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Multi-Fetal Reduction May Be the Better Choice for Multi-Fetal Pregnancies: A Cohort Study

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This study was presented as an oral presentation at "3. Jinekoloji ve Obstetrikte Tartışmalı Konular Kongresi", September 23-26, 2021, Bafra, Turkish Republic of Northern Cyprus.

ABSTRACT Objective: The rate of multiple pregnancies increases the number of pregnancies conceived using assisted reproductive techniques. Although the studies indicate a positive effect of multi-fetal pregnancy reduction on pregnancy outcomes, procedure-associated miscarriages should be considered. Therefore, our study aimed to evaluate the outcomes of pregnancies that have undergone multi-fetal reduction and compare the pregnancies' outcomes without any intervention. **Material and Methods:** Patients from the Perinatology Clinic of Şanlıurfa Training and Research Hospital were selected between July 2017 and May 2021. The patients in the study group were divided into two groups: those with or without multi-fetal reduction. Obstetric outcomes of pregnancies were compared between the groups. **Results:** During this period, 95 gestations with three or more fetuses were applied to our clinic. Eighteen multi-fetal reduction procedures were performed because of multiple pregnancies. Reductions were performed from five to twins in one case, triplets to twins in ten, and quadruplets to twins in seven cases. Patients preferred to continue pregnancies without intervention in 6 quadruplets, one sextile, and 66 triplet pregnancies. Mean gestational age at birth in the intervention group was 34.43±0.40 (32-38) weeks, while in the non-intervened group, that was 30.46±0.48 (24-37) gestational weeks. Gestational age at birth was significantly lower in the non-intervention group. (p: 0.000029). **Conclusion:** Multi-fetal reduction is beneficial in preventing preterm delivery.

Keywords: Multi-fetal pregnancy reduction; multiple pregnancy; premature obstetric labor

Nowadays, due to the rise of postponed pregnancies to older ages, assisted reproductive techniques (ART), there is a rise in the frequency of multiple births. ART are to blame for the vast majority (approximately 80%) of multiple gestations.[1]

Due to risks for the mother and growing children, multiple pregnancies are classified as high-risk pregnancies. Fetal growth restriction, preterm premature rupture of membranes, preterm delivery, and intrahepatic cholestasis are some conditions associated with adverse outcomes in multiple gestations. In addition, preeclampsia, gestational diabetes, anemia, eclampsia, cervical insufficiency, and postpartum hemorrhage are also causes of maternal morbidity in multi-fetal pregnancies.[2]

The number of babies in-utero is inversely related to the neonatal outcomes of multiple gestations. A considerable morbidity of prematurity affects the 10% of twin pregnancies and the 35% of triplet pregnancies that end before 32 weeks of gestation, respectively.[3]

Fetal reduction to improve pregnancy outcomes has become an established practice for multiple gestations. A Cochrane review revealed an advantage of fetal reduction in multi-fetal pregnancies for decreasing pregnancy loss, preterm birth, low-birth weight infants and neonatal deaths.[3]

Although the studies indicate a positive effect of multi-fetal pregnancy reduction on pregnancy outcomes, procedure-associated miscarriage should be

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considered. In the literature, unintended pregnancy loss is increased in higher order multi-fetal gestations who undergo selective fetal termination than twin gestation who undergo the procedure.

In this study, we compared the results of the group without any intervention to those of triplet gestations and gestations with a higher number of fetuses that had undergone multi-fetal pregnancy reduction.

MATERIAL AND METHODS

In the first trimester of pregnancy, patients who applied for pregnancies with three or more fetuses between July 2017 and May 2021 in the Perinatology Department of Şanlıurfa Training and Research Hospital were retrospectively evaluated. All placentas were examined for chorionicity at first-trimester ultrasound and confirmed by histopathology after delivery.

Outcome measures: Gravida, parity, age of patients, whether it is a spontaneously obtained pregnancy or an ART pregnancy, total number of fetuses at the beginning, chorionicity of pregnancies, pregnancies that had undergone intervention for reduction, and obstetric results of all gestations were recorded. In addition, gestational age at the interventions was recorded. Obstetric outcomes of all pregnancies with (Group 1) or without intervention (Group 2) were also evaluated. Early preterm deliveries were described if the baby was delivered between 24 and 28 weeks of gestation. Late preterm delivery is described if the baby is delivered between 34 and 37 weeks.

Patients with a history of repeated miscarriages, premature births, or fetal abnormalities were not included in the study. In addition, pregnancies were excluded if two separate fetuses were monochorionic in multiple pregnancies.

Over the entire study period, the multi-fetal reduction was offered to all pregnant women with multiple pregnancies and three or more fetuses. Informed consent form was signed by the patient and his husband for fetal reduction, and information was given about the procedure.

The fetal reduction procedure was performed by intracardiac injection of 1-2 mL potassium chloride with a 22-gauge needle via the transabdominal route between 12-15 weeks. The targeted number of fetuses after the procedure was two in all cases. The gestational sac's position relative to the cervical os range, the placement of the placenta, and technical feasibility all influence the decision of which fetus(es) will be decreased. To avoid gender-specific selection, the parents were not informed of the fetal gender.

The Harran University Clinical Research Ethics Committee (date: June 7, 2021, no: HRU/21.11.12) provided ethical approval. The Helsinki Declaration principles were used to develop and conduct the study.

The SPSS (SPSS.22, IBM SPSS Statistics for Windows, Version 22.0, IBM Corp., Armonk, NY, USA) was used to conduct the statistical analyses. The normality of the distribution was confirmed using the Kolmogorov-Smirnov test. To describe the data properties for a normal distribution and an atypical distribution, respectively, means or median values were utilized. The significance level for all tests was set at $p<0.05$. Chi-square, Fisher's exact, and t-tests were applied.

RESULTS

A total of 95 multi-fetal pregnancies were detected. Mean maternal age was 28.11±1.37 (20-41) in the reduction group (Group 1) and 27.8±0.69 (19-40) years in the non-reduction group (Group 2) ($p>0.05$). Table 1 displays the demographic information about the patients. Six of these pregnancies were spontaneously conceived, 89 were conceived after ART. Twelve of 95 were intrauterine insemination cycles, and 83 were conceived after ovulation induction cycles. Four patients were removed from the study group because of mono-chorionicity in triplets. While 91 pregnancies were included in the study group, 18 patients preferred the multi-fetal reduction procedure. The targeted number of fetuses after the procedure was two in all of these cases. Reductions were performed from five to twins in one case, triplets to twins in ten, and quadruplets to twins in seven cases. Two miscarriages occurred within the first week after the procedure, one case was reduced from five to twins, and one case was reduced from quadruplet to twins.

TABLE 1: Demographic factors of patients who underwent multi-fetal reduction.

	MFR group (n=18)	Non-intervented group (n=73)	p value
Age	28.11±1.37 (20-41)	27.8±0.69 (19-40)	0.25
Parity	1.66±0.21 (0-3)	2.06±0.12 (0-4)	0.06
BMI	29.0±1.18 (20.8-30.2)	29.1±1.05 (21.5-31.2)	0.13
ART	14	71	0.002*
Spontaneous pregnancy	4	2	0.002*
Triplets	10	66	0.001*
Quadruplets	7	6	0.001*
Quintuplets or more	1	1	0.001*

MFR: Multi-fetal reduction; BMI: Body mass index; ART: Assisted reproductive technologies. *p<.05

TABLE 2: Pregnancy outcomes of patients.

		MFR group (n=18)	Non-intervented group (n=73)	p value
Miscarriages		2	11	NS
Time of delivery	Early preterm (24-28)	0	23	p<0.05
	Preterm (29-33)	4	27	p<0.05
	Late preterm (34-37)	11	12	NS
	Term (>37)	1	0	NA
Average birth weight (grams)		2,383±109.03 (1,500-3,250)	1,343±94.84 (520-3,000)	p<0.01
				t value: -5.39
Mode of delivery	Vaginal	0	0	
	Cesarean	16	62	

MFR: Multi-fetal reduction; NS: Non-significant; NA: Not applicable.

Patients preferred to continue pregnancies without reduction in 6 quadruplets, one sextile and 66 triplet pregnancies, and nine miscarriages in triplets, and 2 in quadruplets were observed during follow-up.

There was no statistically significant difference between the multi-fetal reduction group and the non-reduction group in terms of age or parity (p>0.05). All patients gave birth via cesarean section. The reduced group's mean gestational age at birth was 34.4375±0.407 (32-38), while in the non-reduction group it was 30.464±0.48 (24-37) gestational weeks. There was a statistically significant difference between the groups in terms of gestational age at birth (p<0.01). The gestational week at birth was lower in the non-reduction group (Group 2). Pregnancy outcomes are reported in Table 2.

DISCUSSION

Only 6.4% of multiple pregnancies were spontaneously conceived pregnancies in our study, and 93.6% were ART pregnancies. This ART-associated high multiple pregnancy rate is essential to highlight the growing importance of multi-fetal reduction. The positive effect of multi-fetal pregnancy reduction on pregnancy outcomes in multiple pregnancies has been reported in many studies in the literature. Our results indicate a significantly low rate of early preterm and preterm deliveries in the reduction group. Additionally, compared to the non-reduction group, the average birth weight was considerably higher in the reduction group. In a metaanalysis of a total of 24 studies, multi-fetal pregnancy reduction (MPR) group delivered later than non-reduction group and was less likely to be delivered before 32 or 28 weeks. In this metaanalysis, newborns in the MPR group had significantly higher birthweight at delivery [mean difference 500 g (95% confidence interval 439.95, 560.04)].[4]

In addition, although studies have reported on its effectiveness in twin pregnancies in recent years, this

issue remains controversial. Thirty five dichorionic-diamniotic twin pairs that weren't decreased were compared to 32 twins who were reduced to singletons by Hasson et al. They came to the conclusion that the pregnancy's course and outcome were unaffected dramatically by the decision to reduce twins to singletons.[5] On the contrary to this, in a metaanalysis of Bardin et al., twin reduction to singleton pregnancy decreased the possibility of preterm birth, hypertensive disorders in pregnancy and cesarean delivery.[6]

A 16 percent miscarriage rate was reported in the first new survey of fetal reduction by Evans et al. in 1993. The miscarriage rate following fetal reduction was 8.1%, according to data compiled most recently by Papageorghiou et al. from five additional investigations.[7] In our study, 2 out of 18 multi-fetal pregnancies resulted in miscarriage in the reduction group. The miscarriage rate was 11% in the reduction group and 15% in the non-reduction group. Miscarriage rates (delivery before 24 weeks) were no statistically different between the groups. This rate is consistent with the literature.[8] multi-fetal reduction procedures did not increase miscarriage rates in multi-fetal pregnancies with three or more fetuses.

In our study, the targeted number of fetuses after the procedure was two in all cases but in a metaanalysis of Hessami et al., it is offered to reduce triplets to one fetus. It was found that reduction to twins than one fetus has the lower rate of fetal survival and gestational age.[9]

Before agreeing on several fetal reduction procedures, certain considerations should be discussed with the patients. First, it will make sense to do so if the procedure's goal is to better the course of this pregnancy. For example, freeing the space in-utero may improve the outcome (the over-crowded "lifeboat" principle).[10] Second, parents have a right to healthy children, thus they should take advantage of any procedures that can help their chances of outcome. The fetus's right to a healthy birth is the final consideration.[10]

This study had the disadvantages of being retrospective and non-randomized. A randomized trial is probably not practical, though, considering how contentious the intervention is. Our capacity to draw conclusions about the impact of fetal reduction simply on pregnancy age is constrained by the lack of long-term data on neonates.

The strength of the study was the inclusion and discussion of fetal reduction in higher order multi-fetal gestations as sextile and quadruplets.

CONCLUSION

In conclusion, multi-fetal reduction seems beneficial in preventing preterm delivery and its associated adverse consequences. However, as multiple gestations result from iatrogenic intervention, physicians should be aware of the risk of multiple gestations resulting from ovulation induction and assisted reproductive technologies. Therefore, the most appropriate approach should provide as much monofollicular development as possible in ovarian hyperstimulation.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Alev Esercan;* ***Design:*** *Alev Esercan;* ***Control/Supervision:*** *Emre Ekmekçi;* ***Data Collection and/or Processing:*** *Emre Ekmekçi, Alev Esercan;* ***Analysis and/or Interpretation:*** *Alev Esercan;* ***Literature Review:*** *Alev Esercan;* ***Writing the Article:*** *Alev Esercan;* ***Critical Review:*** *Alev Esercan;* ***References and Fundings:*** *Emre Ekmekçi;* ***Materials:****Emre Ekmekçi.*

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