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Early fetal reduction of dichorionic triplets to dichorionic twin or singleton pregnancies: a retrospective study




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Abstract A retrospective study conducted in an academic reproductive medicine centre evaluated the feasibility and safety of early fetal reduction in dichorionic triplets to dichorionic twin or singleton pregnancies. Thirty-three dichorionic triplets that underwent early transvaginal fetal reduction mechanically between 2002 and 2013 were included, of which 21 patients underwent fetal reduction to dichorionic twins (Group A) and 12 patients underwent fetal reduction to a singleton pregnancy (Group B). A further 84 patients with trichorionic triplets reduced to twins were included as the control group (Group C). The main outcome measures were live birth and preterm labour rates. Both early and late spontaneous abortion rates, were similar in group A compared with groups B and C. Gestational age at delivery was significantly lower in group C versus group A ($P = 0.02$). The preterm labour rate in group A, which was comparable with that in group C, was greater than in group B, but not significantly. Neonatal birth weight, low birth weight rate and neonatal body height were similar among groups. Small for gestational age rates were comparable. Live birth rates were similar among the groups. Early transvaginal fetal reduction for dichorionic triplets to dichorionic twins may be feasible and safe. 

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KEYWORDS: dichorionic triplets, dichorionic twins, early fetal reduction

Introduction

With the increasing success of artificial reproductive techniques, the rate of multiple pregnancies has increased significantly compared with that in natural conception, which is less than 1%. Multiple pregnancies, particularly monochorionic twins or triplets, are associated with an increased risk of maternal and neonatal complications, such as preterm delivery and neonatal low birth weight. Multifetal pregnancy reduction (MPR) is an effective method to decrease the rate of complications, and several methods of MPR have been reported. Transabdominal MPR between 11–14 weeks of gestation is the most widely used procedure. Early MPR is seldom used, even though it obtains good results.

Monozygotic triplets occur in 0.004% of pregnancies at most (Imaizumi, 2003). In cases of dichorionic triplets, it is usually recommended to reduce the dichorionic twins to a monochorionic singleton pregnancy to avoid the complication of twin to twin transfusion syndrome (TTTS).

In China, with the effect of the family planning policy, couples are increasingly eager to have two babies in one delivery. Therefore, the requirements of patients with dichorionic triplets are discussed. Almost a decade ago, early transvaginal fetal reduction in dichorionic triplets was rarely attempted. In this present study, data were retrospectively analysed to evaluate the feasibility and safety of early fetal reduction in dichorionic triplets to dichorionic twin pregnancies.

Materials and methods

Study patients

A total of 141 patients with twin or multiple (triplet and quadruplet) pregnancies underwent early (6–8 gestational weeks) fetal reduction at Sun Yat-sen Memorial Hospital between January 2000 and December 2013, resulting from IVF and embryo transfer or intrauterine insemination (IUI). Medical records of patients who received early fetal reduction of transvaginal fetal puncture and aspiration were retrospectively reviewed. In total, 33 dichorionic triplets were included in this study. Another 84 patients with trichorionic triplets who retained twins were included as a control. Only those patients who completed assisted reproduction techniques and multifetal reduction in our centre were included in this study. Therefore, complete follow-up was available.

The following data were retrieved from medical records: maternal age, body mass index, duration of infertility, maternal gravity, fetal reduction procedure, gestational age (in weeks) at the day of abortion or delivery, birth weights, number of live-born infants and any deformity. Chorionicity was determined according to the report by Sepuvela et al. (1996). The 33 included patients with dichorionic triplets were divided into two groups, of which 21 patients received fetal reduction to dichorionic twins (reduction of one fetus in monochorionic twins) (Group A), and the other 12 received fetal reduction to singleton pregnancy (reduction of both fetuses in monochorionic twins) (Group B). Simultaneously, 84 patients who retained twins (reduction from trichorionic triplets to twins) (Group C) were included for comparison with

Group A. We mainly compared the patients' characteristics and obstetric outcomes of dichorionic triplets that either underwent reduction to twins or singletons. In China, Institutional Review Board and ethical committee approval was not required for the present study due to its retrospective nature.

Multifetal pregnancy reduction (MPR) procedure

Patients were counselled on the risk of higher spontaneous abortion and preterm labour rates in multiple pregnancies and offered the option of fetal reduction. If the couples chose to proceed, the possible risks of the procedure were explained and informed consent was obtained. Especially for dichorionic triplets, reduction into singleton pregnancy was recommended unless the patients strongly wanted to keep two fetuses.

According to patient or physician preference, all of MPR procedures were conducted at 6–8 weeks of gestational age and were carried out by experienced operators in our centre. Before the procedure, a transvaginal ultrasound scan was undertaken to determine the number, location, and sizes of the fetuses and gestational sacs. Fetal heart beats were confirmed in each fetus before starting the procedure. The procedure was not carried out under anesthesia, and 100 mg phenobarbital (Luminal, Tianjin kingyork group CO., LTD. CHINA) was administered intramuscularly for pain relief. The upper and most easily accessible fetus was selected for reduction. The fetus chosen for reduction was the most easily accessed of the dichorionic twins for dichorionic triplets, the fetus closest to the needle in trichorionic triplets, or both monochorionic twins for dichorionic triplets. The reduction of one or two fetuses of dichorionic triplets was according to patient preference. Fetal reduction was achieved by puncturing and aspirating embryonic parts, with no drug injection. A transvaginal ultrasound guided technique was used. A 16-gauge needle was advanced into the site of the fetal heart beat mechanically until the heart beat was arrested. Patients were advised to undergo bed rest for a few hours.

Follow-up

All patients underwent subsequent prenatal routine follow-up in high-risk pregnancy clinics. Hospitalization was only required for obstetric indications. Transvaginal ultrasound examinations were carried out after 1 day, 3 days, 1 week and 1 month. Spontaneous reduction was described as a missed abortion of one fetus in the twin pregnancy after fetal reduction, resulting in a singleton pregnancy. Spontaneous abortion was defined according to the Chinese Ministry of Health as early abortion if it occurred before 12 gestational weeks or late abortion if it occurred between 12–27⁺6 gestational weeks, and preterm labour was delivery between 28–37 gestational weeks. Low birth weight is defined as birth weight less than 2500 g. Small for gestational age infant was defined as birth weight lower than the tenth percentile of the normal neonatal birth weight at the same gestational age. Obstetric outcome and neonatal outcomes were followed up by telephone calls or faxes from a specified person at our center.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 16.0 (SPSS Inc., USA) was used for data analysis. Outcome measures were compared by chi-squared tests with Yates correction, by Fisher's exact tests or by *t*-tests, analysis of variance and rank tests for non-parametric values, as appropriate. A two-tailed probability value below 0.05 was considered statistically significant.

Results

Patients in groups A, B and C were similar in clinical characteristics, such as maternal age, body mass index, duration of infertility and embryo origin. The mean number of embryos transferred in group C was significantly higher than in group A ($P < 0.01$). The mean gravidity and serum HCG level at the first check-up were not significantly different between groups. Four cases of trichorionic triplets were from IUI in group C. The average gestational age at which fetal reduction took place was 6.97–7.73 weeks. No significant difference was observed in the mean gestational weeks at reduction between groups A and C. The mean gestational weeks at reduction in group B, however, was significantly higher than in group A (7.73 ± 0.96 versus 6.97 ± 0.57 , $P = 0.01$) (Table 1).

Spontaneous abortion occurred in eight cases, early abortion in two cases and late abortion in six cases. The spontaneous abortion rate for both early and late abortions was comparable between groups A and B and groups A and C. Spontaneous reduction to singletons after transvaginal fetal reduction occurred in eight cases in group A and five cases in group C. Significant difference in mean weeks of delivery were observed between groups A and C (37.30 ± 1.43 versus 36.09 ± 2.14 ; $P = 0.02$). The preterm labour rate in group A,

which was comparable with that of group C, was higher than that of group B, but not significantly (40% versus 11.11%). No significant difference was observed in the week of preterm labour week (28–34 weeks versus 34⁺ to 37 weeks). Neonatal birth weight, low birth weight rate and neonatal body height were similar between groups A and B and groups A and C. Rates of SGA were also comparable. Live birth rates were similar among groups. The proportion of singleton live births, however, was significantly higher in group A than in group C ($P < 0.001$). The proportion of twin live births in group C was higher than that in group A ($P < 0.001$) (Table 2). In group A, one case underwent artificial induction of labour owing to lung tuberculosis and one neonatal malformation defined as a head tumour. In group B, one case underwent artificial induction of labour due to fetal malformations.

Discussion

Monozygotic multiple pregnancies occur when a single embryo splits before the eighth day after fertilization. If the split occurs in the first 3 days after fertilization, dichorionic, diamniotic gestations occur. If the split occurs between 4 and 8 days after fertilization, a monochorionic, multi-amniotic gestation occurs (Newman, 2003). Several causative factors have been related to the occurrence of monozygotic multiple pregnancies after assisted reproduction technique procedures, including ovarian stimulation, manipulation of the zona pellucida, assisted hatching, intracytoplasmic sperm injection, blastocyst transfer, suboptimal culture conditions, and maternal age (Henne et al., 2005).

Risks associated with multiple pregnancies include higher rates of perinatal mortality, preterm birth, low birth weight, gestational hypertension, placental abruption, and placenta previa (Allen et al., 2006). Monochorionic twins have

Table 1 Patient characteristics in group A compared with groups B and C.

	Group A (n = 21) ^a	Group B (n = 12) ^b	Group C (n = 84) ^c	P-value
Maternal age (years)	31.29 ± 3.42	32.00 ± 3.84	31.60 ± 4.06	NS
Maternal body mass index (kg/m ²)	21.16 ± 3.28	20.40 ± 1.42	21.18 ± 2.31	NS
Duration of infertility (years)	4.71 ± 2.78	5.17 ± 2.12	5.13 ± 2.83	NS
Number of embryos transferred	2.14 ± 0.36	2.33 ± 0.49	2.96 ± 0.25	<0.01 ^d
Number of top-quality embryos transferred	1.24 ± 0.89	1.25 ± 0.97	1.49 ± 0.86	NS
Embryos origin				NS
FET	5	3	28	
IVF	14	9	40	
ICSI/half-ICSI/PESA	2	0	12	
IUI	0	0	4	
Gravidity	0.71 ± 1.15	1.13 ± 1.06	0.93 ± 1.02	NS
HCG level of first check(IU/l)	1058.80 ± 641.40	1015.61 ± 808.13	1388.95 ± 982.00	NS
Gestational weeks at reduction	6.97 ± 0.57	7.73 ± 0.96	7.13 ± 0.80	0.01 ^e

FET, frozen embryo transfer; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; PESA, percutaneous epididymal sperm aspiration.

^aGroup A = dichorionic triplets reduced to dichorionic twins.

^bGroup B = dichorionic triplets reduced to singleton pregnancy.

^cGroup C = trichorionic triplets reduced to twins.

^dComparison between group A and group C.

^eComparison between group A and group B.

Table 2 Obstetric outcomes in group A compared with groups B and C.

	Group A (n = 21) ^a	Group B (n = 12) ^b	Group C (n = 84) ^c	P value
Spontaneous abortion rate (%)	4.76 (1/21)	16.67 (2/12)	5.95 (5/84)	NS
Early abortion rate (%)	0 (0/21)	8.33 (1/12)	1.19 (1/84)	NS
Late abortion rate (%)	4.76 (1/21)	8.33 (1/12)	4.76 (4/84)	NS
Spontaneous reduction (n)	8	–	5	
Gestational age at delivery (weeks)	37.30 ± 1.43	37.88 ± 1.41	36.09 ± 2.14	0.02 ^d
Preterm labour rate (%)	40 (8/20)	11.11 (1/9)	41.77 (33/79)	NS
Preterm labour week				
28–34 weeks	1	0	9	NS
34 ⁺ to 37 weeks	7	1	24	NS
Neonatal birth weight (kg)	2.60 ± 0.52	2.95 ± 0.29	2.43 ± 0.48	NS
Low birth weight rate (%)	41.94 (13/31)	11.11 (1/9)	47.06 (72/153)	NS
Small for gestational age rate (%)	16.13 (5/31)	11.11 (1/9)	19.61 (30/153)	NS
Neonatal body height (cm)	48.81 ± 2.18	48.20 ± 0.84	47.56 ± 2.02	NS
Live birth rate (%)	19/21 (90.48)	9/12 (75.00)	79/84 (94.05)	NS
Singleton live births (%)	8/21 (38.10)	9/12 (75.00)	5/84 (5.95)	<0.001 ^d
Twin live births (%)	11/21 (52.38) ^e	–	74/84 (88.10)	<0.001 ^d

^aGroup A = dichorionic triplets reduced to dichorionic twins (one case underwent medium-term abortion because of tuberculosis).

^bGroup B = dichorionic triplets reduced to singleton pregnancy (one case underwent medium-term abortion because of fetal malformation).

^cGroup C = trichorionic triplets reduced to twins.

^dComparison between group A and group C.

^eOne neonatal malformation defined as head tumour.

a six-fold higher pregnancy loss rate before 24 weeks of gestation and two- to three-fold greater risk of stillbirth and early neonatal death than dichorionic twins. These differences could be attributed to several pathological conditions, such as twin to twin transfusion syndrome and severe birth weight discordance (Gibson and Cameron, 2008). Thirty years ago, MPR was developed to decrease the risks of multiple gestations by reducing the number of live fetuses. It has been proven to be effective. Currently, transabdominal intrathoracic injection of potassium chloride at 11–14 weeks is more widely used, followed by intracranial injection of potassium chloride at 12–18 weeks. Umbilical cord ligation using fetoscopy for fetal reduction and transvaginal fetal aspiration performed at 6–8 weeks of gestation are developing alternatives.

Dichorionic triplets are rare that no consensus has been reached on fetal reduction. Fetal reduction of monochorionic twins and keeping a singleton pregnancy is usually recommended (Geipel et al., 2005; Ulug et al., 2004). To the best of our knowledge, early mechanical fetal reduction in dichorionic triplets to dichorionic twins has rarely been addressed in previous studies (De Catte et al., 2002). Alternatively, the fetal reduction of one of the monochorionic twins only is not attempted because of the risk of injected potassium chloride (KCl) being transferred to the co-twin through the intertwin placental vascular anastomoses, or the death of one fetus leading to haemorrhage from the co-twin into the dead fetoplacental unit, with consequent death or neurodevelopmental impairment. Previous studies (Chaveeva et al., 2013, 2014; Kumar et al., 2013; Lu et al., 2013; Spadola and Simpson, 2005) have proposed a new technique for fetal reduction in dichorionic triplet pregnancies to twins that involves ultrasound-guided laser ablation, radiofrequency ablation, and intrafetal lasering of the pelvic vessels of one of the monochorionic twins in the second trimester 10–14 weeks. It has been reported that the early transvaginal non-KCl method

was a better option for MPR (Lee et al., 2008). Early reduction has two major drawbacks. The first is the possibility that spontaneous reduction of one of the twins may occur later, eliminating the need for fetal reduction, and the second is the inability during early gestation to choose the “right” fetus for reduction, which may result in the reduction of a normal fetus instead of reducing the abnormal one. Despite some controversy, early multifetal reduction from triplets and higher order pregnancies to twins has been increasingly accepted as a therapeutic procedure. One of the hypotheses explaining the favourable perinatal outcome after early MPR is that most of the fetoplacental tissue is aspirated in early MPR as opposed to reduction at 11–14 weeks and therefore may prevent the development of an inflammatory response to the resorbing necrotic fetoplacental tissues.

Previous studies have also shown that the pregnancy outcome of twins after MPR carried out between 11 and 14 weeks was similar to those of non-reduced dichorionic twins (Groutz et al., 1996; Hershko-Klement et al., 2013; Nevo et al., 2003). It is questionable, however, whether the obstetric outcomes of dichorionic twins are similar to singletons from dichorionic triplets and twins from trichorionic triplets after reduction. In 2009, our colleague Professor Li first reported an extremely rare case of a quadruple gestation with one monochorionic triamniotic triplet gestation and one monochorionic monoamniotic singleton gestation after intracytoplasmic sperm injection and the transfer of two day-3 embryos, with selective reduction to a dichorionic twin pregnancy (Li et al., 2009), ultimately achieving a satisfying outcome. To the best of our knowledge, although this research is not the only study to report early mechanical fetal reduction in dichorionic triplets to dichorionic twins, it is the largest series described so far.

The present study showed that the number of embryos transferred mostly resulted in trichorionic triamniotic triplets.

Chorionicity is a major determinant of outcome among multiple pregnancies. Spontaneous abortion among twin pregnancies was reported in one pregnancy with monochorionic placentation in a triplet pregnancy with dichorionic and monochorionic placentation, and was preceded by spontaneous reduction of a fetus in the first trimester (Oloyede et al., 2012). In our study, the mean age in gestational weeks at fetal reduction was greater in group B, which implied a bias in patient selection. For those patients close to 8 gestational weeks with longer crown-rump length, there was a tendency to choose the reduction of two of the monochorionic twins. The spontaneous abortion rate was higher in group B than the other two groups, although the difference did not reach statistical significance, which may be due to the small scale of the study. The lack of a significant difference in the abortion rate between groups in the current study contrasts with a previous study (Li et al., 2013). The number of gestational weeks at delivery was the highest in group B for singleton pregnancies after reduction. Although most of the patients in groups A and C carried twin pregnancies, the number of weeks at delivery in group A was significantly higher than that in group C. This can be explained by the fact that more patients carried singleton pregnancies in group A, including eight cases (8/21 [38.10%]) resulting from spontaneous reduction to singletons after transvaginal fetal reduction, but there were only five cases (5/84 [5.95%]) in group C. This can be clearly found in measurements of the live birth rates of single birth and twins. After early fetal reduction, over 50% of dichorionic triplets resulted in the live birth of twins.

Only one case of neonatal head tumours was found in group A. A previous study discussed malformations as a case report (Paradis et al., 2002). Our study set the time of delivery as the end-point of analysis, meaning that a comparison of the malformation rate was limited.

In China, the number of embryos to be transferred was limited according to the individual patient age and cycle characteristics. In patients under the age of 35 years in the first assisted reproduction technique cycle, no more than two embryos should be transferred and no more than three embryos can be transferred under any circumstances. Recently, decisions were made on the basis of embryo quality, including the fact that no more than two blastocysts were allowed to be transferred. In our centre, the infertility specialist routinely informs patients about the risks of multiple pregnancies after transfer and fetal reduction, and ultimately the couples decide how many embryos to be transferred according to the national policies. In general, infertile couples mostly preferred twins as the first and only choice to make up for lost time and considered them a convenient way to have two children in one pregnancy without being limited by China's family planning policy. On the basis of our previous experiences and some patients' strong desires to retain twins, we tried to reduce only one fetus of monochorionic twins in dichorionic triplet pregnancies.

The limitations of the present study should be mentioned. First, the present study is a retrospective comparative study of the MPR of dichorionic triplets to twins or singletons, and not a randomized controlled trial; therefore, confounding factors could have influenced the results, such as patient selection and the small number of patients. This study, however, may not provide an appropriate point

of reference, as reduction to singletons may have often been carried out as a result of maternal high-risk obstetric conditions or other non-pregnancy-related reasons. Only a few studies (Haas et al., 2014; Lee et al., 2008) have reported obstetric complications such as gestational diabetes and placenta previa, which were not analysed in this study.

Our study shows that early fetal reduction of dichorionic triplet gestations to dichorionic twins obtained almost similar obstetric outcomes to that of a dichorionic triplet gestation reduced to a singleton pregnancy. It should be emphasized that a number of patients whose pregnancies were initially reduced to twins subsequently underwent spontaneous reduction to singletons after transvaginal fetal reduction. Additionally, the spontaneous abortion rate did not noticeably increase. In summary, fetal reduction in the early phase (6–8 gestation weeks) for dichorionic triplets to dichorionic twins may be feasible and safe. For some infertile couples, reduction to dichorionic twins may be a preferred alternative.

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