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A comparison of obstetric and perinatal outcomes of spontaneous and in vitro fertilization (IVF) twin pregnancies

Spontan ve invitro fetilizasyon (IVF) ikiz gebeliklerin obstetrik ve perinatal sonuçlarının karşılaştırılması

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ABSTRACT

Aim: We aimed to compare and analyze the perinatal and obstetric outcomes of in vitro fertilization (IVF) method and spontaneous twin pregnancies.

Material and Method: Pregnant women who had had IVF and those with spontaneous fertilization in a tertiary perinatology center between January 2016 and January 2021 were retrospectively included in this study. The demographic data of the women (gender, age, gestational week) and fertilization types (spontaneous or IVF) were analyzed. Premature rupture of membranes (PROM), preterm delivery (PD), and intrauterine growth restriction (IUGR) was recorded. Additionally, Apgar scores, the presence of fetal anomalies, the need for neonatal intensive care (NICU) and mortality were analyzed.

Results: Overall, 261 women who were pregnant with twins were included in this study. The median age of the mothers was 29 years (min 15-max 40 years), and 23.8% were ≥35 years. Spontaneous and IVF pregnancies occurred in 75.9% and 24.1%, respectively. The most common problems in the twin pregnancies were PROM (14.6%), PD (13.4%), GHT (11.5%), oligohydramnios (6.1%), GDM (4.6%), and polyhydramnios (2.3%). Also, 13.8% had IUGR. The median age of the women with IVF pregnancies was higher than the spontaneous pregnancies (33.0 vs 28.0 years) ($p<0.001$). The maternal age was found to be significantly higher in those women with PD compared to those without PD (33.0 vs 28.0 years) ($p=0.009$). The incidence of PROM and the rate of PD were significantly higher in the IVF pregnancies group compared to the spontaneous pregnancies group ($p<0.001$ and $p<0.001$, respectively). The postnatal 1st and 5th minute Apgar scores of the twin babies were significantly lower in the IVF group ($p<0.001$). Over the half of babies needed NICU and this rate was significantly higher in the IVF group compared to the spontaneous pregnancy group (71.4% vs 50.5%) ($p=0.004$).

Conclusion: IVF twin pregnancies are risky pregnancies in terms of PROM and PD. Additionally, the need for NICU is higher for IVF twin birth pregnancies than for spontaneous twin pregnancies.

Keywords: Twin pregnancy, in vitro fertilization, IVF, PROM, twins

ÖZ

Amaç: Spontan ikiz gebelikler ile invitro fertilizasyon (İVF) yöntemi ile gerçekleşen ikiz gebeliklerin perinatal ve obstetrik sonuçlarını karşılaştırmayı ve analiz etmeyi amaçladık.

Gereç ve Yöntem: Ocak 2016-Ocak 2021 tarihleri arasında üçüncü basamak perinatoloji merkezinde İVF yöntemiyle veya spontan şekilde gerçekleşen ikiz gebeler retrospektif olarak çalışmaya dahil edildi. Gebelerin demografik verileri (cinsiyet, yaş, gebelik haftası) ve doğum şekilleri (spontan ve İVF) analiz edildi. Gebelerde görülen erken membran yırtılması (EMR), preterm doğum (PD) ve intrauterin büyüme geriliği (IUBG) sıklıkları kaydedildi. Ayrıca apgar skorları, fetal anomalilerin varlığı, yenidoğan yoğun bakım (YYB) ihtiyacı ve mortalite oranları analiz edildi.

Bulgular: Toplam 261 ikiz gebe çalışmaya dahil edildi. Ortanca yaş 29 (en az 15-en fazla 40 yıl) ve %23,8 'i ≥35 yaşındaydı. Spontan ve IVF gebelik oranları, sırasıyla, %75,9 ve %24,1 idi. İkiz gebeliklerde en sık görülen sorunlar sırasıyla EMR (%14,6), PD (%13,4), GHT (%11,5), oligohidramnios (%6,1), GDM (%4,6) ve polihidramnios (%2,3) idi. Ayrıca %13,8'inde IUBG vardı. IVF gebelerin ortanca yaşı, spontan gebelere göre anlamlı derecede daha yüksekti (33,0-28,0) ($p<0,001$). Preterm doğum olan gebelerde gebelik yaşı, PD olmayanlara göre anlamlı olarak daha yüksek bulundu ($p=0,009$). IVF yönetiyle gerçekleşen ikiz gebeliklerde EMR ve PD insidansı spontan gebeliklere göre daha yüksekti (sırasıyla $p<0.001$ ve $p<0.001$). İkiz bebeklerin postnatal 1-5. dakika Apgar skorları IVF grubunda daha düşüktü ($p<0,001$).Bebeklerin yarısından fazlasında YYB ihtiyacı mevcuttu ve bu oran IVF grubunda spontan gruba göre anlamlı olarak daha yüksekti (%71,4-%50,5) ($p=0,004$).

Sonuç: IVF ikiz gebelikleri EMR ve PD açısından riskli gebeliklerdir. Ayrıca, IVF ikizlerinde YYB ihtiyacı spontan ikiz bebeklere göre daha yüksektir.

Anahtar Kelimeler: İkiz gebelik, invitro fertilizasyon, IVF, EMR, ikiz

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INTRODUCTION

Twin births constitute 3.1% of all live births and 97.5% of all multiple births (1). While the incidence of spontaneous twins varies by country, with the advent of assisted reproductive techniques [In vitro fertilization (IVF), Gamete intrafallopian tube transfer (GIFT), and Intracytoplasmic sperm injection (ICSI)], the incidence of multiple pregnancies has increased significantly (2). In the study of Kulkarni et al. (3), it was reported that assisted reproductive techniques were used with a frequency of 36% in twin pregnancies and 77% in triplet or more pregnancies.

Due to the development of spontaneous and in vitro fertilization (IVF) methods, the increasing number of multiple pregnancies has led to an increase in obstetric and perinatal risks. Preterm and low birth weight deliveries are reported as the main reasons for this in multiple pregnancies (4). In addition, the higher incidence of gestational diabetes mellitus and hypertensive diseases in multiple pregnancies also causes an increase in perinatal and obstetric complications (5,6). Although it has been reported that IVF in singleton pregnancies causes an increased perinatal and obstetric risk compared to spontaneous ones, this issue is highly controversial in twin pregnancies (7,8). In the literature, studies reporting that the frequency of preterm IVF method births in twin pregnancies is similar to spontaneous twins (9,10). On the other hand, in the study conducted by Tandulwadkar et al. (11), it was shown that the rates of late preterm births in IVF twin pregnancies were slightly increased compared to spontaneous twin pregnancies. However, this result was affected by the fact that the IVF group mothers were older than the spontaneous fertilization mothers', or that there are other factors that increase the risk of preterm birth (pregestational diabetes mellitus, chronic hypertension, etc.) (11).

We aimed to compare and analyze the perinatal and obstetric outcomes of IVF and spontaneous twin pregnancies.

MATERIAL AND METHOD

The study was carried out with the permission of Istanbul Kanuni Sultan Süleyman Training and Research Hospital Clinical Researches Ethics Committee (Date: 26.05.2021, Decision No: 183). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients Selection

All spontaneous and IVF pregnancies during the January 2016 and January 2021 period with mothers aged between 20-42 years were retrospectively included in this study. Singleton pregnancies were excluded from this study.

Data Collection and Assessment of Patients

The demographic data of the pregnant women (gender, age, gestational week) and fertilization types (spontaneous or IVF) were analyzed. Premature rupture of membranes (PROM), preterm delivery (PD), and intrauterine growth restriction (IUGR) was recorded. It was recorded whether the twins were discordant between the twins in terms of their birth weight. Discordance between the birth weights of the newborns was defined as a difference between the birth weights of infants above 25% (12). Gestational hypertension (GHT), gestational diabetes mellitus (GDM), anemia, polyhydramnios, and oligohydramnios during pregnancy were investigated. Apgar scores, the presence of fetal anomalies, the need for neonatal intensive care (NICU) and mortality were analyzed.

Statistical Analysis

Data were analyzed using the SPSS 25.0 (IBM, Armonk, NY: IBM Corp.) program. Continuous variables were expressed as mean ± standard deviation, median (interquartile range, IQR), and categorical variables as numbers (n) and percentages (%). When the parametric test assumptions were met, Student's t-test was used to compare differences between independent groups. When parametric test assumptions were not met, the Mann-Whitney U test was used to compare differences between independent groups. The Chi-square or Fisher's exact probability tests were used to compare demographics. In all analyses, $p<0.05$ was considered statistically significant.

RESULTS

Overall 274 pregnant twins were analyzed. Thirteen twin pregnancies were excluded from the study due to missing data. Therefore, two hundred sixty-one women who were pregnant with twins were included in this study. Their median age was 29 years (min 15-max 40 years), and 23.8% (n=62) were 35 years or older. Spontaneous and IVF pregnancies occurred at rates of 75.9% and 24.1%, respectively (**Table 1**). Nearly half of the IVF pregnancies (42.9%) and only 17.7% of the spontaneous pregnancies were 35 years or older ($p<0.001$). While the median week of delivery was 34+6 (min 17+1-max 40+3 weeks) in all pregnancies, it was 31+6 weeks (min 17+1-max 36+3) in the IVF group and 35+4 weeks (min 24+3-max 40+3) in spontaneous pregnancies group (Table 1). Normal spontaneous vaginal delivery (NSVD) occurred in the majority of the births (92.7%) and cesarean section (C/S) was performed in only 7.3% of cases (**Table 1**).

Table 1. Demographic characteristics of women pregnant with twin

Age (year) [median (min-max)]	29.0 (15-40, 26-34)
Pregnancy [n (%)]	
Spontaneous	198 (75.9)
IVF	63 (24.1)
Pregnancy week [median (min-max)]	34^{+6} (17^{+1}-40^{+3})
Spontaneous	35^{+4} (24^{+3}-40^{+3})
IVF	31^{+6} (17^{+1}-36^{+3})
Birth type [n (%)]	
NSVD	242 (92.7)
C/S	19 (7.3)

C/S: caesarean section, IVF: in vitro fertilization, min: minimum, max: maximum, NSVD: normal spontaneous vaginal delivery

The most common problems in the twin pregnancies were PROM (14.6%), PD (13.4%), GHT (11.5%), oligohydramnios (6.1%), GDM (4.6%), and polyhydramnios (2.3%) (**Table 2**). Additionally, 13.8% of the twin pregnancies had IUGR.

Table 2. Obstetric and prenatal outcomes of twin pregnancies and neonates

Obstetric / Prenatal Outcomes	**n (%)**
PROM	38 (14.6)
IUGR	36 (13.8)
Preterm delivery	35 (13.4)
Pregnancy HT	30 (11.5)
Oligohydramnios	16 (6.1)
Diabetes Mellitus	12 (4.6)
Polyhydramnios	6 (2.3)
Anemia	2 (0.8)
IUFE	8 (3.1)
Fetal anomaly	5 (1.9)
Need for NICU	145 (55.6)

PROM: premature rupture of membranes, HT: hypertension, IUGR: intrauterine growth restriction, IUFE: intrauterine fetal exitus, NICU: neonatal intensive care unit

The median age of the women in the IVF group was statistically significantly higher than the spontaneous pregnancy group (33.0 vs 28.0 years) (p<0.001) (**Table 3**). Also, it was observed that the delivery week of the IVF pregnancy group was significantly lower than the spontaneous pregnancy group (p<0.001) (**Table 3**). The gestational age and IVF or spontaneous pregnancy did not affect the type of delivery (p=0.320 and p=0.785, respectively) (**Table 3**). In addition, the gestational age was found to be significantly higher in those pregnancies with PD compared to those without PD (33.0 vs 28.0, respectively) (p=0.009).

There was no significant difference between the development of GHT and spontaneous or IVF pregnancies (p=0.256) (**Table 3**). In addition, the incidence of PROM and the rate of PD were statistically significantly higher in the IVF group compared to the spontaneous group (p<0.001 and p<0.001, respectively) (**Table 2**).

Table 3. The comparison of pregnancy demographics, features and birth types with spontaneous and IVF pregnancies.

	Pregnancy type		p
	Spontaneous	**IVF**	
Pregnancy age [median (min-max)]	28 (18-40)	33 (21-40)	<0.001
Pregnancy week [median (min-max)]	35^{+4} (24^{+3}-40^{+3})	31^{+6} (17^{+1}-36^{+3})	<0.001
Birth type [n (%)]			0.785
NSVD	184 (92.9)	58 (92.1)	
C/S	14 (7.1)	5 (7.9)	
Pregnancy HT [n (%)]			0.256
+	20 (10.1)	10 (15.8)	
-	178 (89.9)	53 (84.2)	
PROM [n (%)]			<0.001
+	17 (8.6)	21 (33.3)	
-	181 (91.4)	42 (66.7)	
Preterm delivery			<0.001
+	13 (6.6)	22 (34.9)	
-	185 (93.4)	41 (65.1)	

C/S: caesarean section, HT: hypertension, IVF: in vitro fertilization, min: minimum, max: maximum, NSVD: normal spontaneous vaginal delivery, PROM: premature rupture of membranes

The incidence of fetal anomalies in the twin babies was found to be 1.9% (n=5) (**Table 2**). There was no relationship between the presence of IUGR in babies and spontaneous pregnancy or IVF pregnancy (p=0.207) (**Table 4**). In addition, the postnatal 1st and 5th minute Apgar scores of the twin babies were statistically significantly lower in the IVF group (p<0.001) (**Table 4**). While the frequency of discordance between birth weights of the twin babies was 21.1%, it was 26.9% in the IVF group and 19.2% in the spontaneous twin group. There was no significant difference between the two groups in terms of discordance (p=0.215) (**Table 4**). After birth, 55.6% of babies needed NICU and this rate was statistically significantly higher in the IVF group compared to the spontaneous fertilization group (71.4% vs 50.5%, respectively) (p=0.004) (**Table 4**). In addition, while intrauterine fetal exitus (IUFE) occurred in 3.1% (n=5), there were 2 IUFE in the IVF group and 3 in the spontaneous group.

Table 4. The comparison of IUGR, apgar scores, discordance and need for NICU with spontaneous and IVF pregnancies.

	Pregnancy type		p
	Spontaneous	**IVF**	
IUGR			0.207
+	24 (12.1)	12 (19.0)	
-	174 (87.9)	51 (81.0)	
Apgar score [median (IQR)]			<0.001
1st baby (1-5. min)	7 (6-7)-9 (8-10)	6 (3-7)-8 (7-9)	
2nd baby (1-5. min)	7 (6-8)-9 (8-10)	6 (3-7)-8 (6-9)	
Need for NICU			0.004
+	100 (50.5)	45 (71.4)	
-	98 (49.5)	18 (28.6)	
Discordance			0.215
+	38 (19.2)	17 (26.9)	
-	160 (80.8)	46 (73.1)	

IQR: interquantile range, IUGR: intrauterine growth restriction, IVF: in vitro fertilization, min: minute, NICU: neonatal intensive care unit

DISCUSSION

In this study, it has been shown that IVF and spontaneous twin pregnancies have an affect on both obstetric and prenatal outcomes. Accordingly, different problems occur in twins after birth.

The ages of women using assisted reproductive techniques have been reported to be higher than in those with spontaneous pregnancies (13,14). It was reported that 25.8% of twins in Australia were using assisted reproductive techniques and 45.2% of them were 35 years or older (15). In a study conducted by Ozcil MD (16) in our country, it was shown that 9.5% of spontaneous twins and 35% of twins who were conceived by assisted reproductive technique were aged 35 or over. In our study, 42.9% of IVF pregnancies and only 17.7% of spontaneous pregnancies were 35 years or older. While this rate is similar to the literature, it can be observed that the percentage of pregnancies that were ≥35 years was higher in both our IVF group and our spontaneous pregnancy group. Today, the higher gestational age and the more frequent use of assisted reproductive techniques can explain this result.

It was reported that 18% of twin pregnancies in the USA, 18% in the UK, 23.3% in Australia and 41% in Italy are not spontaneous and that assisted reproductive techniques had been used (15-18). In our country, 67-78% of twin births are spontaneous pregnancies (14,16). In this study, similar to the literature, the spontaneous twin pregnancy rate was 75.9%, while the IVF pregnancy rate was 24.1%. In the literature, the C/S ratios in IVF twin pregnancies are significantly higher than in spontaneous twin pregnancies (19,20). Contrary to the literature, in our study, normal birth rates were found to be significantly higher in both groups. The high normal birth rates in both groups were thought to be due to the encouragement of normal birth in our country, and the preference for normal birth except in cases where preterm birth or cephalic presentation are absent.

In the literature, the rates of PROM development in twin pregnancies after IVF are similar to spontaneous twin pregnancies and the use of IVF does not increase this risk (21,22). In a study conducted in our country, the rate of PROM was found to be 22% in IVF twin pregnancies and 19.8% in spontaneous twin pregnancies (16). In our study, contrary to the literature, the risk of PROM was found to be higher in the IVF group than in the spontaneous pregnancy group (33.3% vs 8.6%). The fact that our center is a tertiary referral center and that the majority of pregnancies with PROM are admitted to our center may explain this result.

PD rates are higher in twin pregnancies compared to singleton pregnancies, with a frequency of 36-79% (15,18,23-26). It has been reported that PD rates are similar between spontaneous twin pregnancies and IVF twin pregnancies (15,26,27). In our study, the rate of PD was found to be quite low (13.8%) compared to the literature. The low prevalence of chronic diseases which may increase the rate of PD in pregnancies and the fact that the gestational age is not advanced may explain this low rate of PD. In addition, PD rates were found to be similar between our spontaneous twin pregnancies and IVF twin pregnancies. This finding is in line with the literature.

In the studies conducted by Gluck et al. (10) and Barda et al. (28), GHT increased in IVF twin pregnancies. Additionally, the age of the pregnant women was found to be higher, but advanced age was ignored while reaching this conclusion in these studies. On the other hand, in the meta-analysis published by Pinzauti et al. (29) in 2016, it was stated that GHT rates were similar in IVF and spontaneous twin pregnancies. In our study, while GHT was observed at a rate of 11.5%, which is similar to the literature, there was no difference in the frequency of GHT between IVF and spontaneous twin pregnancies.

In some studies, it was reported that the risk of fetal anomaly increases in IVF twin pregnancies (19). On the other hand, after considering maternal age and accompanying diseases, IVF does not increase the risk of fetal anomaly (20). As only 5 fetal anomalies were observed in our study, no comparison could be made between the two groups.

Many studies are reporting that the discordance seen in twin babies is higher in twin pregnancies using assisted reproductive techniques compared to spontaneous pregnancies (13,30). However, it has been shown recently that there is no discordance difference between IVF and spontaneous twins (14,15,18,31). In our study, the frequency of discordance between the birth weights of the twin babies was found to be similar in both groups. This result is in line with the literature. The incidence of IUGR development in twins has been reported to be between 4.9% and 8.1% in our country (32,33). Some studies have shown that there is no difference between spontaneous twins and IVF twins in terms of IUGR (2,33). In our study, the frequency of IUGR was found to be 13.8%, which is similar to the literature, and there was no significant difference between the two groups.

Intrauterine fetal exitus (IUFE) is a rare complication of multiple pregnancies, and its prevalence was reported to be 3.3% in a study conducted in our country (34). In addition, Sumer et al. (33) reported the frequency of IUFE in spontaneous and IVF pregnancies to be 8.9% and 10.3%, respectively. In our study, similar to the literature, IUFE was found only in 3.1% of the pregnancies, but a

comparison between the two groups could not be made due to the lack of sufficient numbers. Although McDonald et al. (35) showed that the need for NICU is higher in IVF pregnancies, many studies in the literature have reported that there was no difference between these two groups in terms of NICU admissions (34,36). In our study, while more than half of the postnatal babies needed NICU, this rate was significantly higher in the IVF twins group than in the spontaneous twins group.

Limitations of this study; (1) being a single-center study and the low number of cases constitute important limitations in the generalization of our results; (2) Since it is retrospective, follow-ups and the postpartum life expectancy and the development of the fetuses are unknown.

CONCLUSION

IVF twin pregnancies are risky pregnancies in terms of PROM and PD. In addition, while there was no difference in IVF and spontaneous twin babies in terms of IUGR, the need for NICU is higher in IVF twin births than for spontaneous twin births.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Istanbul Kanuni Sultan Süleyman Training and Research Hospital Clinical Researches Ethics Committee (Date: 26.05.2021, Decision No: 183).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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