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Optimal Timing of Multifetal Pregnancy Reduction: The Earlier the Better or Later

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ABSTRACT

Background & Objective: A number of procedures have been developed for multifetal pregnancy reduction (MPR) to reduce the overall number of fetuses in the gestation and improve the maternal outcomes as well as the outcomes of the surviving fetus.

Materials & Methods: An observational historical cohort study was conducted on multiple pregnancies that underwent fetal reduction in Shariati Hospital and Omid Clinic between January 2018 and September 2021. The study population was divided into two groups according to gestational age at fetal reduction: 11–14 weeks' gestation (early reduction group) and 15–19 weeks' gestation (late reduction group). The main outcome measures were the rates of pregnancy complications, pregnancy loss, preterm delivery, and adverse neonatal outcomes.

Results: The study group included 107 patients with twin and multiple pregnancies that underwent abdominal MPR at 11-19 weeks' gestation (79 in the early reduction group and 28 in the late group). The incidence of pregnancy complications (hypertension, diabetes, intrauterine growth disorder, preterm delivery, and pregnancy loss) was not significantly different between the two groups (P >0.05). The percentage of NICU admission was higher in the early reduction group compared to the late group (49% vs 18.5%, P=0.004).

The weight of the first newborn was significantly heavier in the late versus early reduction group (2680.55±777.52 vs 2264.4±796.82, P=0.005).

Conclusion: According to the present study, fetal reduction in twin or multiple pregnancies is a safe procedure with good obstetric outcomes if done by an expert specialist, especially when it is performed in the second trimester.

Keywords: Fetal abnormalities; Multifetal pregnancy reduction; Multiple pregnancy; Perinatal outcome; Selective termination; Twin pregnancy

Introduction

The prevalence of multiple pregnancies has increased significantly in recent decades, mainly due to the widespread use of assisted reproductive technologies as well as the trend of increased reproductive age in recent years **(1-4)**.

Multifetal gestations are at a higher risk of a variety of maternal, fetal, and neonatal complications compared to singleton pregnancies. Ideally, multiple gestations should be prevented by better use of ART (better management of ovulation induction and embryo transfer). A number of procedures have been developed for multifetal pregnancy reduction (MPR) to reduce the

overall number of fetuses in the gestation and thereby improve the maternal outcomes as well as the outcomes of the surviving fetus **(5-9)**.

Selective termination (ST) involves reducing the fetal number in multiple gestations because of a known genetic, structural, or other abnormality identified by ultrasound examination, amniocentesis, or chorionic villus sampling (CVS). The primary justification for MPR is to increase the gestational age at birth and birth weight, thus reducing morbidity and mortality from preterm birth **(10)**. The risks for some maternal complications, such as preeclampsia, are also reduced **(11)**. The economic and psychological impacts of multiple gestations on families are also important and can be additional reasons for MPR **(12-15)**.

The best gestational age for fetal reduction is controversial across studies. Therefore, the present study was conducted to compare procedure complications, abortion, infection, and preterm pregnancy between early reduction at 11-14 weeks and late reduction at 15-19 weeks' gestation.

Methods

This study was an observational cohort and we observed the outcome. All women with a multifetal pregnancy due to induction ovulation or spontaneous conception who underwent fetal reduction to reduce the number of fetuses or for fetal-maternal indications in Shariati Hospital & Omid Clinic between 2018 and 2021 were assessed for possible inclusion. The Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran and the Deputy of Research at Tehran University of Medical Sciences, Tehran, Iran (IR.TUMS.MEDICINE.REC.1400.1097) approved this prospective cohort study. The data of all pregnant women with multiple pregnancies were collected from hospital medical records.

Inclusion criteria were multifetal pregnancy with multichorinicity, abdominal fetal reduction at 11–19 weeks' gestation, and complete data for both the mother and neonate. Pregnancy dating and chorionicity were determined according to ultrasound scan of first trimester

The study population comprised two groups according to GA at reduction: those who underwent MPR or ST at 15–19 weeks' gestation (late reduction group) and those who underwent fetal reduction at 11–14 weeks' gestation (early-reduction group). Demographic and clinical data were collected by examining the medical records of each patient and infant. The missing data was collected through direct telephone interviews with women.

Fetal reduction was performed after local anesthesia by ultrasound-guided injection of potassium chloride with a 22-gauge needle into the fetal heart or thoracic by a highly-skilled specialist.

In the early-reduction group, all patients underwent ultrasound screening for determine nuchal translucency at 11–13 weeks' gestation, most underwent a detailed anomaly scan at 13 weeks, and a few underwent CVS. In this group, the smaller embryo, the embryo with higher nuchal translucency, or the upper or available fetus if no sonographic or genetic abnormalities were found, was selected for reduction. The embryo with a detected anatomic anomaly or genetic abnormality was selected for the reduction in the late reduction group.

Early onset complications like infection, abortion, stillbirth (loss of pregnancy after 24 weeks), preterm delivery, gestational hypertension, intrauterine growth restriction, gestational diabetes, mode of delivery, and neonatal outcomes were the primary outcomes that were studied and compared between the two groups.

The demographic data of the patients including age, parity, body mass index; history of preterm delivery was collected. In addition, the location of the resected fetus relative to the cervix and placental site was determined.

Fetal loss was defined as fetal death diagnosed after the reduction procedure. Any delivery occurring prior to 37 completed gestational weeks was considered as preterm birth. GDM and hypertensive disorders of pregnancy were defined according to guidelines.

Fetal reductions were also divided according to the timing of the procedure, i.e. the first trimester (≤14 weeks' gestation) versus the second trimester (> 14 weeks' gestation).

Statistical Analysis

The normality of the data distribution was tested using the Kolmogorov-Smirnov test. Categorical variables are reported as number and percentage. A number of quantitative variables did not have a normal distribution in this study, to which the Mann-Whitney test was applied. The Mann-Whitney U test was used to compare continuous variables with a non-normal distribution. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. The significance threshold was set at $p<0.05$. Statistical analyses were conducted using the IBM Statistical Package for the Social Sciences (IBM SPSS Statistics for windows, V22.0; IBM Corporation Inc, Armonk, NY, USA).

Results

The study group included 107 patients with twin and multiple pregnancies that underwent abdominal MPR at 11-19 weeks' gestation, of whom 79 were in the early reduction group and 28 were in the late reduction group.

Table 1 displays the demographic and clinical characteristics of the study groups. No significant difference was found in age, BMI, distribution of

gravidity and parity, medical history, and drug history between the groups. In the early reduction group, 2.5% of the patients had an amniocentesis in the current pregnancy compared to 21.5% of patients in the late reduction group (Table 1).

Table 2 displays Comparison of variables and consequences between the two groups.

Table 1. Demographic and clinical characteristics of the study groups

Characteristic	Early reduction (n =79)	Late reduction (n =28)	p value
***Maternal age (years)**	32.49±6.51	34.46±5.87	0.245
BMI at delivery (kg/m2)*	25.22±3.81	24.89±2.43	0.628
***Gravidity**	1.37±0.64	1.71±1.43	0.413
***Parity**	0.26±0.52	0.64±1.56	0.268
History of disease:			
***Hypothyroidism	16(20%)	10(36%)	0.101
chronic hypertension**	4(0.5%)	1(3.5%)	0.608
Overt diabetes**	6(7.5%)	0	0.154
Drug Use			
-ASA***	31(39%)	13(46.5%)	0.507
-Enoxaparin**	25(31.5%)	4(14.5%)	0.088
Methyldopa**	0	1(3.5%)	0.262
Mode of conception***			
IVF	58(73.5%)	27(96.5%)	0.017
Spontaneous	2(2.5%)	1(3.5%)	
Ovulation induction	19(24%)	0	
Amniocentesis in current pregnancy**	2(2.5%)	7(25%)	0.0001
History of IUGR in previous pregnancy**	0	1(3.5%)	0.262
History of preterm labor in previous pregnancy**	6(7.5%)	3(11%)	0.433

Data are presented as mean for continuous variables or as number (percent) for categorical variables.
***Mann –Whitney Test**
****Fisher Exact Test**
*****Chi-Square Test**
BMI – body mass index;
IVF – in vitro fertilization;

Table 2. Comparison of variables and consequences between the two groups

Characteristic	Early reduction (n =79)	Late reduction (n =28)	p value
***NT Thickness (mm)**	1.54±0.41	1.79±0.49	0.024
*****Cause of reduction:**			
Multiple pregnancies	5(6%)	7(25%)	
Triple pregnancy (DCTA, TCTA)	48(61%)	12(43%)	
Twin (Anomaly of one fetus)	0	5(18%)	0.0001
Twin (maternal medical disease)	14(17.5%)	4(17.5%)	

Characteristic	Early reduction (n =79)	Late reduction (n =28)	p value
***Placental site			
Anterior placenta	43(54.5%)	16(57%)	
Posterior placenta	30(38%)	10(36%)	0.970
Lateral placenta	6(7.5%)	2(7%)	
***The redacted fetus cite:			
fetus A (lower fetus)	2(2.5%)	9(32%)	
fetus B	30(38%)	11(39%)	0.0001
fetus C (upper fetus)	30(38%)	2(7%)	
Early complication ***			
leakage	10(13%)	2(7%)	
Bleeding and spotting	15(19%)	7(25%)	0.863
-abortion	1(1%)	0	
-all of them	5(6.5%)	3(10.5%)	
Pregnancy complication:			
-Hypertension***	7(9%)	4(15%)	0.578
-Diabetes**	14(18%)	1(4%)	0.055
-IUGR**	3(4%)	1(4%)	0.546
**-preterm delivery <32 w	12(15.5%)	1(4%)	0.065
-preterm delivery <34 w**	8(10.5%)	3(11%)	0.583
-preterm delivery <37 w	25(32.5%)	5(18.5%)	0.128
Fetal – neonatal complication:			
Fetal death<24 w**	3(4%)	2(7%)	0.392
Fetal death >24w**	1(1%)	0	0.743
Viable neonate***	69(87%)	26(93%)	0.427
Weight of first neonate (gr)*	2264.4±796.82	2680.55±777.52	0.005
*Weight of second neonate(gr)	2006±681.00	1883.33±356.68	0.312
NICU admission ***	36(49%)	5(18.5%)	0.004
*Length of hospital stay	11.62±1.48	8.71±7.22	0.716

Middle fetus in triple pregnancy and upper fetus in twin pregnancy (fetus B)
DCTA: dichorionic three amniotic
TCTA – three chorionic three amniotic
Data are presented as mean for continuous variables or as number (percent) for categorical variables.
***Mann –Whitney Test**
****Fisher Exact Test**
*****Chi-Square Test**

The reduced fetus was mainly the upper one in the early reduction group (38%) and the lower one (32%) in the late reduction group indicating a significant difference. The first newborn was significantly heavier in the late reduction group compared to the early reduction group (2680.55±777.52 vs 2264.4±796.82, *P* =0.005).

The incidence of early complications and pregnancy complications (hypertension, diabetes, intrauterine growth disorder, preterm delivery) was not significantly different between the two groups (*P* >0.05). The rates of pregnancy complications, preterm delivery, and pregnancy loss were also comparable between early and late reduction groups.

The percentage of NICU admission was significantly higher in the early reduction group versus the late group (49% vs 18.5%, *P*=0.004).

Discussion

The present study was conducted to compare the rate of pregnancy complications and neonatal outcomes in multiple pregnancies that were reduced to one or two fetuses between early and late fetal reduction.

The results showed no significant difference in incidence of early complications and pregnancy complications between the two groups. However, the percentage of NICU admission was significantly higher in the early reduction group compared to the late reduction group.

The Zemet study showed that compared to the reduction of twins in the first trimester, the reduction in the second trimester was associated with an increase in the rate of prematurity and adverse neonatal outcomes with no increase in the rate of surgical complications. The rate of preterm delivery before 37 weeks (34 to 36+6) was significantly higher in the late reduction (28.0% vs. 14.0%), preterm delivery between 32-34 weeks (12.0% vs. 1.8%), and before 32 weeks gestation (8.0% vs. 1.8%) **(4)** but in this regard, the present study findings were not significantly different between the two groups.

In seven studies; the outcomes were compared to the results of fetal reduction (twins and multiples) **(16-22)**. The findings of the present study are consistent with the results of studies conducted by Evans, Alvardo, Lynch, Yaron, and Kim **(16-22)** that concluded that GA at the time of reduction did not correlate with the rate of adverse prenatal and neonatal outcomes. Kim *et al.* found that the optimal time for the fetal reduction in multiple pregnancies would be at 11-13 weeks' gestation **(22)**.

Previous studies investigating fetal reduction in multiple pregnancies reported higher rates of preterm pregnancies after 15 weeks' gestation and concluded that first trimester reductions were more appropriate **(22-24)**, which is not consistent with the results of the present study. We did not find any difference in prenatal and neonatal outcomes between first and second trimester reductions.

Zemet reported that fetal reduction of twin pregnancies in the second trimester was associated with an increased risk of prematurity and adverse neonatal outcomes compared to late first trimesters **(4)**. Fetal reduction from a twin to a singleton pregnancy reduces the risk of preterm birth but does not reduce the risk of more severe maternal and perinatal complications **(25)**

Hasson *et al.* **(26)** found that reductions occurring beyond 15 gestational weeks increased the incidence of abortion and preterm delivery compared to reductions before 15 weeks' gestation. Different results of the reports can be found in the mentioned studies **(22-26)**.

The present study found that the first newborn was heavier in the late reduction group compared to the early reduction group. Kim *et al.* reported that the fetal birth weight increased significantly when fetal reduction was performed before 15 weeks' gestation, which is not consistent with the results of the present study **(22)**.

The sample sizes, gestational week at fetal reduction, triple or twin pregnancy, procedures, and specialist's skill may be possible causes of discrepancies between studies.

Given that the feasibility and reliability of first-trimester fetal anatomical scans have been reported over the past two decades **(27-31)**, therefore, it seems that efforts should be made to evaluate the fetus earlier in the first trimester and to avoid postponing the assessments to the second trimester. The reason for the reduction, whether medical, psychological, financial or social, must be considered when assessing the clinical risks and benefits of reducing twins to singles **(26)**.

For more accurate results in this regard, it is recommended to conduct larger multicenter studies; however, clinical trial studies are not recommended due to ethical problems.

The retrospective design and the limited sample size were the main limitations of this study. One of the strengths of this study is that the procedure was conducted in equipped medical centers by an experienced primatologist.

Conclusion

According to the present study, fetal reduction in twin or multiple pregnancies is a safe procedure with good obstetric outcomes if done by an expert specialist, especially when it is performed in the second trimester. However, fetal reduction, especially in the twin-to-single method, cannot be discussed without considering the ethical aspects.

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Conflict of Interest

The authors have no conflict of interest.

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