



ARAŞTIRMA/RESEARCH

Reduction of multifetal gestation to twins: is it always possible to attain natural outcomes?

Çoğul gebeliklerin ikize indirgenmesi: doğal sonuçları elde etmek her zaman mümkün müdür?

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Abstract

Purpose: The aim of this study was to evaluate effects of transabdominal fetal reduction on pregnancy outcomes.

Material and Methods: Women with multifetal gestation whose pregnancies were reduced to twins were compared with spontaneous twins and assisted reproduction twins. The main outcome measures were the duration of pregnancy, premature labor and delivery rates, complication rates during pregnancy, birth weight, APGAR scores, neonatal intensive care unite admission rates, and delivery routes.

Results: 380 twin deliveries followed up at our institution between years 2007-2014 were enrolled. All data concerning perinatal outcomes were compared among three groups. twins conceived spontaneously (group 3, n=165) and via IVF (group 1, n=117) along with IVF conceived high order pregnancies wherein embryo reduction was implemented (group 2, n=49). The duration of pregnancy, the rate of premature and the rate of overall pregnancy associated complications were all favorable in group 1 rather than group 2. As well, the mean birth weight and APGAR scores at 1st and 5th minutes were all found to be lower in group 2 than in group 1.

Conclusion: The results emphasize embryo reduction should be acknowledged as a salvage procedure due to high risk of complications in embryo reduced high-order pregnancies. Embryo reduction yields results comparable to twins conceived via IVF yields poorer results compared to spontaneously conceived twins.

Key words: Multifetal pregnancy, embryo reduction, assisted reproductive technology, spontaneous twins.

Öz

Amaç: Bu çalışmanın amacı transabdominal fetal redüksiyonun gebelik sonuçlarına olan etkisini araştırmaktır.

Gereç ve Yöntem: Redüksiyon yapılan ikiz gebelikler ile spontan ikiz ve yardımcı üreme teknikleri (IVF) ile oluşan ikiz gebelikler karşılaştırıldı. Gebelik süreleri, pematür doğum ve doğum oranları, gebelikteki komplikasyonlar, doğum ağırlığı, APGAR skoru, yenidoğan yoğun bakımda yatış oranı ve doğum şekli açısından karşılaştırıldı.

Sonuç: 2007-2014 yılları arasında takibi yapılan 380 ikiz doğum çalışmaya alındı. Perinatal sonuçlar ile ilgili tüm veriler üç grup arasında karşılaştırıldı. Spontan ikiz gebelikler (grup 3, n=165) ve IVF ile oluşan ikiz gebelikler (grup 1, n=117) ve redüksiyon sonrası ikiz gebelik devam edenler (grup 2, n=49). Gebelik süresi, erken doğum ve gebelik ile ilişkili komplikasyonlar grup 1'deki hastalarda grup 2'ye göre anlamlı olarak iyiydi. Bunun yanı sıra doğum ağırlığı, APGAR 1.ve 5.dakika skorları grup 2'de grup 1'e göre daha düşüktü.

Tartışma: Embriyo redüksiyonu yüksek riskli komplikasyonları olmasına rağmen çoğul gebeliklerde önerilmektedir. Embriyo redüksiyonu, IVF ile olan ikiz gebelikler spontan ikiz gebelikler ile karşılaştırıldığında sonuçları daha olumsuz olarak saptanmıştır.

Anahtar kelimeler: Çoğul gebelik, embriyo redüksiyonu, yardımla üreme teknolojisi, spontan ikizler.

INTRODUCTION

Multifetal high-order pregnancies have increased dramatically in recent years, especially during the last three decades with increasing popularity of artificial reproduction^{1,2}. High-order pregnancies are characterized with increased rates of diabetes, hypertensive disorders, cesarean section and prematurity compared to twin pregnancies³. Embryo reduction is the preferred intervention and appears to be a safe method of reducing perinatal, maternal mortality and morbidity by reducing preterm birth rates^{3,4}. Some of the available data have shown a reduction of preterm birth rates from 66% to 35%, reduction of severe prematurity rates from 23.8% to 10% and also increased rates of pregnancies reaching term from 10% to 57%^{5,6}.

Advent of assisted reproductive technologies (ART) and artificial fertilization techniques increased the rates of multifetal pregnancies⁷. Inadvertently ART provided a venue for physicians to better their management protocols for multifetal pregnancies. However, regardless of a physician's expertise at management of multifetal gestation, multifetal pregnancies are associated with poorer outcome compared to singletons. increased rates of premature labour, low birth weight and maternal complications are encountered in multifetal pregnancies⁸⁻¹⁰. Practice of fetal reduction for multifetal pregnancies of high order, especially three and more, were supported by these findings.

In our study we aimed to determine the effects of fetal reduction on perinatal and maternal outcomes by comparing multifetal pregnancies of high-order that are reduced to twins with spontaneous twin pregnancies and twin pregnancies conceived via IVF. By comparing reduced to twins pregnancies with spontaneous twins and IVF twins, we wanted to evaluate reduction intervention as the major variable between groups. This was we aimed to eliminate most of the confounding factors that would effect the analysis.

MATERIAL AND METHODS

In this retrospective study, twin pregnancies conceived either spontaneously or by via IVF and who also delivered in Ankara University Department of Obstetrics and Gynecology between years 2007 and 2014 were included. The study population was divided into two arms as control

group consisting dichorionic diamniotic twins conceived either via IVF or spontaneously (n: 331), and study group consisting multifetal high-order gestations that underwent fetal reduction and which were successfully reduced to twins (Group 2). The control group was further divided into two subgroups according to conception method (spontaneous and with assisted reproduction, Group 3 and Group 1, respectively). Patients with unsuccessful fetal reduction, ongoing mono-amniotic twin pregnancies after fetal reduction, fetuses with known congenital abnormalities, women with known placental adhesion disorders or chronic disease known to be associated with poor pregnancy outcome (Diabetes, Heart Disease etc.) were excluded from the study.

All fetal reductions were performed between 10-13th gestational weeks via abdominal route using a disposable 20 gauge amniocentesis needle (Cook Medical Inc. , Bloomington IN, USA) with ultrasound assistance. A 0,1-0,3 cc solution of 7,5% potassium chloride was used for intracardiac injection. Absence of cardiac activity was confirmed via ultrasound 1 hour after the procedure. All procedures were performed by a highly skilled clinician with 15 years of expertise in invasive fetal interventions. Reduced fetuses were chosen randomly by the operator. In cases of monozygotic twinning, one of the monozygotic twins was reduced due to documented poorer obstetrical outcomes of monozygotic twins compared to dizygotic twins. All patients were hospitalized for one day and prophylactic antibiotics were avoided. Patient were observed for febrile morbidity and membrane rupture. Information on parity, gestational age at birth, complications, delivery route, birth weight and APGAR scores were all recorded. Groups were formed for statistical analysis. Group 1 consisted of women with twin pregnancies conceived with IVF, Group 2 consisted of women with multifetal pregnancies that underwent embryo reduction, Group 3 consisted of women with spontaneous twin pregnancies. This retrospective study was exempt from ethical approval by Ankara University Ethics commission.

Statistical analysis

Analysis of all groups together were made with ANOVA test for parameters with normal distribution, and with Kruskal Wallis test for parameters with non-normal distribution.

Categorical parameters were compared with chi-square test. Comparison of groups were made with t test for parameters with normal distribution and with Mann Whitney U test for parameters with non-normal distribution. *p* values below 0.05 were considered statistically significant.

RESULTS

Totally 49 high order pregnancies (group 2) were reduced to twin pregnancies. 37 of 49 multifetal pregnancies were triplets, 11 were quadruplets and one was a quintuplet pregnancy. Control groups consisted of 165 twin pregnancies conceived via IVF (group 1) and 117 twin pregnancies conceived spontaneously (group 3) were enrolled in the study.

All demographic parameters of patients are shown in Table 1. Demographic parameters revealed older maternal age in group 2 compared to group 3 and group 1, respectively (33.06 ± 2.37 vs 31.05 ± 6.07 and 29.63 ± 5.22 , $p < 0.001$).

Duration of gestation was significantly longer in spontaneous twin pregnancies compared to IVF twin pregnancies and twin pregnancies with embryo reduction, (250.7 ± 17.1 days vs 239 ± 26.5 and 233.8 ± 31.3 , respectively, $p = 0.005$). Duration of gestation was shorter in group 2 compared to the other groups which was also reflected differences of birth weight and APGAR scores of infants (Table

1). The majority of fetuses were delivered via cesarean and there was not any statistically significant difference among groups (Table 1, Group 1 96.4% n: 159, Group 2 87.6% n: 43, Group 3 82.1% n: 96 $p = 0.073$). However this difference did not reach a statistical significance. Severe prematurity, defined as birth before 24th week of gestation, was more prevalent in group 2 (12.2% n: 6) compared to control groups. Premature delivery rates were 83.6% (n: 138) for IVF twins, 77.6% (n: 38) for embryo reduction twins and 66.7% (n:116) for spontaneous twins. Although premature birth rates were higher in IVF pregnancies and in embryo reduction twins, difference did not reach a statistical significance. (Table 3)

Pregnancy related complications were more prevalent in embryo reduction group with the exception of preeclampsia which was more prevalent in other groups. (Table 2) A comparison was also made for subgroups of embryo reduction group. Reduced triplets (n: 37), quadruplets (n: 11) and quintuplet (n: 1) were compared with each other for maternal-fetal outcomes and pregnancy complications. Subgroup analysis did not show any significant differences between subgroups.

In our research group we experienced three short term complications related to procedure with one chorioamnionitis and two early membrane ruptures.

Table 1. Comparison of clinical features of study groups

Variable	Grup I (n=165)	p1	Grup II (n=49)	P2	Grup III (n=117)	P3
Age	29.63±5.22	0.001	33.06±2.37	0.024	31.05±6.07	0.008
Gravida (mean±min-max)	1.18 (1-4)	0.014	1.53(1-10)	0.029	1.79(1-5)	<0.001
Parity (mean ±min-max)	0.05(0-1)	0.086	0.16(0-1)	0.002	0.56(0-3)	<0.001
Duration of Pregnancy	239±26.5	0.424	233.8±31.3	0.005	250.7±17.1	0.006
Birth Weight	2177±512	0.358	2056±734	0.004	2447±516	0.005
APGAR Score (Minute 1)	7.16(0-9)	0.091	6.5(0-9)	0.047	7.47(3-9)	0.098
APGAR Score (Minute 5)	8.8(0-10)	0.011	7.83(0-10)	0.001	9.2(4-10)	0.002

p1 comparison of group 1 and group 2; p2 comparison of group 2 and group 3; p3 comparison of all groups; PROM: Premature rupture of membranes

Table 2. Comparison of delivery types, complications of study groups

	IVF Twins (n=165)	P ¹	Embryo Reduction Twins (n=49)	P ² (G II ile G III)	Spontaneo us Twins (n=117)	P ³
Delivery Route						
Cesarean Section	159(96.4%)	0.150	43(87.6%)	0.403	96(82.1%)	0.073
Vaginal Birth	6 (3.6%)		6(12.2%)		21(17.9%)	
Intrauterine Fetal Death	6 (3.6%)	0.425	4(8.2%)	0.393	3(2.6%)	0.413
Complications						
Preeclampsia	15(9.1%)	0,09	1(2%)	0.163	9(7.7%)	0.262
Threatened abortion	0	<0,01	11(22.4%)	<0.01	0	<0.01
Premature Labour	3(1.8%)	<0,01	10(20.4%)	<0.01	3(2.6%)	<0.01
PROM	0	0,09	2(4.1%)	0.028	0	0.03
Chorioamnionitis	0	0,066	1(2%)	0.121	0	0.056
HELLP syndrome	0		0	0.258	3(2.6%)	0.063

p¹ comparison of group 1 and group 2; p² comparison of group 2 and group 3; p³ comparison of all groups

Table 3. Comparison of birth weeks of study groups

Birth Week	IVF Twins (n=165)	P ¹	Embryo Reduction Twins (n=49)	P ²	Spontaneous Twins (n=117)
≥37 weeks	27(16.4%)	0.62	11(22.4%)	0.22	39(33.3%)
34≤ and <37 weeks	84(50.9%)	0.07	16(32.7%)	0.50	48 (41%)
32≤ and <34 weeks	30(18.2%)	0.63	11(22.4%)	1.00	24(20.5%)
28≤ and <32 weeks	15(9.1%)	0.54	7(14.3%)	0.13	3(2.6%)
24≤ and <28 weeks	6(3.6%)	0.49	0	0.42	3(2.6%)
Below 24 weeks	3(1.8%)	0.19	4(8.2%)	0.13	0

p¹ comparison of group 1 and group 2; p² comparison of group 2 and group 3.

DISCUSSION

More than two decades later since its first use, selective fetal reduction is still the preferred intervention for high-order multifetal pregnancies¹¹. Method of embryo reduction varies between institutions and transvaginal aspiration of embryo during early pregnancy seems to have a small advantage over other methods in regards of safety and ease of the procedure. The recommended window for transabdominal procedure is between 11th and 13th week of gestation¹².

To point out the strong points of our research ; All of the patients were followed-up in our institution which has 19 years of experience with management

of multifetal pregnancies and embryo reduction. All of the interventions were done by the same experienced operators which eliminates human factor as a variable between patients. Weak points of our research were being retrospective and a small amount of patients with missing records could not be included in embryo reduction arm. We also had limited number of patients in high-order pregnancy arm with four or more embryos. However contemporary regulations on ART does not allow transfer of more than two embryos, which explains the limited number of patients we received over the last 7 years.

Evans et al. reported an overall 9,6% pregnancy loss rate in patient undergoing embryo reduction but

argued outcome of embryo reduction is operator dependent and increasing experience improves results. We observed 8,7% (n: 4) pregnancy loss rate in our research group in concordance with published literature¹³.

Prognosis of pregnancies undergoing embryo reduction was similar to that of IVF twin pregnancies. Overall results did not show any statistically significant difference for duration of gestation, premature labor rates, birth weight or APGAR scores. Stone at al. reported, in a group of patients that underwent embryo reduction by transvaginal aspiration of embryos had comparable outcomes to spontaneous dichorionic diamniotic twin pregnancies. In contrast this finding, our study has shown embryo reduction pregnancies last shorter and they are more prone to premature labor and lower birth weights compared to spontaneous twins, also reflected by lower APGAR scores of fetuses in embryo reduced patients compared to the spontaneous twins. Difference perhaps could be explained by the transabdominal versus early transvaginal technique. Although reduced to twins pregnancies lasted shorter than spontaneous twins, we did not observe a statistically significant difference in overall preterm birth rates among all groups¹⁴.

More than a decade has passed since the first description and use of transvaginal aspiration technique. During that time transvaginal approach allowed for an earlier intervention window compared to transabdominal approach. Whether this edge of transvaginal approach is still present should be questioned. Perhaps transabdominal intervention performed during earlier weeks will yield results comparable to transvaginal approach. A study comparing two methods performed within same weeks of gestation could provide useful information. Number of embryos reduced did not affect the pregnancy outcomes. Indeed there are some reports claiming number of embryos reduced adversely effects pregnancy outcome. Beck at al. reported reducing triplet pregnancies to a singleton doubled the pregnancy loss rate compared to reducing triplets to twins. We did not observe any increase in pregnancy complications with increasing number of reduced embryos. However this may be due to relative small number of patients in quadruple and quintuple (n: 11 and n:1 respectively) pregnancy study arms. In Turkey, there is an imposed restriction on the number of transferred

embryos per cycle (limited to two). This strict enforcement dramatically changed the rate of high-order multifetal pregnancies and subsequently led to a reduced number of patients referred to our institution for embryo reduction^{14,15}. The limitation of our study is retrospective nature.

In summary; our study has shown embryo reduction is an effective way of improving pregnancy outcomes for women with high-order multifetal gestation. Contrary to current literature we observed poorer outcome of embryo reduced twins compared to spontaneous twins. Embryo reduction twins fared similar to IVF twins in terms of pregnancy duration, premature birth, birth weight and APGAR scores. Our results could be inferred as it is not always possible to attain good results with embryo reduction, i.e similar to spontaneous twins. Embryo reduction is a salvage procedure, most often used as a remedy to ART's complication of high-order multifetal pregnancy. Strict adherence to embryo transfer restrictions is a probably better way to deal with high order multifetal pregnancies rather relying on embryo reduction. Embryo reduction should be kept in mind as a salvage procedure and physicians should focus more on preventing high-order multifetal pregnancies rather than treating it.

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