



SELECTIVE FETAL REDUCTION; PROCEDURAL FACTORS ASSOCIATED WITH ADVERSE PREGNANCY OUTCOMES

SEÇİCİ FETAL REDÜKSİYON; OLUMSUZ GEBELİK SONUÇLARIYLA İLİŞKİLİ PROSEDÜREL FAKTÖRLER

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ABSTRACT

Introduction: The aim of this study was to investigate the factors associated with selective fetal reduction (SFR) procedures that result in adverse pregnancy outcomes.

Methods: The study cohort comprises all multiple pregnancies that underwent SFR during the period of six years. The SFR procedure has been performed for two main indications: first, in cases of fetal anomaly; and secondly, electively to reduce the number of fetuses in triplet and higher-order pregnancies. Preterm birth or preterm premature rupture of the membranes prior to 34 weeks of gestation, placental abruption, pregnancy loss before 24 weeks of gestation, and intrauterine fetal death defined as adverse pregnancy outcomes. Procedural factors associated with adverse pregnancy outcomes were evaluated.

Results: A total of 39 SFR procedures were performed on 33 multiple pregnancies, with 31 resulting in live birth. A higher rate of adverse pregnancy outcomes was observed in pregnancies that underwent elective SFR, more than one procedure, were having triplets or higher-order pregnancies prior to the procedure, or were having twin or higher-order pregnancies post-procedure. Elective SFR procedures and multiple procedures have been demonstrated to be associated with an 8-fold and a 13.3-fold increased risk of adverse pregnancy outcomes. The risk ratio of triplet or higher-order pregnancies prior to the procedure and twin or higher-order pregnancies post-procedure was found to be 6.5 and 5.8, respectively, for adverse pregnancy outcomes.

Conclusions: Instead of considering SFR as the first option in the management of higher order pregnancies, it is recommended that assisted reproductive technologies be used in a way that does not lead to high-order pregnancies. In cases where the prevention of a higher order pregnancy has not been possible, SFR should be considered in terms of its risks and benefits as a method of reducing adverse pregnancy outcomes.

Keywords: Selective fetal reduction, multifetal pregnancy, higher order multiple pregnancy, multifetal pregnancy reduction, perinatal outcome

ÖZET

Giriş: Bu çalışmanın amacı, seçici fetal redüksiyon (SFR) uygulamalarında olumsuz gebelik sonuçlarına yol açan prosedürel faktörleri araştırmaktır.

Yöntemler: Çalışma kohortu, altı yıllık süre boyunca SFR uygulanan tüm çoğul gebelikleri içermektedir. SFR prosedürü iki ana endikasyon için uygulanmıştır: birincisi, fetal anomali vakalarında; ikincisi ise, üçüz ve daha yüksek dereceli gebeliklerde fetüs sayısını azaltmak için elektif olarak. 34. gebelik haftasından önce preterm doğum veya preterm prematür membran rüptürü, plasental abrupsiyon, 24. gebelik haftasından önce gebelik kaybı ve intrauterin fetal ölüm olumsuz gebelik sonuçları olarak tanımlanmıştır. Olumsuz gebelik sonuçları ile ilişkili prosedürel faktörler değerlendirilmiştir.

Bulgular: 33 çoğul gebeliğe toplam 39 SFR işlemi uygulanmış ve bunların 31'i canlı doğumla sonuçlanmıştır. Elektif endikasyon ile SFR uygulanan, birden fazla işlem uygulanan, işlem öncesinde üçüz veya daha yüksek dereceli veya işlem sonrasında ikiz veya daha yüksek dereceli gebeliklerde daha yüksek oranda olumsuz gebelik sonuçları gözlenmiştir. Elektif SFR prosedürlerinin ve birden fazla işlemin olumsuz gebelik sonuçları riskinde 8 kat ve 13,3 kat artışla ilişkili olduğu gösterilmiştir. İşlem öncesinde üçüz veya daha yüksek dereceli gebeliğe ve işlem sonrasında ikiz veya daha yüksek dereceli gebeliğe sahip olmak olumsuz gebelik sonuç riskini sırasıyla 6,5 ve 5,8 kat arttırmaktadır.

Sonuç: Seçici fetal redüksiyon işleminin yüksek dereceli gebeliklerin yönetiminde ilk seçenek olarak görülmesi yerine, yardımcı üreme teknolojilerinin yüksek dereceli gebeliklerin oluşmasına yol açmayacak şekilde kullanılması önerilmektedir. Yüksek dereceli gebeliğin önlenmesinin mümkün olmadığı durumlarda, olumsuz gebelik sonuçlarını azaltmanın bir yöntemi olarak seçici fetal redüksiyon risk ve faydaları açısından değerlendirilmelidir.

Anahtar Kelimeler: Seçici fetal redüksiyon, multifetal gebelik, yüksek dereceli çoğul gebelik, multifetal gebelik redüksiyonu, perinatal sonuçlar

INTRODUCTION

Monozygotic twinning occurs at a constant rate of approximately 4 per 1000 (1/250). Conversely, dizygotic twinning rates have been demonstrated to vary according to a number of individual characteristics, including race (low in Asians, high in blacks), increases with advanced maternal

age and parity, and family history, especially on the maternal side (1). Recent decades have seen a notable increase in the incidence of multiple pregnancies, largely attributable to the advanced maternal age and increased utilisation of assisted reproductive technologies such as in vitro

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Submission Date: 28.01.2025 **Acceptance Date:** 10.03.2025

Cite as: Eyisoy OG, Tasdemir U, Ozdemir ME, Gezer M, Demirci O. Selective fetal reduction; procedural factors associated with adverse pregnancy outcomes. Eskisehir Med J. 2025; 6(1): 50-55. doi: 10.48176/esmj.2025.180.

fertilization and ovulation induction (2). Despite the implementation of some measures have been taken to reduce multiple pregnancy rates, such as restricting the number of embryos transferred, this increase could not be completely prevented due to gonadotropin use and embryo splitting (3).

It is an established fact that the perinatal outcomes of multiple pregnancies are not equivalent to those of singleton pregnancies. In addition to higher perinatal mortality and morbidity due to increased preterm birth rates, maternal complications such as preeclampsia, gestational diabetes, and postpartum haemorrhage are also more common than in singleton pregnancies (4). The aforementioned risks are more pronounced in higher-order multiples, with one third of triplets expected to give birth prior to 32 weeks (5). Due to the reduced viability of the aneuploid fetus chromosomal anomalies are less prevalent in multiple pregnancies than in singleton pregnancies. However, structural anomalies are more common in multiples and usually affect a single fetus (6). In the cases of multiple pregnancies accompanied by an anomaly in one of the fetuses, the healthy fetus is more prone to elevated risks such as low birth weight and preterm birth.

Fetal reduction is an intervention employed in cases of multiple gestations with the objective of reducing the overall number of fetuses. It is achieved by inducing termination of one or more fetuses, with the intention of enhancing pregnancy outcomes (2). Selective termination is also performed in multiple gestations where one fetus exhibits severe fetal growth restriction or discordant fetal anomalies in order to improve the outcomes of the healthy fetus (7). Although the term 'selective termination' is used for fetuses of advanced gestational age, the term 'selective fetal reduction' is an overall term that includes selective termination.

The primary factor determining the method employed in selective termination is chorionicity. In pregnancies uncomplicated with monochorionicity, asystole is achieved within a short time with ultrasound-guided intracardiac, intrathoracic or umbilical vein injection of KCl. This procedure can be performed even in advanced gestational ages, with a low incidence of complications (8, 9). However, in the event of reduction being performed on a fetus with a monochorionic pair, methods such as bipolar cord coagulation, radiofrequency ablation or intrafetal laser ablation should be used to prevent neurological damage or fetal death in the healthy twin pair (10).

The present study examined the results of selective fetal reduction procedures performed by potassium chloride (KCl) injection in a tertiary perinatology center retrospectively. The objective of the research was to investigate the procedural factors that contribute to adverse pregnancy outcomes.

METHODS

This retrospective cohort study evaluated all selective fetal reduction cases in the Perinatology Clinic of Zeynep Kamil Women and Children Diseases Training and Research Hospital. The study protocol was approved by the institutional ethical committee (Approval number:168, Date:20.12.2023). All procedures were conducted in accordance with the Declaration of Helsinki, and informed consent was obtained for all examinations and procedures.

The study group consists of multiple pregnancies that underwent selective fetal reduction between January 2018 and December 2024. Patients with known uterine anomalies, cervical insufficiency or a history of preterm labour were excluded from the study. The demographic and clinical information of the patients was obtained from the electronic archives or patient files.

The selective fetal reduction procedure was performed for two primary indications. Firstly, the procedure was performed when there was a structural or genetic anomaly that could result in severe sequelae or be incompatible with life in one of the fetuses in a multiple pregnancy. Secondly, the procedure was performed electively in triplets and higher order pregnancies, with the objective of reducing the complications associated with multiple pregnancies. All potential risks associated with multiple pregnancies and selective fetal reduction procedures were thoroughly explained to the family, and informed consent was obtained from all patients prior to the procedure. The decision of the number of live fetus(es) to be preserved subsequent to the procedure was established on the basis of patient preference, technical applicability and chorionicity. The fetus(es) to be reduced was decided according to the presence of fetal anomaly or the ease of application of the procedure.

Prior to the procedure, anatomical screening was performed on all fetuses, irrespective of gestational age. All selective fetal reduction procedures were performed transabdominally by an expert perinatologist. The selective fetal reduction procedure was performed with ultrasound guidance using a 20-G spinal needle. The injection of KCl was administered either intracardiac or intrathoracic, or, if the gestational age was appropriate, into the umbilical vein. Fetal cardiac activity was observed for a minimum of two minutes; if this persisted, an additional KCl injection was administered. The procedure was terminated after ensuring asystole. If more than one fetus was to be reduced, the procedure was repeated for each fetus. Following the procedure, a re-evaluation of all patients was conducted after a 2-hour observation period. The determination of asystole in the fetus(es) that underwent reduction and continuation of cardiac activity in the other fetus(es) was deemed to be indicative of procedural success. In the period of one week following the procedure, pain more than

expected, vaginal bleeding and amniotic fluid leakage were considered as acute complications.

The mode of conception, timing and number of the procedure, indication, number of procedures, development of acute complications, multiple pregnancy feature and reduced pregnancy feature were evaluated in terms of their effects on adverse pregnancy outcomes. Adverse pregnancy outcomes are defined as follows: preterm birth or preterm premature rupture of the membranes prior to 34 weeks of gestation, placental abruption, pregnancy loss before 24 weeks of gestation, and intrauterine fetal death. The present study categorised pregnancies resulting from ovulation induction, with or without intrauterine insemination, and in vitro fertilisation as assisted pregnancies. In the timing of the procedure, the first trimester corresponds to the period up to the 14th week of gestation and the second trimester corresponds to the period between 14-28 weeks of gestation. Multiple pregnancy feature prior to selective fetal reduction procedure was categorised as twin and triple or higher-order, the reduced pregnancy feature was categorised as single and twin or higher-order.

The primary outcome of the study was to identify the factors that affect the outcome of the pregnancy. The data for the continuous variables was expressed in terms of mean \pm standard deviation or median, together with minimum and maximum values, according to the distribution of the data. Categorical variables were expressed as numbers and percentages. For the comparison of categorical variables Fisher exact test was used due to low expected counts. The relative risk for an adverse pregnancy outcome is subsequently calculated. The statistical analysis was conducted using IBM SPSS Statistics version 22.0 (IBM Corporation, Armonk, New York, United States). The level of statistical significance was established as $p < 0.05$.

RESULTS

Selective fetal reduction procedures were performed on 33 multiple pregnancies over a 6-year period. The total number of procedures carried out was 39. The earliest and most advanced gestational weeks at which the procedure was performed were 100/7 and 260/7 weeks, respectively. Ten complications arising from the procedure itself was observed. None of the acute complications resulted in pregnancy loss. A total of 10 patients experienced adverse pregnancy outcomes. Preterm birth occurred in four patients prior to the 34th week of gestation. Preterm premature rupture of the membranes was observed in three patients before the 34th week of gestation. Abruption placentae was diagnosed in one patient in the 35th week of pregnancy. Only in one pregnancy that was reduced from quintuplets to triplets at 14 weeks of gestation, pregnancy loss occurred 3 weeks after the procedure. IUFD occurred in a fetus reduced from DKDA twin pregnancy at 23 weeks of gestation due to unknown reason. 43 newborns were born from 31

pregnancies that resulted in live births. Neonatal death occurred in 1 newborn born at 24 weeks of gestation due to severe prematurity. The clinical characteristics of the patients are shown in Table 1.

Table 1. Clinical characteristics of the patients (n=33)

Age (years)	33.9 \pm 7.3
Parite (n)	0 [0-3]
Mode of conception	
Spontaneous	8 (24.2)
Ovulation induction	7 (21.1)
In vitro fertilisation	18 (54.5)
Multifetal pregnancy feature	
Dichorionic-diamniotic twin pregnancy	17 (51.5)
Trichorionic-triamniotic triplet pregnancy	8 (24.2)
Dichorionic-triamniotic triplet pregnancy	3 (9.1)
Quadruplet and above multiple pregnancy	5 (15.2)
Fetal Reduction Feature	
Reduction to singleton	20 (60.6)
Reduction to twin	12 (36.4)
Reduction totriplet	1 (3.0)
Gestational week at the procedure	15.2 \pm 4.0
Number of performed procedures (needle insertions)	1 [1-3]
Procedural complication	
No	23 (69.7)
Pain	4 (12.1)
Bleeding	1 (3.0)
Amnion leakage	5 (15.2)
Indication	
Fetal anomaly	18 (54.5)
Elective	15 (45.5)
Adverse Pregnancy Outcome	10 (30.3)
Preterm delivery<34th gestational week	4
PPROM<34th gestational week	3
Ablatio placenta	1
Pregnancy loss before 24th gestational week	1
Still birth	1
Pregnancies resulted in live birth	31 (93.9)
Number of live born fetuses	43 (91.5)
GA at birth (weeks)	35,36 \pm 3.96
Birth weight (gram)	2458.2 \pm 924.9
Way of birth*	
Vaginal	6 (18.8)
Ceserean	26 (81.3)
APGAR 1	7 [3-9]
APGAR 5	9 [5-10]
pH	7.31 \pm 0.18
NICU admission**	16 (37.2)
Neonatal death**	1 (2.3)

*one pregnancy loss was excluded **one pregnancy loss and one intrauterine fetal death were excluded. The data was shown as mean \pm standard deviation; median [min-max]; n (%)

Table 2. Comparison of clinical characteristics associated with multifetal reduction in terms of adverse pregnancy outcomes (n=31)

	Adverse Pregnancy Outcome		p
	No (n=21)	Yes (n=10)	
Mode of conception			0.116
Spontaneous	8 (88.9)	1 (11.1)	
Assisted	13 (59.1)	9 (40.9)	
Reduction timing			0.597
First trimester	12 (66.7)	6 (33.3)	
Second trimester	9 (69.2)	4 (30.8)	
Reduction indication			0.019
Elective	7 (46.7)	8 (53.3)	
Fetal anomaly	14 (87.5)	2 (12.5)	
Acute Complication	7 (77.8)	2 (22.2)	0.375
Multiple procedures (multiple needle insertions)	1 (20.0)	4 (80.0)	0.027
Pregnancy feature before the procedure			0.035
Twin	13 (86.7)	2 (13.3)	
Triplet or higher order	8 (50.0)	8 (50.0)	
Pregnancy feature after the procedure			0.036
Reduction to single	15 (83.3)	3 (16.7)	
Reduction to twin or higher order	6 (46.2)	7 (53.8)	

*one pregnancy loss was excluded **one pregnancy loss and one intrauterine fetal death were excluded. The data was shown as mean±standard deviation; median [min–max]; n (%)

In two out of 33 SFR performed pregnancies, labour occurred before 34 weeks of gestation due to severe pre-eclampsia. Following the exclusion of these two cases, a comparison was made of the clinical characteristics of the remaining 31 patients in terms of adverse pregnancy outcome (Table 2). A higher rate of adverse pregnancy outcomes was observed in pregnancies that underwent elective SFR, had undergone multiple procedures, were having triplets or higher-order pregnancies prior to the procedure, or were having twin or higher-order pregnancies after the procedure ($p < 0.05$). The study found that the mode of conception, trimester of multifetal reduction performed, and the development of procedural complications were not significant factors in the occurrence of an adverse pregnancy outcome ($p > 0.05$).

The findings of the study indicated that there was an 8-fold and a 13.3-fold increased risk of adverse outcomes when the SFR procedure was performed electively and multiple times.

As expected, risk of adverse outcomes was elevated in triplet or higher-order pregnancies before the procedure, and in twin or higher-order pregnancies after the procedure. The risk ratio was determined to be 6.5 and 5.8, respectively. The frequency of adverse pregnancy outcomes was found not to be significantly affected by the mode of conception, the timing of the procedure, or the occurrence of acute procedural complications.

Table 3. Adverse pregnancy outcome risk based on clinical characteristics (n=31)

	RR (95% confidence interval)	Frequency
Assisted pregnancy	2.595 (0.586 – 52.331)	70.9%
Fetal reduction at first trimester	1.125 (0.243 – 5.207)	58.1%
Elective procedure	8.000 (1.328 – 48.183)	48.4%
Acute Complication	0.500 (0.083 – 3.011)	29.0%
Multiple procedures	13.333 (1.242 – 143.151)	16.1%
Triplet or higher order before the procedure	6.500 (1.094 – 38.633)	51.6%
Twin or higher order after the procedure	5.833 (1.119 – 30.403)	41.9%

RR, Risk ratio

DISCUSSION

It is widely documented that multiple pregnancies are associated with an elevated risk of perinatal complications, including fetal anomalies, hypertensive disorders, and gestational diabetes, compared with singleton pregnancies. The primary issue relating to infant morbidity and mortality is preterm birth. The Royal College of Obstetricians and Gynaecologists and the American College of Obstetricians and Gynecologists (ACOG) recommend the discussion of selective fetal reduction as a potential procedure for the reduction of perinatal complications in higher-order pregnancies (11, 12).

A previous systematic review reported that reducing trichorionic triamniotic (TCTA) multiple pregnancies to twins resulted in a decrease in preterm birth rates, but an increase in miscarriage rates when compared to expectant management (13). Chaveeva et al also confirmed the current

findings in their study, and also found that miscarriage rates increased and preterm birth rates decreased even more in TCTA multiple pregnancies reduced to singleton pregnancies. (14). A more recent review has shown that reducing TCTA multiple pregnancies to twin pregnancies reduces preterm birth rates without significantly increasing miscarriage rates (15). In this study, no instances of miscarriage were observed among patients who underwent reduction of triplet pregnancies to singleton or twin pregnancies, thereby corroborating the existing findings. Moreover, a meta-analysis of 769 patients who underwent reduction from triplet to singleton pregnancies revealed a decline in preterm birth, neonatal mortality, hypertensive diseases of pregnancy, antenatal hospitalization rates, and cesarean section rates, along with an increase in birth weights. These findings emphasise the significance of counselling families about the risks and benefits of selective fetal reduction in triplet and higher-order pregnancies (16).

In twin pregnancies where there are no maternal or fetal complications, selective fetal reduction depending on the family's request is controversial (11). In the present study, all fetal reduction procedures performed in twin pregnancies were carried out due to the presence of fetal anomalies that were deemed to be incompatible with life or capable of causing serious sequelae. Selective fetal reduction performed in the second trimester of twin pregnancies has been reported to be associated with an elevated risk of miscarriage and preterm birth when compared with the first trimester (17). Although it is possible to diagnose most of the major structural malformations with first trimester fetal anatomical screening, this is not possible for all fetal anomalies. Sometimes, the time required for the completion of fetal genetic studies that will provide an indication for selective fetal reduction necessitates that the procedure be performed in the second trimester. Contrary to the findings reported in the existing literature, our results did not reveal any statistically significant difference in adverse perinatal outcomes based on the trimester of procedure performed.

The acute complication rate of selective fetal reduction in the present study was 30.3%. This appears to be slightly higher than the complication rates reported in the extant literature (18, 19). The most prevalent acute complication was amniotic fluid leakage, which occurred in 5 cases (15.2%). It has been reported that selective termination with KCl injection can result in the occurrence of pain or amniotic fluid leakage. The primary cause of amniotic fluid leakage is usually the reduced fetal sac. However, vaginal bleeding is not a common complication (10). In the present study, postprocedural vaginal bleeding was observed in only one patient (3.0%). As the origin of amniotic fluid cannot be definitively ascertained, all observed amniotic fluid leakages in this study were defined as acute complications. This may have resulted in an increased incidence of complications. No pregnancy loss occurred in any patient following the

observed complications. After the complications were observed, no patient experienced pregnancy loss before the 24th week of gestation. In addition, since no significant increase in the risk of adverse pregnancy outcomes was found, it can be concluded that the occurrence of acute complications does not have a negative effect on long-term outcomes.

The results of the study demonstrate that selective fetal reduction, performed in triplet or higher-order pregnancies before the procedure and in twin or higher-order pregnancies post-procedure, is associated with increased adverse pregnancy outcomes. It is evident that the incidence of adverse perinatal outcomes in multiple pregnancies is higher than in singleton pregnancies. The rates of twin and higher-order pregnancies have increased in conjunction with the utilisation of assisted reproductive techniques (5, 10). The present study found that pregnancies resulting from assisted methods, procedures performed with elective indications, and multiple procedures were associated with an increased risk of adverse pregnancy outcomes. Performing selective fetal reduction electively is considered as an option to avoid perinatal complications in higher order pregnancies. However, the increased adverse perinatal risk in pregnancies with assisted methods, elective procedures, and multiple procedures can be mainly attributed to the risks associated with higher order pregnancies. In this context, instead of considering selective fetal reduction as the first option in the management of higher order pregnancies, single embryo transfer should be the priority in patients undergoing in vitro fertilization (20). Single embryo transfer has been shown to reduce the incidence of multiple pregnancies, though not entirely prevent it (21). In circumstances where the prevention of a higher order pregnancy has not been possible, selective fetal reduction should be considered as a method of reducing the risk of adverse pregnancy outcomes.

It must be accepted that this study is not free from certain limitations. These include the retrospective design and the relatively low number of patients. Furthermore, the heterogeneity of multiple gestations that undergo selective fetal reduction is another limitation of this study. Consequently, further research comprising a larger patient cohort and ensuring uniformity with the type of multiple pregnancy could provide more accurate and detailed data.

CONCLUSION

Triplets and higher-order pregnancies, electively indicated procedures requiring multiple interventions have been shown to be associated with an increased risk of adverse pregnancy outcomes. Assisted reproductive technologies (ART) should be used in a manner that does not lead to higher order pregnancies, rather than the utilisation of SFR as a primary option.

Acknowledgements: We would like to express our gratitude to the secretaries of the perinatology clinic for their assistance in obtaining retrospective data.

Ethics Committee Approval: The study protocol was approved by Zeynep Kamil Women and Children Diseases Training and Research Hospital Clinical Investigations Ethical Committee (Approval number:168,Date:20.12.2023).

Informed Consent: An informed consent form was obtained from the patient/patient's representative to collect and publish the patient's clinical information.

Authorship Contributions: Idea/Concept:ÖGE, MG, Design: ÖGE, MEÖ, Supervision: OD, Data Collection and Processing: ÖGE, MG, ÜT, Analysis or Interpretation: MEÖ, ÜT, Literature Search:MG, ÜT, Writing: ÖGE, Critical Review: MEÖ, ÜT, OD, References and Fundings: -, Materials: -.

Conflict of Interest: All authors declare that they have no conflict of interest.

Financial Disclosure: The author(s) reported there is no funding associated with the work featured in this article.

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