and foetal accessibility. Eighty-four DCTA triplets were reduced to MC singleton pregnancies (group A), 149 DCTA triplet pregnancies were reduced to MCDA twin pregnancies (group B), and 65 DCTA pregnancies were managed expectantly (group C).

The maternal demographic characteristics, ultrasound findings and procedure details of the IVF-ETs and MFPRs were recorded in the medical records. The pregnancy and obstetric outcomes were followed up by telephone or fax. The pregnancy and perinatal outcomes were defined as follows: miscarriage was defined as pregnancy loss before 20 gestational weeks; preterm delivery referred to childbirth at a minimum of 20 gestational weeks but before 37 gestational weeks; very preterm birth (VPB) was defined as delivery at or later than 20 gestational weeks but before 32 gestational weeks; and term delivery was defined as delivery at or later than 37 gestational weeks but before 42 gestational weeks [24]. Additionally, a live birth was defined as the delivery of a live infant after 20 gestational weeks who survived for at least 7 days. A stillbirth was defined as the delivery of a deceased infant after 20 gestational weeks [25]. Perinatal mortality included stillborn infants at 20 gestational weeks and neonatal deaths of live-birth infants during the first 28 days [26]. Low birth weight (LBW) was defined as a birth weight less than 2500 g, and very low birth weight (VLBW) was defined as a birth weight less than 1500 g [24].

Statistical analyses were conducted using SPSS version 17.0 software (SPSS, Inc., Chicago, IL, USA). Descriptive statistics are presented as the means ± standard deviations (SDs) and as percentages for the enumerated data. Differences in the means between the two groups were analysed using Student's t-test. The chi-squared test or Fisher's exact test was used to determine statistical significance between percentages. Statistical significance was set at $P< 0.05$.

Results

Groups A, B and C were statistically similar regarding maternal age (29.6 ± 4.2 vs. 29.4 ± 3.9 vs. 28.4 ± 3.7 years), body mass index (21.5 ± 2.7 vs. 21.7 ± 3.0 vs. 21.9 ± 3.1 kg/m^2), infertility duration (4.4 ± 3.5 vs. 4.3 ± 2.8 vs. 4.1 ± 3.2 years), transfer cycles (1.2± 0.5 vs. 1.1± 0.5 vs. 1.1± 0.5), infertility type, cause of infertility, and insemination methods (P > 0.05) (Table 1).

Group A had significantly lower rates of preterm delivery (11.9 vs. 89.2%; odds ratio (OR) 0.016, 95% confidence interval (CI) 0.006–0.045; P < 0.001), caesarean section (CS, 66.3 vs. 83.6%; OR 0.385, 95% CI 0.169–0.875; P = 0.02), VPB (6.3 vs. 26.2%; OR 0.188, 95% CI 0.064–0.547; P = 0.001), LBW (9.2 vs. 92.9%; OR 0.008, 95% CI 0.003–0.021; P < 0.001), VLBW (0 vs. 16.9%; P < 0.001) and perinatal mortality (5.0 vs. 15.8%; OR 0.279, 95% CI 0.095–0.824; P = 0.015) than group C. GA at delivery (37.9 ± 3.8 vs. 32.8 ± 3.7 weeks; P < 0.001) and the live birth weight (3168 ± 557 vs. 1863 ± 410 g; P < 0.001) were significantly higher in group A than in group C. Additionally, there was no significant difference in the

miscarriage rate (4.8 vs. 6.2%; OR 0.763, 95% CI 0.183–3.172; P = 0.729) or live birth rate (90.5 vs. 86.2%; OR 1.527, 95% CI 0.554–4.205; P = 0.411) between these two groups (Table 2).

Group B had significantly lower rates of preterm delivery (51.7 vs. 89.2%; OR 0.129, 95% CI 0.055–0.301; P < 0.001), neonatal death (1.0 vs. 4.4%; OR 0.229, 95% CI 0.060–0.873; P = 0.027), VPB (11.7 vs. 26.2%; OR 0.374, 95% CI 0.174–0.801; P = 0.01), LBW (59.0 vs. 92.9%; OR 0.111, 95% CI 0.057–0.214; P < 0.001) and VLBW (4.4 vs. 16.9%; OR 0.226, 95% CI 0.108–0.471; P < 0.001) than group C. In addition, GA at delivery (35.0 ± 4.2 vs. 32.8 ± 3.7 weeks; P = 0.001) and the live birth weight (2351 ± 484 vs. 1863 ± 410 g; P < 0.001) were significantly higher in group A than in group C. There was no significant difference in the miscarriage rate (2.7 vs. 6.2%; OR 0.421, 95% CI 0.102–1.737; P = 0.249) or live birth rate (87.2 vs. 86.2%; OR 1.100, 95% CI 0.469–2.580; P = 0.827) between these two groups (Table 3).

In addition, Group A had significantly lower rates of preterm delivery (11.9 vs. 51.7%; OR 0.126, 95% CI 0.061–0.263; P < 0.001), CS (66.3 vs. 82.1%; OR 0.429, 95% CI 0.229–0.804; P = 0.007), LBW (9.2 vs. 59.0%; OR 0.071, 95% CI 0.031–0.160; P < 0.001) and perinatal mortality (5.0 vs. 13.4%; OR 0.339, 95% CI 0.117–0.978; P = 0.037) than group B. Additionally, GA at delivery (37.9 ± 3.8 vs. 35.0 ± 4.2 weeks; P < 0.001) and the live birth weight (3168 ± 557 vs. 2351 ± 484 g; P < 0.001) were significantly higher in group A than in group B. However, there was no significant difference in the miscarriage rate (4.8 vs. 2.7%; OR 1.813, 95% CI 0.441–7.443; P = 0.464) or the live birth rate (90.5 vs. 87.2%; OR 1.388, 95% CI 0.580–3.325; P = 0.46) between these two groups (Table 4).

Discussion

In the present study, we analysed the pregnancy and obstetric outcomes of women with a DCTA pregnancies conceived from IVF-ET who underwent MFPR at 11–13^{+6} gestational weeks or were managed expectantly. We demonstrated that the MFPR of DCTA pregnancies to either MC singleton or MCDA twin pregnancies improved the pregnancy and obstetric outcomes, by significantly decreasing the risks of preterm delivery, VPB and LBW and significantly increasing the GA at delivery and the live birth weight, without significantly reducing the miscarriage risk or the live birth rate. Specifically, among the options for management, the reduction of DCTA pregnancies to MC singleton pregnancies resulted in minimal risks for VPB, CS, perinatal mortality and LBW; a maximal GA at delivery; and a maximal live birth weight.

The most frequently applied method for MFPR is ultrasound-guided transabdominal injection of KCl into the foetal heart or thoracic cavity, which has been shown to be relatively safe [27]. In the present study, MFPR was performed for 233 DCTA pregnancies with the injection technique. Ultrasound examination within 24 hours of the procedure demonstrated that retained MC singletons or retained MCDA twins were all alive, and only 1.3% (3/233) of cases (2 cases of DCTA pregnancy reduced to a singleton pregnancy and 1 case of DCTA pregnancy reduced to a MCDA pregnancy) miscarried in the subsequent 2 weeks. The procedure was technically successful in all cases.

Women with DCTA pregnancies carry both the risk associated with triplets, such as VPB, selective growth restriction and foetal malformation, and the risks associated with MC twins due to vascular anastomoses in the single placental bed, such as twin-to-twin transfusion syndrome (TTTS) and selective intrauterine growth restriction (SIUGR) [5, 28]. Patients should be informed in detail about all possible complications. Data from previous studies [29, 30] demonstrated that MFPR is effective and feasible in decreasing some adverse outcomes for pregnancies with MC pairs.

Some studies [5, 29, 31] indicated that when the reduction of dichorionic (DC) triplet pregnancy to MC singleton pregnancy was compared to expectant management, reduction resulted in a significantly decreased risk of preterm birth (< 34 gestational weeks), an increased GA at delivery and an increased birth weight, as well as a non-significantly increased risk of miscarriage (< 24 gestational weeks). Similarly, the present data showed that in DCTA pregnancies that were reduced to singleton pregnancies, the VPB rate decreased by 26.2 to 6.3%, the GA at delivery increased from 32.8 to 37.9 weeks, and the live birth weight increased from 1863 to 3168 g; however, the impact on the miscarriage rate (4.8 vs. 6.2%, respectively) was limited.

A systematic review and meta-analysis in the literature [16] demonstrated that the reduction of a DCTA pregnancy to a MC twin pregnancy (n = 15) neither significantly increased the risk of miscarriage (< 24 gestational weeks; 13.3% vs. 8.5%, respectively) nor significantly decreased the risk of preterm birth (< 34 weeks; 46.2 vs. 51.9%, respectively) compared with expectant management (n = 200). In contrast, there was a significant decrease in the VPB rate from 26.2 to 11.7% and a slight decrease in the miscarriage rate from 6.2 to 2.7% among DCTA pregnancies reduced to MCDA pregnancies in the present study. The difference in outcomes between the meta-analysis and the present data is potentially due to an inadequate number of patients with DCTA pregnancies reduced to MC twin pregnancies in the meta-analysis.

Reduction in women with a MC twin pregnancy is not appropriate by injection because of inter-twin placental vascular anastomoses. In addition, acute haemorrhage of the survivor may occur soon after the death of the co-twin through placental vascular anastomoses [32]. Relatively new vascular-occlusive techniques have enabled the possibility of a triplet pregnancy containing a MC twin pregnancy reduced to a DC twin pregnancy. However, the risks of these complication-associated techniques and the potentially increased rate of the intrauterine demise of the co-twin that have been reported with limited data make vascular-occlusive techniques an unattractive option for the management of triplet pregnancies with MC twins [3, 32, 33]. Chaveeva P *et al.* [34] reported 61 DC triplet pregnancies that were reduced to DC twin pregnancies by intrafoetal laser ablation; 45.9% of co-twins were miscarried within the subsequent 2 weeks, which was likely attributed to incomplete vascular occlusion and retrograde haemorrhage of the survivor through placental vascular anastomoses into the dead co-twin. Based on the uncertainty regarding the balance between the benefits and risks, we have not applied these techniques to the reduction of DC triplet pregnancies.

Rong Li *et al.* [30] reported that the MFPR of DC triplet pregnancies to singleton pregnancies had better pregnancy outcomes than those reduced to DC twin pregnancies by early transvaginal embryo reduction, which was consistent with the findings of the present study. The present data showed that reduction of DCTA pregnancies to singleton pregnancies further decreased the risks of LBW and perinatal mortality and further increased the live birth weight compared with reduction to MCDA pregnancies.

To our knowledge, this is the largest study to examine the outcomes of patients with DCTA pregnancies via IVF-ET undergoing MFPR or expectant management. However, this study also has some limitations. One limitation of the present study is the lack of data regarding morbidity among live infants, which is obviously more important than the live rate alone, and successful ART is defined as the delivery of a healthy and living baby by an infertile patient. In addition, our centre is only a reproductive centre, and all pregnancy outcomes were obtained by telephone call or fax; therefore, we do not have reliable information about the frequency of TTTS in DCTA pregnancies reduced to MCDA pregnancies or in those that were managed expectantly. This was a retrospective analysis, and we probably missed some information regarding women who conceived DCTA triplets. Additionally, these women with DCTA pregnancies reduced to MCDA pregnancies were exposed to the risks of TTTS and SIUGR.

In summary, in women with DCTA pregnancies conceived from IVF-ET who underwent MFPR at 11–13^{+6} gestational weeks or were managed expectantly, the MFPR of DCTA pregnancies to either singleton and MCDA pregnancies resulted in better pregnancy outcomes than the pregnancies that were managed expectantly. The perinatal outcomes of the reduction of DCTA pregnancies to singleton pregnancies were better than those of the reduction of DCTA pregnancies to MCDA pregnancies. Our data can assist physicians in counselling patients with DCTA pregnancies via IVF-ET; however, reduction is a remedial measure to reduce a MFP. We recognize that the most effective measure to prevent unnecessary MFPs is to restrict the number of embryos transferred in women undergoing ART and encouraging selective single-blastocyst transfers.

Abbreviations

DCTA: dichorionic triamniotic; IVF-ET: in vitro fertilization-embryo transfer; MCDA: monochorionic diamniotic; OR: odds ratio; CI: confidence interval; LBW: low birth weight; MFP: multifoetal pregnancies; ART: assisted reproductive technology; HOMPs: higher-order multiple pregnancies; MC: monochorionic; GA: gestational age; NT: nuchal translucency; VPB: very preterm birth; ET: embryo transfer; VLBW: very low birth weight; SDs: standard deviations; CS: caesarean section; TTTS: twin-to-twin transfusion syndrome; SIUGR: selective intrauterine growth restriction; DC: dichorionic.

Declarations

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Availability of data and material

The data analysed during this study are included in the tables in this published article. The datasets used during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Pei Cai performed the study design, literature search, data extraction, statistical analysis, and the writing and revision of the manuscript. All authors contributed to the design of the study. Xihong Li, Fei Gong and Yan OuYang interpreted the study findings and performed the overall quality assessment and revision of the final manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Reproductive and Genetic Hospital of CITIC-Xiangya (LL-SC–2019–013).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Due to technical limitations, all Table(s) are only available as a download in the supplemental files section.

Figures

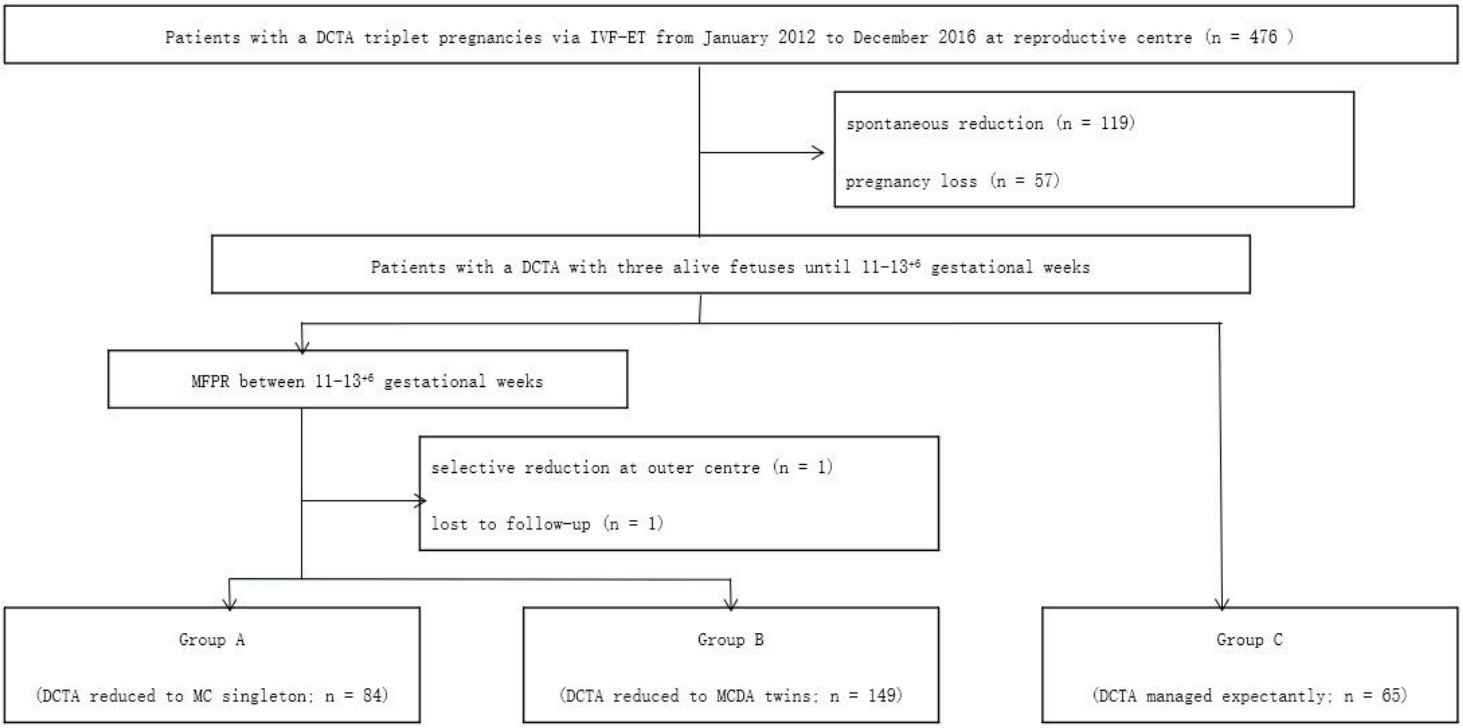

Figure 1

Flow diagram showing the cases included in among group A, B and C. DCTA = dichorionic triamniotic; IVF-ET = in vitro fertilization-embryo transfer; MFPR = multifoetal pregnancy reduction; MCDA = monochorionic diamniotic.

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