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Original Article

Comparison of Obstetric Outcomes in Patients with Intrahepatic Cholestasis of Pregnancy Between Pregnancies Following *In Vitro* Fertilization and Spontaneous Conception: Four-Year Experience in a Tertiary Care Hospital

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ABSTRACT

Objective: Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy-specific liver disease, associated with a 4 to 10-fold increased risk of stillbirth if appropriate interventions are not taken. The aim of the study was to compare the obstetric outcomes of singleton pregnancies with ICP in which pregnancies were achieved spontaneously and by *in vitro* fertilization (IVF).

Methods: Women who gave birth between January 2018 and September 2022 were evaluated retrospectively. After applying the inclusion criteria, a total of 91 patients with ICP were eligible, consisting of spontaneously conceived (group 1, n=74) and IVF-conceived (group 2, n=17) pregnancies. The participants in group 2 were classified into two subgroups: fresh embryo transfer (n=9) and frozen embryo transfer (n=8), depending on the method of embryo transfer.

Results: Perinatal outcomes and demographic characteristics, with the exception of age, gravidity, and parity, were similar. While age was significantly higher in group 2 [32 (27-35) vs. 27 (24-31), p=0.017], gravidity and parity were significantly higher in group 1 [2 (1-3) vs. 1 (1-2), p=0.021 and 0 (0-1) vs. 0 (0-0), p=0.009]. Aspartate (AST) and alanine (ALT) transaminase levels, fasting total bile acid (FTBA) level, and treatment dose of ursodeoxycholic acid were significantly higher in the frozen embryo transfer group than in the fresh embryo transfer group [126 (83-242) vs. 32 (31-43), p=0.001; 200±123.9 vs. 51±39.4, 0.001; 44±20.4 vs. 15±5.0, p=0.001, and 100 (750-1250) vs. 750 (750-750), p=0.004].

Conclusion: Our results suggest that there is an association between high FTBA, ALT, and AST levels due to estrogen treatment in IVF pregnancies, especially when the frozen embryo transfer method was used.

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is the most prevalent pregnancy-related liver disease, characterized by high serum bile acid concentrations and varying degrees of itching, ranging from mild to intolerable.[1,2] The disease usually occurs in late pregnancy and recovers dramatically within a week after birth. The disease occurs with varying frequency in different parts of the world, with the lowest incidence (0.8%) in the USA and the highest incidence (27.6%) among the Araucanos Indians in Chile.[3,4] Although the reasons for the large variation in incidence are not fully understood, the disease is thought to be influenced by geographical and regional differences, variations in genetic vulnerability of ethnic groups, and differences in environmental components, as it is more common in certain regions with intense winters.[5-7] On the other hand, the diagnosis may be overlooked, and the true incidence not determined, especially in cases where the symptoms occurred shortly before delivery and there was insufficient time for serum bile acids to rise.[8]

In addition to geographical, genetic, ethnic, and environmental risk factors, hormonal factors also appear to play an important role in the pathogenesis, as ICP occurs more frequently in conditions with increased estrogen production, such as twin pregnancies and pregnancies with ovarian hyperstimulation.[9-11] The rapid regression of the disease after the birth of the placenta, which is the main source of pregnancy hormones, again points to the effect of estrogen, while there is still no clear evidence for the effect of progesterone.[11] Recent research has identified ICP-specific mutations of genes such as the multidrug resistance protein 3 (Mrp3) gene, which encodes transport proteins involved in canalicular bile secretion.[12,13] The risk for the occurrence of cholestasis increases with age, parity, presence of underlying chronic liver disease, and family and personal history of ICP.[5,14-16] The exact trigger of ICP is unclear and the etiology is also multifactorial. It is therefore a diagnosis of exclusion, which is only made after dermatological diseases with pruritus, and liver and biliary tract diseases have been ruled out. Although there are no specific skin lesions characteristic of ICP, scratch marks, excoriations, and prurigo nodules caused by intense scratching may occur.

In recent years, due to various factors such as financial security, career priority, and lack of emotional and psychological preparation, women tend to postpone the decision to become pregnant until an older age when their reproductive capacity declines. Accordingly, the number of pregnancies conceived using assisted reproductive techniques, including IVF, and the associated complications are increasing. Therefore, the management of high-risk conditions such as ICP, which are more common in this pregnancy population, must be well understood.

As there are few studies comparing ICP in spontaneous and IVF pregnancies, we aimed to examine and compare such patients to investigate the possible association between exogenous estrogen exposure and the development of ICP or the severity of ICP in some IVF pregnancies.

MATERIALS AND METHODS

Study Design

We conducted a retrospective cohort study of singleton pregnancies with ICP between January 1, 2018, and September 1, 2022, in the perinatology clinic of a large tertiary referral hospital. After obtaining ethical approval (date: 24.10.2022, decision no.: 14/08), the data were collected by reviewing the medical records. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. As this was a retrospective study and not all participants could be contacted, it was not possible to obtain written informed consent. The Ethics Committee, therefore, waived informed consent for participation and publication.

Characteristics of Study Population

Pregnant women with multiple fetuses, congenital fetal malformations and genetic abnormalities, diseases such as choledocholithiasis and pancreatitis leading to extrahepatic biliary tract obstruction, liver diseases with damage to the liver parenchyma, hemolysis, elevated liver enzymes, low platelet syndrome, acute fatty liver of pregnancy, women taking medications that may alter liver function, and patients with missing data were excluded. Patients with a history of ICP were also not included in the study.

Imaging Methods, Laboratory Measurements and Definitions

Fetal biometry and other sonographic examinations were performed with the GE Voluson 730 Ultrasound System (General Electric Medical Systems, Milwaukee, WI, USA), using a 4-8 MHz transabdominal probe and a 5-9 MHz transvaginal probe when more detail was required. Gestational age was calculated from the first day of the last menstrual period (LMP) and confirmed by sonographic dating. If the two calculations differed by ≤7 days, the calculation based on LMP was used.

Blood samples for biochemical parameters and viral serology were collected in tubes containing a separating gel and analyzed in a Roche Cobas e801 chemiluminescence immunoassay analyzer (Roche Diagnostics International Limited, Rotkreuz, Switzerland). For the determination of fasting total bile acids (FTBA) in serum, blood samples of at least 2 mL were collected in tubes containing a separating gel and analyzed using an enzymatic method (3alpha-hydroxysteroid dehydrogenase) after 8 hours of fasting. After excluding other pruritic disorders and hepatobiliary diseases in the differential diagnosis, ICP was diagnosed by the presence of generalized pruritus, predominantly on the palms and soles, without specific skin lesions typical of dermatological diseases, together with elevated serum FTBA levels (>10 μmol/L).[17] After confirmation of the diagnosis, all patients were treated perorally with a dose of

10-15 mg/kg/day of ursodeoxycholic acid. The total dose was divided into two or three doses per day with peroral capsules containing 250 mg ursodeoxycholic acid. After the initiation of treatment, regular follow-up examinations were carried out to assess fetal well-being. To evaluate the treatment, aspartate transaminase (AST), alanine transaminase (ALT), and FTBA were retested, and the intensity of pruritus was questioned.

Data Collection

Demographic data, including body mass index (BMI), age, gravidity, parity, miscarriage, and sonographic fetal biometry, gestational age at diagnosis; laboratory measurements, including FTBA levels, anti-hepatitis C antibody, and hepatitis B surface antigen, and antenatal, perinatal, and neonatal characteristics were obtained from the hospital database and patient records.

Statistical Analysis

Statistical analyses were carried out with R Statistical Software Version 2021.09.4+403.pro3 (R Foundation for Statistical Computing, Vienna, Austria). Variables were analyzed using visual (histogram, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test) to investigate whether they were normally distributed or not. Levene's test was applied in order to assess the variance homogeneity. Descriptive analyses for normally distributed variables were presented using standard deviations and mean values. These parameters were compared between the groups using the t-test for independent samples. Descriptive analyses for the non-normally distributed numerical data were presented using medians, first and third quartiles. These parameters were compared between the groups using Mann-Whitney U-tests. Descriptive analyses for the categorical variables were performed using percentage and frequency. The chi-square test or Fisher's exact test (when the assumptions of the chi-square test did not hold due to low expected cell counts) were used to analyze the correspondences between categorical variables. The correlation coefficients and their significance were calculated using the Pearson test if the parameters had a normal distribution. When analyzing associations between non-normally distributed parameters, the Spearman test was used to calculate the correlation coefficients and their significance. A p-value of less than 0.05 was considered a statistically significant result.

RESULTS

In the period of almost 4 years covered by the study, there were 38,127 births, of which 116 (3.3%) were diagnosed with ICP. After applying inclusion criteria, a total of 91 patients with ICP were eligible, consisting of spontaneously conceived (Group 1, n=74) and IVF-conceived (Group 2, n=17) pregnancies. Group 2 was divided into two groups: fresh embryo transfer (n=9) and frozen embryo transfer (n=8), depending on the embryo transfer method used (Figure 1). Demographic characteristics such as BMI, number of previous miscarriages, gestational age at diagnosis (GAD), number of patients complaining of pruritus, laboratory tests such as AST, ALT, FTBA, the minimum dose of ursodeoxycholic acid (UDCA) to relieve symptoms, and birth characteristics such as delivery mode, gestational age at birth, birthweight, neonatal gender, appearance, pulse, grimace, activity, respiration scores at the first and fifth minute (APGAR 1 and 5) did not differ between the two groups, while age was significantly higher in Group 2 [32 (27-35) vs. 27 (24-31), p=0.017] and gravidity and parity were significantly higher in Group 1 [2 (1-3) vs. 1 (1-2), p=0.021 and 0 (0-1) vs. 0 (0-0), p=0.009] (Table 1).

A comparison of the clinical features of the participants

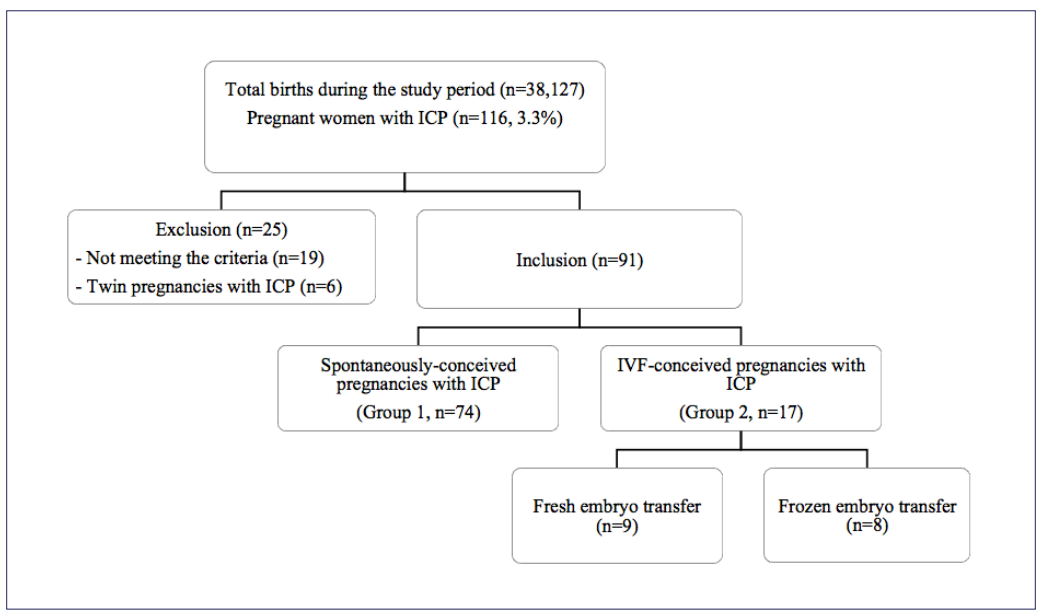

Figure 1. Flow chart of the study.

Table 1. Comparison of demographic and birth characteristics of women with ICP by type of fertilization

Variable	Group 1 (n=74)	Group 2 (n=17)	Total (n=91)	p
Age (years)	27 (24-31)	32 (27-35)	28 (24-32)	**0.017**
BMI (kg/m^2)	27 (24-30)	25 (21-27)	26 (23-30)	0.067
Gravida (number)	2 (1-3)	1 (1-2)	1 (1-3)	**0.021**
Parity (number)	0 (0-1)	0 (0-0)	0 (0-1)	**0.009**
Miscarriage (number)	0 (0-1)	0 (0-0)	0 (0-0)	0.435
Gestational age at diagnosis (weeks)	34 (32-35)	34 (32-35)	34 (32-35)	0.758
AST level at diagnosis (IU/L)	67 (41-101)	45 (32-126)	59 (38-103)	0.661
ALT level at diagnosis (IU/L)	80 (47-164)	81 (31-194)	81 (44-167)	0.831
Fasting total bile acids (μmol/L)	16 (11-32)	20 (13-45)	16 (11-35)	0.341
Patients with pruritus (number)	55 (74.3)	16 (94.1)	71 (78.0)	0.106
Ursodeoxycholic acid (mg/day)	750 (750-750)	750 (750-1000)	750 (750-750)	0.249
Mode of Delivery				
Vaginal (number)	31 (41.9)	6 (35.3)	37 (40.7)	0.821
Cesarean (number)	43 (58.1)	11 (64.7)	48 (59.3)	
Gestational age at birth (weeks)	37 (36-37)	37 (36-37)	37 (36-37)	0.888
Birthweight (grams)	2917 (2658-3297)	2870 (2745-3579)	2910 (2680-3360)	0.222
Neonatal gender				
Male (number)	34 (45.9)	7 (41.2)	41 (45.1)	0.724
Female (number)	40 (54.1)	10 (58.8)	50 (54.9)	
APGAR 1 (scores)	9 (9-9)	9 (9-9)	9 (9-9)	0.847
APGAR 5 (scores)	10 (10-10)	10 (10-10)	10 (10-10)	0.593

ALT: Alanine aminotransferase; APGAR: Appearance, pulse, grimace, activity and respiration; AST: Aspartate transaminase; BMI: Body-mass index; GAD: Gestational age at diagnosis; ICP: Intrahepatic cholestasis of pregnancy; IU/L: International units per liter; IVF: *In-vitro* fertilization; Kg/m^2: Kilograms per square meter; μmol/L: Micromole per liter. Data are presented as median (quartile 1-quartile) or number (percentage) where applicable. A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

with ICP in whom the pregnancy was conceived by IVF is shown in Table 2. AST, ALT, FTBA, and the treatment dose of UDCA were significantly higher in the frozen embryo transfer group than in the fresh embryo transfer group [126 (83-242) vs. 32 (31-43), p=0.001; 200±123.9 vs. 51±39.4, p=0.001; 44±20.4 vs. 15±5.0, p=0.001, and 1000 (750-1250) vs. 750 (750-750), p=0.004, respectively].

In all pregnant women diagnosed with ICP, there was a statistically significant positive correlation between FTBA and AST (r=0.388, p<0.001), ALT (r=0.343, p=0.002), and treatment dose of UDCA (r=0.262, p=0.024), while gestational age at diagnosis showed a negative correlation with FTBA (r=-0.262, p=0.036). There were lack of correlations found between age and FTBA both in Group 2 and in overall pregnancies with ICP (p<0.05). In IVF pregnancies with ICP, there was a statistically significant positive correlation between FTBA and AST (r=0.692, p=0.004) and treatment dose of UDCA (r=0.646, p=0.005), while there was no correlation between FTBA and AST and GAD (Table 3).

Symptoms and/or laboratory findings associated with ICP resolved in all patients within one week of delivery. There were no maternal deaths or near misses, while only one stillbirth occurred in Group 1. Ten patients developed preeclampsia [7 (9.5%) in Group 1 and 2 (11.8%) in Group 2].

DISCUSSION

Intrahepatic cholestasis of pregnancy is a serious condition associated with perinatal morbidity and mortality and carries a 4 to 10-fold increased risk of stillbirth if appropriate interventions are not taken.[3] The pathophysiology of stillbirth in women with ICP is not clearly understood, but it is assumed that elevated maternal serum FTBA levels, which are cardiotoxic to the fetus, are responsible.[18] To date, there is no universally accepted method for the diagnosis, management, and treatment of ICP. On the other hand, there is only a consensus that total bile acid levels are closely related to perinatal outcome. The risk of fetal death increases in particular with FTBA values of 100 μmol/L and above. On this basis, the decision on the timing of delivery is made depending on the initial FTBA values. At our clinic, we follow the recommendations of the Royal College of Obstetricians and Gynecologists' guideline for women with ICP, which recommends a planned delivery at 40, 38 to 39, and 35 to 36 weeks' gestation for peak bile acid levels <40 μmol/L, 40-99 μmol/L, and ≥100 μmol/L respectively.[19] On the other hand, the rate of induced preterm births in women with ICP has increased due to fetal and/or maternal concerns. In addition, rates of spontaneous preterm birth have also increased for various reasons, including the effect of increased bile acids inducing the expression of myometrial oxytocin receptors.[2]

Table 2. Comparison of ICP pregnancies conceived by IVP according to the embryo transfer method used

Variable	Fresh Embryo Transfer (n=9)	Frozen Embryo Transfer (n=8)	p
Age (years)	32±4.1	29±4.6	0.198
BMI (kg/m^2)	26.9±5.51	22.4±2.50	0.051
Gravida (number)	1 (1-2)	1 (1-1)	0.277
Parity (number)	0 (0-1)	0 (0-0)	0.481
Miscarriage (number)	0 (0-1)	0 (0-0)	0.743
Gestational age at diagnosis (weeks)	34±2	34±1	0.960
AST level at diagnosis (IU/L)	32 (31-43)	126 (83-242)	**0.001**
ALT level at diagnosis (IU/L)	51±39.4	200±123.9	**0.004**
Fasting total bile acids (μmol/L)	15±5.0	44±20.4	**0.001**
Patients with pruritus (number)	8 (88.9)	8 (100)	1.000
Ursodeoxycholic acid (mg/day)	750 (750-750)	1000 (750-1250)	**0.004**
Mode of Delivery			
Vaginal (number)	2 (22.2)	4 (50.0)	
Cesarean (number)	7 (77.8)	4 (50.0)	0.335
Gestational age at birth (weeks)	35 (35-37)	37 (36-37)	0.963
Birthweight (grams)	3036±461.9	3251±501.9	0.373
Neonatal gender			
Male (number)	5 (55.6)	2 (24.5)	
Female (number)	4 (44.4)	6 (75.1)	0.335
APGAR 1 (scores)	9 (7-9)	9 (9-9)	0.481
APGAR 5 (scores)	10 (9-10)	10 (10-10)	0.481

ALT: Alanine aminotransferase; APGAR: Appearance, pulse, grimace, activity and respiration; AST: Aspartate transaminase; BMI: Body-mass index; ICP: Intrahepatic cholestasis of pregnancy; IU/L: International units per liter; IVF: In-vitro fertilization; Kg/m^2: Kilograms per square meter; μmol/L: Micromole per liter. Data are presented as median (quartile 1-quartile 3), mean±standard deviation or number (percentage) where applicable. A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

Table 3. Correlation of FTBA levels with various parameters in women with ICP

	All pregnancies with ICP					IVF-conceived pregnancies with ICP				
	Age	AST	ALT	UDCA	GAD	Age	AST	ALT	UDCA	GAD
FTBA										
r	-0.140	0.388	0.343	0.262	-0.235	0.050	0.692	0.426	0.646	-0.306
p	0.215	**<0.001**	**0.002**	**0.024**	**0.036**	0.850	**0.004**	0.088	**0.005**	0.233

ALT: Alanine aminotransferase; AST: Aspartate transaminase; FTBA: Fasting total bile acid; GAD: Gestational age at diagnosis; ICP: Intrahepatic cholestasis of pregnancy; IVF: *In-vitro* fertilization; UDCA: Ursodeoxycholic acid. A p value of <0.05 indicates a significant difference. Statistically significant p-values are in bold.

Luteal phase support with exogenous progesterone, gonadotropin-releasing hormone agonists, or human chorionic gonadotropin is a known intervention for almost all IVF cycles, whereas exogenous estrogen support is not initiated in all IVF cycles. Since estrogen exposure plays an important role in the pathogenesis of ICP and estrogen support to prepare the endometrium for implantation is a common treatment application, we conducted this study comparing spontaneously conceived and IVF-conceived women with ICP, taking into account whether fresh or frozen embryo transfer methods were used. As far as we know, this study is the first to compare women with ICP conceived by IVF according to the type of embryo transfer. According to the results of our study, although FTBA and transaminase levels did not differ by fertilization method, when patients in the IVF group were compared by embryo transfer method, FTBA and transaminase levels were significantly higher in the frozen ET group than in the fresh ET group. Therefore, the severity of ICP appears to be closely related to the effect of exogenous estrogen on the liver, which is used during the endometrial preparation period for implantation and sometimes even up to 12 weeks of pregnancy in patients undergoing frozen embryo transfer.

In a study by Bolukbas et al.[20] although the number of

women with a history of ICP, a strong risk factor for recurrence of ICP, was significantly higher in the spontaneous pregnancy group, serum FTBA levels were significantly higher in the IVF pregnancy group. In our study, however, we did not find a similar result but observed a significant difference in FTBA values depending on the embryo transfer method in the IVF group. Serum FTBA levels were significantly higher in the frozen embryo transfer group, as were AST and ALT levels. In addition, FTBA levels were inversely correlated with gestational age at diagnosis. On the other hand, it is noteworthy in the study by Bolukbas et al.[20] that there were multiple pregnancies in both groups, but the rate of multiple pregnancies was significantly higher in the IVF group. A study by Batsry et al.[16] which investigated the perinatal outcomes of ICP in twin pregnancies versus singleton pregnancies, also found that FTBA levels were significantly higher in twin pregnancies. In another study comparing spontaneous twin pregnancies with ICP with IVF twin pregnancies with ICP, there was also no significant difference in FTBA levels.[21] Therefore, significantly high FTBA serum levels are more likely associated with consecutive multiple pregnancies rather than with IVF itself. In the study by Bolukbas et al.[20] in addition to the high number of multifetal pregnancies, the hormone treatments used in the IVF cycles also explain the high FTBA values in the IVF pregnancy group. We believe that the results of our study will be more accurate as there were no multiple pregnancies in the study groups. On the other hand, in the same study, there were no differences between the groups in terms of family history of ICP. In our study, maternal and perinatal outcomes were similar in both groups and no difference was found between the spontaneous and IVF pregnancy groups in terms of preterm birth. In the study by Bolukbas et al.[20] the rates of spontaneous preterm birth were higher in the IVF group, which is closely related to the high number of multifetal pregnancies in the same group.

Our study has limitations, mainly because of its retrospective nature and relatively small sample size. Besides, it was not possible to collect data on the duration and dosage of estrogen exposure in all patients who underwent frozen embryo transfer. However, as multiple pregnancies, which are an important risk factor for ICP, were not included, the effect of estrogen treatment on ICP could be analyzed more precisely. Despite the retrospective nature of the study, the study was conducted in a large tertiary referral hospital where the same algorithms for diagnosis, treatment, and follow-up were applied, which was a major strength.

Conclusion

In conclusion, our results show that there is an association between high FTBA, ALT, and AST levels due to estrogen treatment in IVF pregnancies, especially when the frozen embryo transfer method was used. This is a comprehensive investigation that can serve as a basis for future research. If the results are supported by multicenter, prospective, randomized controlled studies, they can serve as a guideline for the clinical use of estrogen in such pregnancies.

Ethics Committee Approval

This study approved by the Ankara Etlik Zübeyde Hanım Maternity Training And Research Hospital Ethics Committee (Date: 24.10.2022, Decision No: 14/08).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: M.L.D., A.K.Ö.; Design: E.M., P.Y., S.Ö.; Supervision: E.M., P.Y., Y.E.Ü.; Materials: Y.A., Ö.K., F.B.F.; Data: E.M., S.Ö., F.B.F.; Analysis: P.Y., M.L.D., A.K.Ö., S.T.S.; Literature search: M.L.D., P.Y., S.T.S., A.K.Ö; Writing: M.L.D.; Critical revision: E.M., P.Y., Y.E.Ü.

Conflict of Interest

None declared.

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In Vitro Fertilizasyon ve Spontan Gebelikler Arasından İntrahepatik Gebelik Kolestazı Gelişen Hastaların Obstetrik Sonuçlarının Karşılaştırılması: Üçüncü Basamak Bir Hastanede Dört Yıllık Deneyim

Amaç: Gebeliğin intrahepatik kolestaz (GİK), uygun müdahaleler yapılmazsa ölü doğum riskinin 4 ila 10 kat artmasıyla ilişkili, gebeliğe özgü en yaygın karaciğer hastalığıdır. Çalışmanın amacı, spontan ve *in vitro* fertilizasyon (IVF) ile elde edilen gebelikler arasında GİK gelişen tekil gebeliklerin obstetrik sonuçlarını karşılaştırmaktır.

Gereç ve Yöntem: Ocak 2018 ile Eylül 2022 tarihleri arasında doğum yapan kadınlar geriye dönük olarak değerlendirildi. Dahil etme kriterleri uygulandıktan sonra, spontan olarak gebe kalan (grup 1, n=74) ve IVF ile gebe kalan (grup 2, n=17) toplam 91 GİK'li hasta çalışmaya uygun bulundu. Grup 2'deki hastalar embriyo transfer yöntemine göre taze embriyo transferi (n=9) ve dondurulmuş embriyo transferi (n=8) olmak üzere iki alt gruba ayrıldı.

Bulgular: Yaş, gravidite ve parite dışındaki perinatal sonuçlar ve demografik özellikler benzerdi. Grup 2'de yaş anlamlı derecede yüksek iken [32 (27-35) vs. 27 (24-31), p=0,017], gravidite ve parite grup 1'de anlamlı olarak yüksekti [2 (1-3) vs. 1 (1-2), p=0.021 and 0 (0-1) vs. 0 (0-0), p=0.009]. Aspartat (AST) ve alanin (ALT) transaminaz seviyeleri, total açlık safra asit (TASA) düzeyleri ve ursodeoksikolik asit tedavi dozu, dondurulmuş embriyo transfer grubunda taze embriyo transfer grubuna göre anlamlı derecede yüksekti [126 (83-242)'ya karşı 32 (31-43), p=0.001; 200±123.9'a karşı 51±39.4, 0.001; 44±20.4'e karşı 15±5.0, p=0.001, and 100 (750-1250)'e karşı 750 (750-750), p=0.004].

Sonuç: Sonuçlarımız, özellikle donmuş embriyo transfer yönteminin kullanıldığı IVF gebeliklerinde östrojen tedavisine bağlı olarak yüksek TASA, ALT ve AST düzeyleri arasında bir ilişki olduğunu göstermektedir. Eksojen östrojenin etkisini netleştirmek için geniş örneklemli prospektif çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Gebeliğin intrahepatik kolestazı; perinatal sonuçlar; perinatal yönetim; total açlık safra asidi; tüp bebek.