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Multifetal pregnancy reduction outcomes from triplets to singletons and twins

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Abstract

Objective: To study the obstetric and neonatal outcomes of reduction to singleton and twin pregnancies by multifetal pregnancy reduction (MPR) in patients with triplet pregnancies.

Methods: The multifetal reduction was performed in 27 patients with triplet pregnancies. Fourteen patients were reduced to singleton pregnancies and 13 patients to twin pregnancies. Obstetric and neonatal outcomes were compared between the two groups.

Results: The mean gestational age at the time of the procedure was 12.43±0.76 weeks in patients reduced to singleton pregnancies and 12.08±0.64 weeks in those reduced to twin pregnancies. The most common complications of the procedure were abdominal pain (21.4%) in women with singleton pregnancies and both the presence of abdominal pain and vaginal bleeding (30.8%) in women with twin pregnancies. Gestational age at birth (33.07±5.73 versus 35.78±6.14 weeks, p=0.009) and neonatal birth weight (1998.46±808.07 versus 2765±803.03 gram, p=0.003) was significantly higher in the group reduced to singleton pregnancies than in twin pregnancies.

Conclusion: The MPR procedure is a good and acceptable option for patients with multiple pregnancies of three or more children. Multifetal pregnancy reduction of triplets to singletons is associated with better pregnancy outcomes such as birth at higher weeks of gestation and higher neonatal birth weight than MPR of triplets to twins.

Keywords: Multiple pregnancies, multifetal pregnancy reduction.

Introduction

The widespread use of ovulation induction agents and assisted reproductive technologies have significantly increased the incidence of multiple pregnancies in recent years.[1–4] Efforts are being made to reduce the incidence of these multiple pregnancies by limiting the number of embryos transferred in women undergoing assisted reproductive technologies.[5] However, this situation cannot be completely avoided, as a triplet or multiple pregnancies with monozygotic twins may occur after single or double embryo transfer, or multiple pregnancies with triples or more may occur after ovulation induction.[6] Although good clinical practice in multiple pregnancies has increased in recent years,[7] multiple pregnancies with triplets or more, in particular, are associated with an increased number of adverse obstetric and perinatal outcomes,[8–10] and these risks increase with the number of fetuses.[11] To reduce the increased maternal and perinatal risks associated with multiple pregnancies, fetal reduction has been incorporated into the management of multiple pregnancies.[11] The most commonly used multifetal pregnancy reduction (MPR)

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method is intrathoracic potassium chloride (KCl) injection, administered transabdominally at 11–14 weeks of gestation.[1] The other alternative methods for MPR are transvaginal fetal aspiration in 6–8 weeks of gestation, intrafetal laser embryo reduction, radiofrequency ablation, and microwave ablation.[11–13]

Maternal and perinatal outcomes have improved after fetal reduction in multiple pregnancies.[11] Specifically, it has been reported that reduction from triplet pregnancies to twin pregnancies is associated with better pregnancy outcomes such as higher perinatal survival and lower preterm birth compared to triplet pregnancies.[8,14] However, few studies are investigating obstetric and perinatal outcomes after reducing triplet pregnancies to twins or singletons.[1,15,16] This study aimed to compare the obstetric and perinatal outcomes of triplet pregnancies after reduction to singleton or twin pregnancies in a single tertiary center.

Methods

This retrospective cohort study was conducted between June 2016 and October 2018 at Istanbul Kanuni Sultan Suleyman Training and Research Hospital, a prenatal diagnosis and treatment center. After approval from the ethics committee of our hospital, data were collected from all triplet pregnant women who underwent elective fetal reduction to twin or singleton pregnancy in our hospital during the study period.

The study group included triplet pregnancies (n=27) in which MPR was performed between 11–14 weeks of gestation. Before the procedure, all patients were informed about the expected risks and benefits in triplet pregnancies and after MPR in singleton or twin pregnancies. The patients were offered the option to reduce the number of embryos based on the current literature on expected outcomes in triplet pregnancies compared to outcomes after MPR. The decision to reduce to twins or a single embryo was based on the patients' personal preferences and the technical feasibility of fetal reduction. Fetuses to be reduced were selected primarily on the basis of the presence of fetal abnormalities, chorionicity, and ease of use of the procedure. According to this, all dichorionic triamniotic (DCTA) triplet pregnancies (n=11) were reduced to singleton pregnancies to avoid the adverse outcomes of monochorionic twin pregnancies. Of the 16 trichorionic triamniotic (TCTA) triplet pregnancies, 13 were reduced to dichorionic diamniotic twin pregnancies and 3 to singleton pregnancies. Written informed consent was obtained from all patients undergoing the procedure.

All procedures were performed by perinatal specialists with experience in invasive procedures. An ultrasound scan was performed before the procedure to assess the chorionicity, number, location, size, and cardiac activity of the embryos. The entire procedure was performed under the guidance of a transabdominal ultrasound (Voluson 730 Expert; General Electric Healthcare, Milwaukee, WI, USA). After cleaning the mother's abdominal skin with an antiseptic solution, a 20-G spinal needle was used to penetrate first through the anterior uterine wall into the targeted gestational sac and then into the fetal thorax. 1–3 ml of 10% KCl (2 meq/ml) was injected into the fetal thorax. Cardiac activity was observed for at least 2 minutes. If cardiac activity persisted, additional KCl was injected. Reduction of other fetuses was performed with the same needle puncture or, less frequently, with a separate needle puncture. The total duration of the procedure was less than 10 minutes. After the procedure, the women were clinically observed for an average of two hours for pain, water leakage, and bleeding. The patients were discharged after a follow-up ultrasound to confirm the presence of asystole in the reduced fetus and cardiac activity in the others. An ultrasound was performed in all patients 1 week after the procedure to check fetal viability.

The demographic, obstetric, and neonatal clinical data of all patients included in the study were evaluated using electronic archives or patient records. The study patients were divided into two groups: Triplet pregnancies reduced to singletons (n=14) and triplet pregnancies reduced to twins (n=13). The demographic data, complications related to the reduction procedure (post-procedure complications), various pregnancy complications such as early spontaneous abortion (pregnancy loss before 24 weeks), preterm birth (≤32, <34, and <37 weeks), gestational diabetes mellitus (GDM), gestational hypertensive disorders, preterm premature rupture of membranes (PPROM), and intrauterine growth restriction (IUGR) were compared in both groups. GDM was diagnosed with a 75-g oral glucose tolerance test (OGTT) between 24 and 28 weeks of gestation. The threshold values for fasting, 1-h and 2-h plasma glucose levels were 92 mg/dl, 180 mg/dl, and 153 mg/dl, respec-

tively. If at least one of these values was reached or exceeded, the pregnant woman was diagnosed with GDM.[17] Preeclampsia was identified as maternal hypertension >140/90 mmHg without a previous history of hypertension and 300 mg/L proteinuria without a history of renal disease.[18,19] PPROM was described as a rupture of the fetal membranes before 37 weeks of completed gestation.[20] IUGR was defined as EFW < 3rd centile based on sonographic measurements of fetal biparietal diameter, head circumference, AC, and femur length, and no end-diastolic flow loss on Doppler examination.[21,22]

Statistical analysis

Pregnancy reduction was determined as the primary outcome variable for this descriptive study, which was retrospectively planned. SPSS 20.0 (IBM Corp., released in 2011. IBM SPSS Statistics for Windows, Version 20.0; Armonk, NY, USA) was used to analyze the data obtained in the study. Student's t-test and Mann-Whitney U-test were applied to compare the continuous variables in the study where groups were formed by reducing triplet pregnancies to twin and singleton pregnancies. The group-specific assumptions about normal distribution were tested using Shapiro-Wilk and Kolmogorov-Smirnov tests. These results were used to decide whether parametric or nonparametric hypothesis tests should be used for comparison. The chi-square test or Fisher's exact test was performed to examine the difference between the distributions of the categorical variables. The p-values of the exact test were used when the number of cells with an expected value of less than 5 was more than 25% of the total number of cells. Mean-standard deviation, median-range, and frequency distributions-percentiles were used as descriptive statistics to summarize the results. Statistical significance was taken as p-value <0.05.

Results

During the study period, 27 patients with triplet pregnancy between 11–14 weeks of gestation underwent reduction. Of these 27 triplet pregnancies, 14 were reduced to singleton pregnancies and 13 to twin pregnancies. The comparison of patients' demographic and clinical data including maternal age, number of pregnancies, type of pregnancy, gestational age at the time of the procedure, and post-procedure complications are given in **Table 1**.

At the time of the procedure, the mean gestational age was 12.43±0.76 weeks for singleton pregnancies and 12.08±0.64 weeks for twin pregnancies. Of the 27 patients, 22 (81.48%) developed triplet pregnancies after an in vitro fertilization (IVF) treatment, 3 (11.1%) after ovulation induction with gonadotropin, and 2 (7.4%) were naturally occurring triplet pregnancies. One of the triplet pregnancies that occurred after ovulation induction was a pregnancy by intrauterine insemination (IUI). Of the 27 triplet pregnancies in which a reduction procedure was performed, 16 (59.3%) were TCTA pregnancies and 11 (40.7%) were DCTA pregnancies. The most common complication of the procedure was abdominal pain in singleton pregnancies (21.4%), and both the presence of abdominal pain and vaginal bleeding (30.8%) in twin pregnancies.

Table 1 shows obstetric complications by procedure MPR. There was no significant difference between the two groups in obstetric complications including the prevalence of GDM, gestational hypertensive disorders, PPROM, and IUGR.

A comparison of the perinatal outcomes of patients reduced from triplet pregnancies to singletons and twins is given in **Table 2**. Compared to singleton pregnancies, twin pregnancies had significantly earlier weeks of gestation (33.07±5.73 weeks versus 35.78±6.14 weeks, p=0.009) and lower birth weight (1998.46±808.07 g versus 2765±803.03 g, p=0.003). It was also observed that the rate of births before 37 weeks of gestation (46.2% versus 28.6%, p=0.440) was higher in pregnancies reduced to twins than in pregnancies reduced to singletons, although this was not statistically significant. In the group reduced to singleton pregnancies, no delivery occurred before 34 or 32 weeks of gestation. In addition, in the group reduced to twin pregnancies, 2 (15.4%) patients delivered at less than 34 weeks of gestation and 1 (7.7%) patient delivered at less than 32 weeks of gestation.

Before 24 weeks of gestation, pregnancy loss was 7.1% and 15.4% in the groups reduced to singletons and twins, respectively. One patient who was reduced to twin pregnancy after fetal reduction experienced premature rupture of membranes and was delivered at 33 weeks and 4 days of gestation. Intrauterine fetal demise occurred at 15 weeks of gestation in one patient who was reduced to a singleton pregnancy. Postneonatal death occurred in two patients in the group reduced to twins,

Table 1. Comparison of the demographic and clinical data of patients reduced from triplet pregnancies to singletons and twins.

	Triplet pregnancies reduced to singletons (n=14)		Triplet pregnancies reduced to twins (n=13)		
	Mean±standard deviation	Median– range	Mean±standard deviation	Median–range	p-value
Age, years	32.71±6.58	30–23	33.31±6.1	31–22	0.810*
Gravidity, n	1.57±0.85	1–3	1.46±0.88	1–3	0.569†
Gestational age at reduction	12.43±0.76	12–3	12.08±0.64	12–2	0.223†
Nulliparity	10	71.4	11	84.6	0.648
Mode of conception					0.162
Spontaneous	2	14.3	0	0.0	
Ovulation induction	0	0.0	2	15.4	
Ovulation induction / Intrauterine insemination	0	0.0	1	7.7	
In vitro fertilization	12	85.7	10	76.9	
Number of procedures					1.000
1	13	92.9	13	100.0	
2	1	7.1	0	0.0	
Procedure complications	3	21.4	5	38.5	0.420
Abdominal pain	2	14.3	0	0.0	
Vaginal bleeding	0	0.0	0	0.0	
Amniotic fluid leakage	0	0.0	1	7.7	
Abdominal pain + vaginal bleeding	1	7.1	4	30.8	
Gestational diabetes mellitus	0	0.0	2	15.4	0.480
Gestational hypertensive disorders	2	14.3	5	38.5	0.209
Preterm premature rupture of membranes	0	0.0	1	7.7	1.000
Intrauterine growth restriction	1	7.1	2	15.4	1.000
Cerclage	0	0.0	0	0.0	N/A
Antepartum hemorrhage	0	0.0	3	23.1	0.220

*Refers to Student's t-test and †for Mann-Whitney U test, all others from Fisher's exact test p-values.

and both patients were at <25 weeks of gestation (18 and 24 weeks of gestation). There was no significant difference between the two groups in terms of the type of birth. The most preferred birth method was cesarean section (92.9% versus 84.6%). The need for a neonatal intensive care unit (NICU) was not significant between the two groups (p=0.209).

Discussion

Multiple pregnancies are taking an increasingly important place in obstetrics due to the increasing advances in assisted reproductive technologies. Reduction of multiple pregnancies is a widely used procedure to reduce the risk of perinatal morbidity and mortality.[1] Although the reduction is a therapeutic option in the management of multiple pregnancies, it should not be the first choice to prevent multiple pregnancies. Patients undergoing assisted reproductive techniques such as IVF should be recommended a single embryo transfer as a priority.[23] Single embryo transfer has been shown to significantly reduce the incidence of multiple pregnancies[24] but does not completely eliminate them. Therefore, MPR is an alternative option for multiple pregnancies with three or more fetuses because it improves pregnancy outcomes. The main goal of fetal reduction is to reduce preterm birth and associated neonatal morbidity.

Our study shows that the group reduced to a twin pregnancy delivered at an earlier week of gestation and

Table 2. Comparison of the perinatal outcomes of patients reduced from triplet pregnancies to singletons and twins.

	Triplet pregnancies reduced to singletons (n=14)		Triplet pregnancies reduced to twins (n=13)		
	Mean±standard deviation	Median–range	Mean±standard deviation	Median–range	p-value
Week of gestation at birth	35.78±6.14	38–24	33.07±5.73	35–19	**0.009***
Birthweight, g	2765±803.03	3040±3150	1998.46±808.07	2350–2720	**0.003***
Neonatal intensive care unit admission, days	5±2.83	5±4	16.2±3.03	15–8	0.051*
	n	%	n	%	p-value
Miscarriage <24 weeks	1	7.1	2	15.4	0.596
Live birth	13	92.9	11	84.6	0.596
<32 weeks preterm birth	0	0.0	1	7.7	0.481
<34 weeks preterm birth	0	0.0	2	15.4	0.222
≤37 weeks preterm birth	4	28.6	6	46.2	0.440
Cesarean delivery	13	92.9	11	84.6	0.596
Neonatal intensive care unit admission	2	14.3	5	38.5	0.209
Surviving neonates	13	92.9	11	84.6	0.596

*Refers to Mann-Whitney U test, all others from Fisher's exact test p-values.

had a lower birth weight than the group reduced to a singleton pregnancy. These results indicate positive outcomes after reduction to a singleton pregnancy similar to previous studies.[15,16] In contrast, there was no statistically significant difference between groups in preterm birth rate and pregnancy loss before 37, 34, and 32 weeks of gestation. The rate of births below 37 weeks of gestation was 28.6% in the group reduced to a singleton pregnancy and 46.2% in the group reduced to a twin pregnancy. Moreover, in our study, no deliveries were observed at <34 weeks or <32 weeks in all pregnant women reduced to a singleton pregnancy.

The risk of miscarriage before 24 weeks of gestation after the MPR procedure is controversial. While previous studies reported that the risk of miscarriage increased after the procedure,[11] more recent studies report that the risk of pregnancy loss before 24 weeks is similar in pregnancies with and without reduction.[25] Some studies have reported that the risk of miscarriage is higher with the reduction from triplets to singleton pregnancies than with reduction to twin pregnancies (62% versus 4%).[12,26] There are studies suggesting that this may be due to the resorption of the remaining dead fetoplacental tissue rather than the procedure itself.[9,10,27,28] However, more recent studies have shown that reduction of triplet pregnancies to singleton rather than twin pregnancies is associated with higher weeks of gestation and better perinatal outcomes.[15,16,29] In our study, the overall pregnancy loss rate was 3.7%. Similar to the literature, the fetal loss rate below 24 weeks was not significantly different between the two groups (7.1% in singleton pregnancies, 15.4% in twin pregnancies, p=0.596), which may be due to the small number of patients in both groups in the present study. Also, our study concluded that one patient with singleton pregnancy experienced in utero death at 15 weeks of gestation and two patients with twin pregnancy delivered at <25 weeks' gestation (18 and 24 weeks of gestation). It was observed that the group reduced to singleton pregnancy had higher gestational weeks and birth weights.

Belogolovkin reported that pregnancy reduction did not seem to increase the IUGR incidence after adjusting for potential confounders, including placental pathology and the use of assisted reproduction, where available.[30] However, Audibert et al. concluded that embryo reduction was the only significant risk factor for the development of birth weight discordance.[31] In our cohort, the IUGR prevalence in triplet pregnancies reduced to twins was 15.4%, and in triplet pregnancies reduced to twins was 7.1%. We found no significant difference

between the groups regarding IUGR, but the sample size of 27 patients was low to draw any conclusion.

The frequency of maternal morbidity is greater in higher-order pregnancies. Gestational hypertensive disorders are observed in 12.7% to 19.6% of multiple pregnancies compared with 6.5% of singletons.[32] Moreover, compared with mothers of twins, mothers of triplets and quadruplets were more likely to be diagnosed with PPROM, GDM, and antepartum and postpartum hemorrhage, to require tocolytic agents, and to be delivered by cesarean section.[33] In our study, the prevalence of gestational hypertensive disorders, GDM, PPROM, and antepartum hemorrhage was higher in triplet pregnancies reduced to twins (38.5%, 15.4%, 7.7%, and 23.1%, respectively) than in triplet pregnancies reduced to singletons (14.3%, 0%, 0%, and 0%, respectively). However, these differences were not statistically significant. We consider that the lack of statistically significant difference was due to the low sample size.

There are some limitations to this study. The main limitation is the low sample size. The fact that the decision MPR was difficult for these patients because this is a retrospective study, multiple pregnancies are rare, and these patients became pregnant after long-term infertility treatment may not be sufficient to detect the differences between the perinatal outcomes of the two groups. There are also no long-term neonatal outcomes.

Conclusion

We indicated that reducing triplet pregnancies to singleton pregnancies instead of twin pregnancies leads to better obstetric outcomes such as higher birth weights and further birth weeks. However, prospective studies with a larger number of patients are needed to contribute more to the literature on the clinical significance of this difference and to better counsel parents on the risks and benefits of MPR.

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Compliance with Ethical Standards: The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

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