

## Comparison of pregnancy and neonatal outcome in spontaneous and invitro fertilization (IVF) twin pregnancies

### Spontan ve invitro fertilizasyon ikiz gebeliklerinde gebeliğe ait ve neonatal verilerin karşılaştırılması

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#### Abstract

**Background:** This study aimed to investigate whether the differences between twin invitrofertilization (IVF) and twin spontaneous pregnancies in terms of pregnancy and perinatal outcome.

**Material and Methods:** This is a retrospective cohort study carried out by examining the data of dichorionic-diamniotic twin pregnancies with live births in a private hospital between 2015 and 2018. There were two study groups which were the twin pregnancy group with spontaneous pregnancy and the IVF twin group with pregnancy via assisted reproductive techniques.

**Results:** Pregnancy and birth problems did not differ between the two groups. The IVF twin pregnancies were observed to have higher rates of preterm birth, low birthweight and APGAR 1st minute scores. Perinatal mortality rates were found similar in both groups.

**Conclusion:** In conclusion, it was shown in this study that the risks of preterm birth and low birthweight which are already higher in twin pregnancies than in singleton pregnancies were even higher in the IVF twin pregnancies. It is recommended in accordance with these results that single embryo transfers should be preferred and iatrogenic multiple pregnancies should not be encouraged.

**Keywords:** Twin pregnancies, single pregnancies, IVF, neonatal outcome

#### Öz.

**Amaç:** Bu çalışmanın amacı invitro fertilizasyon(IVF) tedavisi ile gerçekleşen ikiz gebelikler ile spontan gerçekleşen ikiz gebeliklerin gebelik ve perinatal dönem bulguları açısından karşılaştırılmasıdır.

**Materyal ve Method:** Bu çalışma, 2015-2018 yılları arasında, canlı doğumu gerçekleştiren dikoryonik diamniotik ikiz gebeliklerin verileri incelenerek gerçekleştirilmiş bir retrospektif kohort çalışmasıdır. Bu çalışmada gebeliği spontan olarak gerçekleşmiş ikiz gebelikler grubu ve yardımcı üreme teknikleri kullanılarak gebe kalmış IVF ikiz grubu olmak üzere iki çalışma grubu vardır

**Bulgular:** Gebeliğe ve doğuma ait problemler her iki grup arasında farklılık göstermemiştir. IVF ikiz gebeliklerinde prematürite, düşük doğum ağırlığı ve 1. Dakika APGAR skor düşüklüğü oranlarının daha fazla olduğu görülmüştür. Perinatal mortalite oranları her iki grupta benzer bulunmuştur.

**Sonuç:** Bu çalışmada gösterilmiştir ki; ikiz gebeliklerde tek gebeliklere göre zaten daha yüksek riske sahip olan erken doğum ve düşük doğum ağırlığı riskleri, IVF ikiz gebeliklerinde daha da fazla artmaktadır. Bu sonuçlar gözönüne alınarak tek embryo transferine yönelmek ve iatrojenik çoğul gebeliklere destek vermemek önerilmelidir.

**Anahtar Kelimeler:** İkiz gebelikler, tekil gebelikler, IVF, neonatal sonuçlar

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## Introduction

Multiple pregnancies are associated with increased prematurity, low birthweight, perinatal morbidity and mortality (1,2). More than one embryos are transferred to increase success rate in IVF applications, which increases multiple pregnancies in return (3). Several studies stated that fetal loss, ectopic pregnancy, prematurity, low birthweight and perinatal complications raise in IVF pregnancies (4). Negative perinatal outcomes such as increased prematurity, low birthweight in IVF applications may be related to increased rate of multiple pregnancies, while it is also possible that they stem from physical, psychological, immunological, and social problems which are observed more frequently among subfertile patients (5,6,7,8,9).

This study aimed to investigate whether the differences between single IVF and single spontaneous pregnancies apply to twin IVF and twin spontaneous pregnancies.

## Material and Methods

This is a retrospective cohort study carried out by examining the data of dichorionic-diamniotic twin pregnancies with live births in a private hospital between 2015 and 2018. There were two study groups which were the twin pregnancy group with spontaneous pregnancy and the IVF twin group with pregnancy via assisted reproductive techniques. The spontaneous twins group have data on 72 pregnancies while the IVF twins group have data on 36 pregnancies. Monochorionic-monoamniotic twins, mothers at the age of 40 years or older, mothers with pre-pregnancy systemic health problems, those who were through chronic medication, and triple pregnancies reduced to twins via reduction were not included in the study.

Demographics of the mothers, gestational weeks at birth, birthweight, clinical problems during pregnancy and at birth and parameters determining the newborn's wellbe-

ing were recorded and compared between the two groups with appropriate statistical methods. Babies born under 2500 g were accepted to have low birthweight whereas babies born under 1500 g were accepted to have very low birthweight.

The study was approved by the local ethical committee and has no informed consent forms by its retrospective nature.

## Statistical Analysis

All statistical analyses were performed using SPSS for Windows 11.5 software program.(SPSS Inc., Chicago, IL, USA). The compatibility of data with normal distribution was examined graphically and with the Kolmogorov-Smirnov test. Quantitative variables were stated as mean  $\pm$  standard deviation (SD) and median (min-max), and categorical variables as number (n) and percentage (%). In the examination of a statistically significant difference between the categories of a qualitative variable with two categories in terms of a quantitative variable, the Student's t-test was used if the normal distribution assumption was met, otherwise the Mann-Whitney U test was used. The Chi-Square test and Fisher-Exact were applied to compare relationship between categorical outcomes. The Linear Regression test was used to examine the effects of independent variables on a quantitative dependent variable. The Logistic Regression test was used to examine the effects of independent variables on a categorical dependent variable. A value of  $p < 0.05$  was considered statistically significant.

## Results

Findings of 36 IVF twin pregnancies and 72 spontaneous twin pregnancies (108 pregnancies in total) were reviewed in the study. Comparisons of demographics, gestational age at birth and birthweights are shown in Table 1.

**Table 1.** Comparisons of demographics and clinical characteristics between IVF and spontaneous twins groups.

Variables	Spontaneous twins group			IVF twins group			p value
	N	Mean $\pm$ SD	Median (Min.-Max.)	N	Mean $\pm$ SD	Median (Min.-Max.)	
Gravidity (n)	72	2.14 $\pm$ 1.12	2.00 (1.00-6.00)	36	1.31 $\pm$ 0.71	1.00 (1.00-4.00)	<0.001 <sup>b</sup>
Parity (n)	72	0.87 $\pm$ 1.03	1.00 (0.00-5.00)	36	0.11 $\pm$ 0.40	0.00 (0.00-2.00)	<0.001 <sup>b</sup>
Maternal Age (Year)	72	28.83 $\pm$ 6.28	29.00 (17.00-39.00)	36	30.58 $\pm$ 7.01	30.50 (19.00-39.00)	0.192 <sup>a</sup>
Maternal BMI (kg/m <sup>2</sup> )	72	29.53 $\pm$ 5.14	25.78 (23.54-34.53)	36	29.74 $\pm$ 4.36	26.57 (22.60-36.84)	0.213 <sup>a</sup>
Gestational age (week)	72	36.24 $\pm$ 2.28	36.40 (27.20-38.85)	36	34.71 $\pm$ 3.0	34.40 (25.14-38.28)	0.003 <sup>a</sup>
Mean Birthweight of Twins (g)	72	2239.51 $\pm$ 452.22	2285.00 (1150.00-3235.00)	36	1932.74 $\pm$ 607.36	1905.00 (581.00-2925.00)	0.004 <sup>a</sup>

a: Student's t test, b: Mann-Whitney U test

Regarding the genders of the twins, (M: Male, F: Female) numbers (percentages) of MF, FF, MM twins were 22 (30.6), 47 (65.2), 3 (4.2) in the spontaneous twins group and 26 (72.2), 6 (16.7), 7 (11.1) in the IVF twins group. A statistically significant difference was found between the two groups by gender ( $p < 0.001$ ).

There was no statistically significant difference between the two groups by repeated pregnancy loss (RPL) ( $p = 0.257$ ). Numbers (percentages) of the patients with and without history of RPL were found to be 1 (1.4), 71

(98.6) in the spontaneous twins group and 2 (5.6), 34 (94.5) in the IVF twins group. Likewise, no statistically significant difference was observed by chronic hypertension ( $p = 0.551$ ). Numbers (percentages) of the patients with and without chronic hypertension were found to be 2 (2.8), 70 (97.2) in the spontaneous twins group and 0 (0.0), 36 (100.0) in the IVF twins group.

The data on clinical problems recorded during pregnancy and at birth are presented comparatively in Table 2.

**Table 2.** Clinical parameters about pregnancy and birth

Variables		Spontaneous twins group		IVF twins group		p value
		n	%	n	%	
IUGR	No	68	94.4	32	88.9	0.437 <sup>b</sup>
	Yes	4	5.6	4	11.1	
Hypertension/Preeclampsia	No	66	91.7	31	86.1	0.501 <sup>b</sup>
	Yes	6	8.3	5	13.9	
Gestational Diabetes	No	67	93.1	30	83.3	0.175 <sup>b</sup>
	Yes	5	6.9	6	16.7	
Vasa previa	No	72	100.0	36	100.0	-
Cervical insufficiency	No	72	100.0	36	100.0	-
Polyhydramnios	No	71	98.6	36	100.0	1.000 <sup>b</sup>
	Yes	1	1.4	0	0.0	
Oligohydramnios	No	59	81.9	35	97.2	0.032 <sup>b</sup>
	Yes	13	18.1	1	2.8	
PPROM	No	61	84.7	27	75.0	0.220 <sup>a</sup>
	Yes	11	15.3	9	25.0	
Antenatal bleeding	No	71	98.6	34	94.4	0.257 <sup>b</sup>
	Yes	1	1.4	2	5.6	
Postpartum bleeding	No	68	94.4	34	94.4	1.000 <sup>b</sup>
	Yes	4	5.6	2	5.6	
HELLP Syndrome	No	71	98.6	34	94.4	0.257 <sup>b</sup>
	Yes	1	1.4	2	5.6	
Cesarean Section	No	2	2.8	1	2.8	1.000 <sup>b</sup>
	Yes	70	97.2	35	97.2	
Blood transfusion	No	63	87.5	34	94.4	0.330 <sup>b</sup>
	Yes	9	12.5	2	5.6	
Neonatal mortality	No	71	98.6	36	100.0	1.000 <sup>b</sup>
	Yes	1	1.4	0	0.0	

a: Chi-square test, b: Fisher-exact test

Table 3 shows the newborn data of both study groups comparatively.

**Table 3.** Problems of newborn twins

Variables		Spontaneous twins group		IVF twins group		p value
		n	%	n	%	
Preterm birth between 37 <sup>th</sup> -34 <sup>th</sup> weeks	No	27	37.5	27	75.0	<0.001 <sup>a</sup>
	Yes	45	62.5	9	25.0	
Preterm birth before 34 <sup>th</sup> weeks	No	51	70.8	13	36.1	0.001 <sup>a</sup>
	Yes	21	29.2	23	63.9	
Malformation	No	71	98.6	36	100.0	1.000 <sup>b</sup>
	Yes	1	1.4	0	0.0	
Malpresentation	No	17	23.6	12	33.3	0.283 <sup>b</sup>
	Yes	55	76.4	24	66.7	
Low APGAR 1 <sup>st</sup> min	No	54	75.0	19	52.8	0.020 <sup>a</sup>
	Yes	18	25.0	17	47.2	
Low APGAR 5 <sup>th</sup> min	No	70	97.2	33	91.7	0.331 <sup>b</sup>
	Yes	2	2.8	3	8.3	
Macrosomia	No	72	100.0	36	100.0	-
Low birthweight	No	20	27.8	13	36.1	0.375 <sup>a</sup>
	Yes	52	72.2	23	63.9	
Very low birthweight	No	62	86.1	26	72.2	0.080 <sup>a</sup>
	Yes	10	13.9	10	27.8	

a: Chi-square test, b: Fisher-exact test

According to the linear regression analysis between the mean weight of twin newborns and mother's age, the model was not found statistically significant ( $p=0.192$ ). The logistic regression performed to ascertain the effect of age on the likelihood that participants have low birthweight showed that the model was statistically significant ( $p= 0.009$ ). The model explained 9.6% (Nagelkerke R<sup>2</sup>) of the variance in low birth weight and correctly classified 70.4% of the cases. Decreasing age was associated with an increased likelihood of exhibiting low birth weight. In addition, a logistic regression was performed to ascertain the effect of age on the likelihood that participants have very low birthweight but the logistic regression model was not statistically significant ( $p= 0.271$ ). And a logistic regression was performed to ascertain the effect of age on the likelihood that participants have IUGR but the logistic regression model was not statistically significant ( $p= 0.960$ ).

A logistic regression was performed to ascertain the effect of age on the likelihood that participants have neonatal mortality but the logistic regression model was not statistically significant ( $p= 0.261$ ).

## Discussion

This study compared the pregnancy and perinatal outcomes of spontaneous twin pregnancies and IVF twin pregnancies. Pregnancy and birth problems did not differ between the two groups. The IVF twin pregnancies were observed to have higher rates of preterm birth, low birthweight and APGAR 1st minute scores. Perinatal mortality rates were found similar in both groups.

No difference was observed between the two groups by hypertensive and diabetic problems during pregnancy. According to the studies comparing spontaneous and IVF twin pregnancies in the literature, pregnancy-related hypertension was higher in the IVF group (10,11). Studies investigating the risk of gestational diabetes in twin pregnancies showed that gestational diabetes were higher in the IVF group (12, 13). In contrary to our study, patients of these studies were chosen from the group with similar ages and parities. As parity increased, the risk of diabetes increased along (14) while parity in the spontaneous twin group was higher than in the IVF twin group in our study. This might be the reason why we could not observe the difference between the two groups.

It was observed in this study that risk of preterm birth increased in IVF twin pregnancies compared to spontaneous twin pregnancies. There are several studies conducted with broad series in the literature to support this finding (12, 15,16,17). There are studies which found that cervical length during pregnancy was longer or the same in the spontaneous twins group than in the IVF twins group (10,13). Our study involved no information on cervical length; there was information only on cervical insuffi-

ciency and no such finding was observed in any of the patients. The reason is that only the viable twins were included in our study; it is highly likely that births/abortions occurred before patients with cervical insufficiency could reach viability.

In this study no difference could be shown between the spontaneous and IVF twins groups by low birthweight or very low birthweight. In two different metaanalyses, birthweight was shown to be lower in IVF twins (16,18). It was shown in a study which observed no difference between IVF and spontaneous twins by low birthweight or very low birthweight that the rate of discordance in birthweight was higher in IVF twins than in spontaneous twins (19). In our study, birthweights of the twins were not evaluated in terms of discordance.

Difference between the spontaneous and IVF twin pregnancies by amniotic liquid- and placenta-related abnormalities and antenatal-postpartum bleeding was not shown in this study. There are studies available in the literature which showed that such risks increased in IVF twins (5,20) and showed no difference whatsoever (19, 21). Studies reporting higher cesarean section rates in IVF twins (10) and rates which did not differ (13) have been published in the literature; cesarean section rates did not differ in our study; however, almost every birth was by c-section in both groups in the first place.

As for the neonatal outcome evaluation, low 1st minute APGAR scores were found to be higher rate in the IVF twins group. 5th minute APGAR scores were found to be the same in both groups. Bendsdorp et al. (22) did not find APGAR scores to be different between the two groups while Nassar et al. (23) found the 1st minute APGAR scores and Caserta (13) the 5th minute APGAR scores to be lower in the IVF group. In our study, neonatal mortality was found not to be different between the two groups. Most of the studies comparing the pregnancy outcomes of IVF and spontaneous twins addressed perinatal mortality rates (22, 24,25). Addressing live births, our study took neonatal mortality as basis, and there was only one case of neonatal mortality.

This study was performed to compare pregnancy and neonatal outcome data of spontaneous and IVF twin pregnancies which is a subject yet to be clarified in the literature. The most important limitation to this study is the insufficient number of patients. Not every desired parameter could be included in the study due to data losses. Since there are too many parameters in both groups and they are affected by them individually, it is quite difficult to evaluate the data of such a study. Adolescent and advanced age pregnancies and monozygotic twins were not included in our study to be able to create more homogenous study groups. The study would have been more valuable in the literature if it had been conducted with homogenous and well-defined subgroups and

with a higher number of patients by keeping the record of the whole pregnancy process without any data loss.

In conclusion, it was shown in this study that the risks of preterm birth and low birthweight which are already higher in twin pregnancies than in singleton pregnancies were even higher in the IVF twin pregnancies. It is recommended in accordance with these results that single embryo transfers should be preferred and iatrogenic multiple pregnancies should not be encouraged.

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