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Comparison of ICSI and Spontaneous Pregnancy Outcomes in Women with Unexplained Infertility

Açıklanamayan İnfertilite Tanısı Almış Kadınların ICSI ve Spontan Gebelik Sonuçlarının Karşılaştırılması

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ABSTRACT

Aim: This study aimed to investigate whether there is a difference between the results of intracytoplasmic sperm injection (ICSI) pregnancies and subsequent spontaneous pregnancies with a diagnosis of unexplained infertility.
Material and Methods: In this retrospective study, a total of 48 women who first conceived with ICSI and then achieved spontaneous pregnancy were included. Duration and causes of infertility, time to spontaneous conception, pregnancy outcomes, and maternal and neonatal complications were evaluated.
Results: Maternal age was older in the spontaneous pregnancy group compared to the ICSI group (p=0.029). The gestational age at delivery was found similar in both groups. Although birth weight was higher in the spontaneous pregnancy group, the difference between the groups was not statistically significant (p=0.382). The time to achieve pregnancy was shorter in the spontaneous pregnancy group (p=0.001). Gestational diabetes was significantly higher in the spontaneous pregnancy group (p=0.001), while amniotic fluid abnormality, gestational hypertension (p=0.001), and preterm delivery (p=0.001) were significantly higher in the ICSI group. While the number of babies with the 1st-minute low Apgar score was higher in the ICSI group (%4.16 vs 2.08%, p=0.001), the 5th-minute Apgar score was similar.
Conclusion: Even if couples are evaluated as infertile, it should be taken into consideration that they can achieve spontaneous pregnancy. It may be rational to wait for spontaneous pregnancy in eligible couples with unexplained infertility and not to refer the patient for early assisted reproductive techniques.
Keywords: ICSI; spontaneous pregnancy; pregnancy outcomes; unexplained infertility.

ÖZ

Amaç: Bu çalışmada, açıklanmayan infertilite tanısı alarak intrasitoplazmik sperm enjeksiyonu (intracytoplasmic sperm injection, ICSI) ile elde edilen gebelikler ile daha sonradan elde edilen spontan gebeliklerin sonuçları arasında bir farklılık olup olmadığının incelenmesi amaçlanmıştır.
Gereç ve Yöntemler: Retrospektif nitelikteki bu çalışmaya önce ICSI ile gebe kalmış ve sonrasında ise spontan gebelik elde etmiş olan toplam 48 kadın dahil edildi. İnfertilite süreleri ve nedenleri, spontan gebelik elde etmek geçen süre, gebelik sonuçları ile maternal ve neonatal komplikasyonları değerlendirildi.
Bulgular: ICSI grubu ile karşılaştırıldığında, maternal yaş spontan gebelik grubunda daha büyüktü (p=0,029). Doğum anındaki gebelik haftası her iki grupta benzer bulundu. Spontan gebelik grubunda doğum ağırlığı daha yüksek olmasına rağmen gruplar arasındaki fark istatistiksel olarak anlamdı değildi (p=0,382). Gebelik elde etmek için geçen süre spontan gebelik grubunda daha kısaydı (p=0,001). Gestasyonel diyabet spontan gebelik grubunda daha yüksek iken (p=0,001), amnion mai anormalliği, gestasyonel hipertansiyon (p=0,001) ve preterm doğum (p=0,001) ICSI grubunda anlamlı olarak daha yüksekti. 1. dakika düşük Apgar skoru olan bebek sayısı ICSI grubunda daha yüksekken (%4,16'ya karşı %2,08 p=0,001), 5. dakika Apgar skoru benzerdi.
Sonuç: Çiftler infertil olarak değerlendirilse bile sonrasında spontan gebelik elde edebilecekleri göz önünde bulundurulmalıdır. Açıklanamayan infertilite tanısı almış uygun çiftlerde spontan gebelik için beklemek ve hastayı erkenden üremeye yardımcı teknikler için yönlendirmemek akılcı bir tutum olabilir.
Anahtar kelimeler: ICSI; spontan gebelik; gebelik sonuçları; açıklanamayan infertilite.

INTRODUCTION

The commonly used definition of infertility is the inability to achieve pregnancy for 12 months despite unprotected intercourse (1). Many couples suffer from this situation. In the studies conducted, 12.6%-17.5% of couples were diagnosed with infertility, although the population and region screened varied (2). This means that around 50 million couples worldwide are seeking treatment for infertility (3,4). In women, tubal and uterine disorders, ovulation dysfunction and endocrinologic disorders often cause infertility, while in men, abnormal sperm count and function, obstruction of the reproductive tract, and hormonal disorders cause infertility. But in some couples, conventional methods cannot reveal the cause of infertility. This condition is called unexplained infertility (5). Infertility treatment has been available for more than 40 years. However, infertility treatment requires extensive biomedical and surgical interventions (6). All of these treatments are mentally, physically, and economically exhausting for the couple in addition to the high cost, especially in case of repeated treatment failure. For this reason, it is important that the resources allocated for treatment are used rationally. Another noteworthy issue is that 18-20% of all couples who had previously achieved pregnancy by receiving infertility treatment were able to conceive spontaneously afterward (7,8). This brings to mind the question of whether couples are referred early for assisted reproductive technology (ART) treatment. In terms of pregnancy outcomes, ART pregnancies carry a greater risk of adverse perinatal outcomes such as preeclampsia, gestational hypertension, and gestational diabetes than spontaneous pregnancies (9).

This study aimed to compare the live births of women who had undergone in vitro fertilization (IVF) treatment for unexplained infertility and the live births achieved by spontaneous pregnancies of these women.

MATERIAL AND METHODS

This retrospective cohort study was conducted between April 2018 and April 2022 in the Department of Obstetrics of Duzce University, a tertiary medical center, after obtaining institutional review board (Non-interventional Health Research Ethics Committee of Düzce University, 02.05.2017, 77) approval. Informed consent was obtained from all participants included in the study. The study population consisted of 48 women who were treated for unexplained infertility and had a singleton live birth and then became pregnant spontaneously and had a singleton live birth. Demographic data, pregnancy data, and delivery information of the patients who were included in the study and delivered in our hospital were obtained from the electronic data recording system of our hospital. Gestational age at birth was determined by adding 14 days after an embryo transfer in ART pregnancies and by the last menstrual period or first-trimester sonography in spontaneous pregnancies. Gestational diabetes mellitus was defined as an abnormal fasting blood glucose level or an abnormal glucose tolerance test result between 24 and 28 weeks of gestation (10). Gestational hypertension was diagnosed when blood pressure was 140/90 mmHg and above, not accompanied by proteinuria and similar systemic findings after the 20th week of pregnancy (11). Preeclampsia is a pregnancy disorder characterized by new-onset hypertension, typically occurring after 20 weeks of gestation and often near term. While it is frequently accompanied by new-onset proteinuria, some women may exhibit hypertension and other signs or symptoms of preeclampsia without the presence of proteinuria (12). Based on previous studies examining perinatal outcomes of pregnancies after IVF and spontaneous conception (13), to investigate whether major adverse obstetric outcomes were relevant and whether there was a 30% increase in the rate of major adverse obstetric outcomes, we included all women who met the inclusion criteria.

Statistical Analysis

The data in the study were analyzed using IBM SPSS Statistics for Windows v.21.0 (IBM Corp, Armonk, NY). The normality was evaluated using the Shapiro-Wilk test. The quantitative data are presented as the median, minimum, and maximum values, or mean, and standard deviation, and the categorical data as numbers and percentages. Statistical analyses were performed using the Mc-Nemar test and Wilcoxon signed rank test when appropriate. Data were determined at the 95% confidence level and a p-value of <0.05 was accepted as statistically significant.

RESULTS

Subsequent spontaneous pregnancies of 48 women who had previously undergone ICSI for unexplained infertility and had a live birth were evaluated in this study.

In terms of demographic data, maternal age was statistically significantly higher in the spontaneous pregnancy group (30.2±5.02 vs 27.1±5.36 years, p=0.029). While gestational week (39.3±2.12 vs 37.4±3.52, p=0.051) and birth weight (3390±588 vs 3270±741 gram, p=0.382) were similar between the groups, the time required to achieve pregnancy was significantly shorter (3.17±2.56 vs 4.12±2.87 years, p=0.001) in the spontaneous pregnancy group (Table 1.)

While gestational diabetes was found significantly higher in the spontaneous pregnancy group (6.25% vs 4.16%, p=0.001), amniotic fluid abnormality, gestational hypertension (8.33% vs 6.25%, p=0.001), and preterm delivery (10.4% vs 6.25%, p=0.001) were significantly higher in the ICSI group (Table 2).

Although the number of babies with 1st-minute low APGAR scores was higher in the ICSI group (4.16% vs 2.08%, p=0.001), the 5th-minute Apgar scores were similar for both groups (2.08% vs 2.08%, p=1.000). No perinatal mortality was observed in both groups. Although

Table 1. Clinical characteristics of the ICSI and spontaneous pregnancy groups

	ICSI (n=48)	Spontaneous (n=48)	p
Maternal age (year)	27.1±5.36	30.2±5.02	**0.029**
Gestational week	37.4±3.52	39.3±2.12	0.051
Birth weight (gram)	3270±741	3390±588	0.382
Time to achieve pregnancy (year)	4.12±2.87	3.17±2.56	**0.001**

ICSI: intracytoplasmic sperm injection, data were shown as mean±standard deviation

Table 2. Pregnancy and labor complications

	ICSI (n=48)	Spontaneous (n=48)	p
Gestational diabetes	2 (4.16)	3 (6.25)	**0.001**
Polihidramios	3 (6.25)	2 (4.16)	**0.001**
Oligohidramnios	3 (6.25)	2 (4.16)	**0.001**
Gestational hypertension	4 (8.33)	3 (6.25)	**0.001**
Preeclampsia	3 (6.25)	3 (6.25)	1.000
Preterm labor	5 (10.4)	3 (6.25)	**0.001**
Placental abruption	1 (2.08)	0 (0.00)	-

ICSI: intracytoplasmic sperm injection, data were shown as number (percentage)

Table 3. Maternal and neonatal outcomes

	ICSI (n=48)	Spontaneous (n=48)	p
1st-minute Apgar <7	2 (4.16)	1 (2.08)	**0.001**
5th-minute Apgar <7	1 (2.08)	1 (2.08)	1.000
Perinatal mortality	0 (0.00)	0 (0.00)	-
Cesarean delivery	40 (83.3)	43 (89.6)	0.383

ICSI: intracytoplasmic sperm injection, data were shown as number (percentage)

the cesarean section rate was higher in the spontaneous pregnancy group (89.6% vs 83.3%, p=0.383), but the difference was not statistically significant (Table 3).

DISCUSSION

The main finding from this study is that adverse perinatal outcomes are more common in ICSI pregnancies, although the women who become pregnant are the same. Although the gestational age at delivery is similar, clinicians may choose to end ICSI pregnancies earlier in the presence of pregnancy complications. We believe that the main motivation for this is the desire of the couple to take home a live baby.

Similar to our study, Hayashi et al. (13) evaluated ART pregnancies and found that the frequency of preterm delivery and placental invasion anomalies increased in ART pregnancies, while vaginal delivery rates decreased. While the underlying mechanisms for adverse obstetric outcomes in pregnancies of subfertile women remain unclear, potential explanations include the medical conditions that led to subfertility, sperm factors, and, in ART pregnancies, ovarian stimulation, embryo culture, and freezing (14). Raatikainen et al. (15) compared women who conceived after ART and women who achieved spontaneous pregnancy in a subfertile population and found similar rates of preterm delivery, need for neonatal intensive care unit (NICU), and low Apgar score. They concluded that infertility treatment alone cannot be associated with adverse pregnancy outcomes. In our study, preterm delivery and low Apgar score rates were higher in the ICSI group. Similar to us, Ludwig et al. (7) in their study on spontaneous pregnancies after ART found that 20% of couples became spontaneously pregnant within 2 years. In the couples included in our study, the time to achieve pregnancy after ICSI was approximately 3 years. In our study, the average age of women undergoing ICSI is relatively higher. These women have a longer fertility period ahead of them. The likelihood of spontaneous pregnancy after ICSI increases inversely with the woman's age (7). Couples who have a live birth after ART should definitely receive family planning counseling. The unexpected, spontaneous conception of additional children can lead to unanticipated social, economic, and psychological effects, especially for families experiencing multiple births after undergoing ICSI treatment. It should be emphasized that spontaneous pregnancy rates after ART are not low at all, couples who want to conceive again can conceive naturally, and couples who do not want to have children should use a contraceptive method.

The major limitation of our study is its retrospective design and relatively small sample size. Our study cohort was composed of women from a single hospital, making it challenging to generalize our findings to the broader female population. However, spontaneous pregnancies after ART is a critical issue, although it is not covered much in the literature and the information on this subject is very limited. With this study, we aimed to fill this gap in the literature.

CONCLUSION

When infertile couples are evaluated, especially those who are young age may be given a chance for spontaneous pregnancy for a while longer instead of being referred for ART quickly. In ART pregnancies, both the cost to achieve pregnancy is high and pregnancy complications are more common. Further studies are needed to validate these findings in clinical practice.

Ethics Committee Approval: The study was approved by the Non-interventional Health Research Ethics Committee of Düzce University (02.05.2017, 77).

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