Özgün Araştırma / Original Article

Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology - Obstetrics and Neonatology

DOI:10.38136/jgon.1410939

Assessing the Relationship Between Intrahepatic Cholestasis of Pregnancy and Exogenous Progesterone Intake

Gebeliğin İntrahepatik Kolestazı ile Ekzojen Progesteron Alımı Arasındaki İlişkinin Değerlendirilmesi

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ÖZ

Amaç: İntrahepatik gebelik kolestazı (IGK) olan hastaların serumunda progesteron metabolitlerinin yüksek olduğu bilinmektedir ve erken gebelikte eksojen progesteron takviyesi progesteron metabolitlerinde artışa neden olabilir. Bu çalışmanın amacı IGK ile eksojen progesteron alımı arasındaki ilişkiyi araştırmaktır.

Gereçler ve Yöntem: Bu çalışma Ocak 2015- Kasım 2023 tarihleri arasında yapılmış retrospektif bir vaka-kontrol çalışmasıdır. Grupların karaciğer fonksiyon testleri, total safra asidi düzeyleri, anne yaşı, vücut kitle indeksi, parite, kolestaz öyküsü, progesteron kullanım öyküsü, kaşıntı semptomlarının ortaya çıktığı gebelik haftası, IGK tanısı konulan gebelik haftası, ursodeoksikolik asit kullanım öyküsü, obstetrik patoloji, annenin eşlik eden ek hastalık varlığı, doğum haftası, doğum şekli, doğum ağırlığı ve APGAR skorları hastanemiz veri tabanından elde edilerek karşılaştırıldı.

Bulgular: Çalışmaya 79'u IGK'lı ve 300'ü kontrol grubu olmak üzere toplam 379 gebe dahil edildi. Nulliparite, kolestaz öyküsü ve progesteron kullanımı IGK grubunda kontrol grubuna göre anlamlı derecede yüksekti ($p<0.005$, hepsi için).

Sonuç: Erken gebelik döneminde eksojen progesteron kullanımı IGK'ya neden olabilir ve fetus üzerinde olumsuz etkilere neden olabilir. IGK gelişiminde progesteronların rolünün araştırılması için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: İntrahepatik gebelik kolestazı, total safra asitleri, ursodeoksikolik asit, ekzojen progesteron

ABSTRACT

Aim: Progesterone metabolites are known to be elevated in the serum of patients with intrahepatic cholestasis of pregnancy (ICP), and exogenous progesterone supplementation in early pregnancy may cause an increase in progesterone metabolites. The aim of this study is to investigate the relationship between ICP and exogenous progesterone intake.

Materials and Methods: This study is a retrospective case-control study conducted between January 2015 and November 2023. The groups liver function tests, total bile acids, maternal age, body mass index, parity, history of cholestasis, history of progesterone use, gestational week in which pruritus symptoms occurred, gestational week, in which ICP was diagnosed, history of ursodeoxycholic acid intake, obstetric pathology, maternal comorbidities, week of delivery, delivery method, birth weight, APGAR scores were obtained from the database of our hospital and compared.

Results: A total of 379 pregnant women including 79 with ICP and 300 control were included in the study. Nulliparity, history of cholestasis, and history of progesterone intake were significantly higher in the ICP group than in the control group ($p<0.005$, for all).

Conclusion: Intake of exogenous progesterone in early pregnancy may lead to ICP and have adverse effects on the fetus. Further studies are needed to investigate the role of progesterone in the development of ICP.

Keywords: Intrahepatic pregnancy cholestasis, total bile acids, ursodeoxycholic acid, exogenous progesterone

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Başvuru tarihi: 27.12.2023
Kabul tarihi:20.05.2024

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is defined by the presence of pruritus and an increase in serum maternal total bile acids (TBA). This syndrome is accompanied by high liver enzyme and rarely bilirubin levels (1). ICP occurs most commonly in the third trimester of pregnancy but can begin in any trimester of pregnancy. ICP is the most common liver disease that occurs only during pregnancy (2). The incidence varies from 1% to 27.6% worldwide (3). ICP increases the risk of perinatal morbidity and mortality and adverse obstetric outcomes such as stillbirth, respiratory distress syndrome, meconium passage, and fetal asphyxia (4, 5).

The etiology of ICP is not fully understood, but it likely involves a combination of genetic predisposition, hormonal factors, and environmental factors. The development of ICP has been associated with the effects of sex hormones during pregnancy. It has been reported that progesterone metabolites increase in the serum of ICP patients (6, 7). The risk of miscarriage is described as vaginal bleeding that occurs before the twentieth week of pregnancy. It occurs in 20% of pregnancies and increases the risk of miscarriage by 2.6 times, with a 17% chance of subsequent pregnancy complications. The risk of miscarriage depends on the mother's acceptance or rejection of the allogeneic embryo. In a normal, healthy pregnancy, the number of progesterone receptors in maternal lymphocytes that come into contact with the embryo's antigen increases, and there is a corresponding shift in the maternal immune system toward T helper (Th) 2 lymphocytes. However, in the presence of impending miscarriage and preterm labor, no increase in progesterone receptors in lymphocytes is observed and a shift toward Th1 occurs. This may lead to an increase in interferon gamma, which is detrimental to pregnancy. Based on this information, studies suggest that progesterone use may be effective in treating impending miscarriage. There are very few data evaluating progesterone treatment in terms of maternal and fetal effects. Progesterone (in capsule, gel, or ampoule form), dydrogesterone, and hydroxyprogesterone caproate can be used as progesterone therapy.

In our study, the association between exogenous progesterone intake and clinical features and laboratory results of ICP patients was retrospectively investigated.

MATERIAL AND METHODS

This retrospective case-control study was carried out in a tertiary obstetric care center, in Ankara, Turkey, between January 2015 and November 2023 with the approval of the Ethics Committee (Approval number: AESH-EK1-2023-732). A verbal and written informed consent was obtained from all participants. At our hospital, fasting TBA levels are measured in women presenting during pregnancy with severe pruritus and/or abnormal liver function tests (LFT). For this study, two separate groups were formed: the ICP group: pregnant women who were found to have high fasting TBA levels (≥ 10 micromoles / L) in the presence of pruritus symptoms and/or due to an elevated LFT level, and the control group: it consisted of normal, healthy pregnant women without LFT elevation and pruritus symptoms. LFT elevation was defined as ≥ 40 international units/L for aspartate transaminase (AST) and alanine transaminase (ALT). Groups were compared with respect to their progesterone treatment history. Progesterone treatment included the use of oral, intramuscular injection or vaginal progesterone for at least 1 week to diagnose first trimester miscarriage or to prevent preterm delivery.

LFT, TBA, maternal age, body mass index (BMI), history of progesterone use, gestational week of pruritus symptoms, gestational week of ICP diagnosis, history of ursodeoxycholic acid (UDCA) use, obstetric pathology (intrauterine growth retardation, preterm labor, amniotic fluid abnormalities), maternal comorbidities (gestational hypertension, gestational diabetes mellitus, preeclampsia, HELLP syndrome), week of delivery, delivery method, birth weight, APGAR score information were recorded in hospital archives. Multiple pregnancies and pregnant women with severe fetal anomalies (out of soft marker) were excluded from the study.

Statistical Package for the Social Sciences -SPSS 22 (SPSS Inc. Chicago, IL) was used for data analysis. In the analysis of normality, nonparametric test procedures were used because the values for "BMI, number of pregnancies, week of pregnancy" measured with the Shapiro-Wilk test did not have a normal distribution. In this context, Mann Whitney U test was used to determine the relationships between parameters. Results were evaluated within the 95% confidence interval and a p-value of < 0.05 was considered significant.

RESULTS

Seventy-nine of 119 pregnant women whose TBA levels were measured because of pruritus and/or elevated LFT levels had high TBA levels (66.38%). All patients diagnosed with ICP had pruritus symptoms and 47 of them had concomitant elevated LFT levels (59.49%). Elevated LFT levels and concomitant cholelithiasis were found in 2 of 40 patients in whom TBA elevation had not been detected. Eight of 38 pregnant women who had a normal abdominal ultrasound had elevated LFT levels, but there were no recurrent TBA levels and no ICP diagnosis could be made. A total of 379 pregnant women, 79 of whom had ICP, and 300 control patients were enrolled in the study. The demographic and clinical characteristics of the mothers and newborns were compared in Table 1. There were no significant differences between groups in maternal age, BMI, obstetric conditions, maternal comorbidities, neonatal APGAR scores 1 and 5, and fetal death. Nulliparity, history of cholestasis, and history of progesterone use were significantly higher in the study group than in the control group, and gestational age and birth weight at delivery were significantly lower than in the control group.

Table 1. Comparison of maternal/neonatal characteristics and clinical features

	ICP (n=79)	Control (n=300)	P value
Maternal features			
Age [median (IQR)]	28.00 (9)	27.00 (9)	0.777
BMI [median (IQR)]	27.00 (4)	27.00 (5)	0.512
Nulliparity n (%)	40 (50.63)	78 (26.00)	**<0.001**
History of cholestasis n (%)	14 (17.72)	0	**<0.001**
Progesterone use n (%)	17 (21.52)	17 (5.66)	
First trimester n (%)	13 (16.45)	12 (4)	**0.001**
Second trimester n (%)	4 (5.06)	5 (1.66)	
Obstetric pathology n (%)	19 (24.05)	74 (24.66)	0.807
Comorbidity n (%)	24 (30.37)	92 (30.66)	0.477
Gestational age at birth [median (IQR)]	37.00 (1.0)	38.60 (1.4)	**<0.001**
Vaginal birth n (%)	66 (83.5)	170 (56.6)	**<0.001**
Neonatal features			
Birth weight [median (IQR)]	3000(520)	3210 (535)	**<0.001**
1 min. APGAR [median (IQR)]	9.0 (0)	9.0 (0)	0.235
5 min. APGAR [median (IQR)]	10.0 (0)	10.0 (0)	0.145
Fetal death n (%)	1 (1.26)	0	0.051

In the study group, the gestational age at which the pruritus symptom occurred ranged from 15 to 38 weeks (median 32.0), and the gestational week at which ICP was diagnosed ranged from 16 to 39 weeks (mean 33.04). Sixty-five of the patients with ICP were treated with UDCA. The median AST and ALT values were significantly higher in the study group than in the control group ($p < 0.001$, $p < 0.001$, respectively), and the median (IQR) was determined to be 18.00 (10), 12.00 (19), and 46.00 (61), 58.00 (95), respectively. The median (IQR) TBA value in the study group was 18.40 (20.4).

DISCUSSION

This study was conducted to understand the role of progesterone metabolites in the pathogenesis of ICP. As a result, it was found that the use of progesterone was higher in the ICP group than in the control group.

The pathogenesis of ICP is relatively complex, and researchers generally associate it with factors such as genetic, endocrine, and immunological disorders, as well as selenium deficiency (8-11). It has been suggested that high levels of estrogen and progesterone may be a triggering factor in the pathophysiology of ICP (12, 13). Studies have shown that a genetic predisposition may lead to bile acid accumulation by causing dysfunction of transmembrane transporters for bile acids in hepatocytes (14,15). In hyperestrogenism (i.e., pregnancy or use of birth control pills), this dysfunction becomes apparent and the patient develops typical symptoms such as pruritus (14,15). Most data suggest that cases of early-onset ICP in the first trimester are associated with elevated physiologic estrogen levels (ie, multiple pregnancies, ovarian hyperstimulation syndrome). In addition, pregnancies resulting from cycles of ovarian stimulation followed by embryo transfer are at higher risk for early-onset ICP (16).

The literature consistently emphasizes that progesterone metabolites play a greater role in the development of ICP than estrogens. These metabolites cause competitive inhibition of the binding of bile acids to receptor proteins on plasma membranes involved in excretion. Serum concentrations of progesterone metabolites are elevated in women with ICP and may be more concentrated in bile. Alternatively, the change in ICP could be due to overproduction of sulfated progesterone metabolites. It has been suggested that more progesterone metabolites are present here than in maternal plasma, because concentrations are lower in umbilical cord plasma. It is produced by the mother and then transferred to the fetus.

Family history is of great importance in the etiopathogenesis of ICP. Previous studies have shown that genetics is an underlying factor affecting estrogen levels and bile metabolism, and that individuals carrying an ICP susceptibility gene (e.g., a mutated ABCB4 gene (17) are more susceptible to ICP (18). Another important risk factor is ICP in previous pregnancies. Cholestasis develops in 60-70% of subsequent pregnancies in women with a history of ICP (19). In our current study, nulliparity, history of cholestasis, and progesterone use were found to be significantly more common in the ICP group than in the control group. Only one of the pregnant women with a history of cholestasis was taking progesterone. Other ICP patients receiving progesterone had no history of cholestasis. This finding suggests that the development of ICP may be dependent on the use of progesterone. However, further studies are needed to investigate the relationship between the appropriate form and dose of progesterone and the risk of developing ICP.

In clinical practice, the diagnosis of ICP is usually made on the basis of serum TBA concentration, but the mechanism of this metabolic disorder is not fully understood. While the total amount of estrogen and progesterone circulating in the blood or excreted in the urine is similar in ICP patients as in normal pregnant women, this is not true for the levels of their metabolites. Although progesterone synthesis appears to be intact, the profiles of progesterone metabolites in plasma and urine differ from those of normal pregnancies and contain a greater proportion of mono- and disulfated metabolites. TBA is the mainstay of the clinical diagnosis of ICP and the most important laboratory evidence for the diagnosis of ICP. In addition, bile acids promote the release of prostaglandins, and ICP can induce preterm labor in pregnant women (20). The ICP group (TBA ≥ 10μmol/L) was included in this study. Gestational age and birth weight were significantly lower in our ICP group than in the control group. In our study, there was no significant difference between the patient and control groups in obstetric pathologies (intrauterine growth retardation, preterm delivery, amniotic fluid abnormalities), maternal comorbidities (gestational hypertension, gestational diabetes mellitus, preeclampsia, HELLP syndrome), and neonatal APGAR scores. In addition, the gestational week at which ICP was diagnosed in our study was 16-39 (mean 33.04), and 65 of the patients were treated with UDCA. The additional administration of UDCA improves ICP symptoms. The hypothesis is that UDCA acts by removing hydrophobic endogenous bile salts from the bile acid pool, protecting hepatocytes from their toxic effects and improving the excretion of bile acids by the fetus via the placenta. Daily progesterone synthesis in late pregnancy is about 250 to 350 mg/dl. Sulfated pregnanolones, pregnanediols, and 5α-pregnan-3α,20α,21-triol are found in plasma in μmolar concentrations that increase with the duration of pregnancy. Concentrations of most of these sulfates were significantly increased in women with ICP. It is unclear whether this abnormality is primary or secondary to cholestasis. Sulfated and glucuronidated progesterone metabolites are excreted in bile in late pregnancy, and bile concentrations and fecal steroid excretion are lower in ICP than in normal pregnancy. Oral administration of UDCA to patients with early-onset ICP (before 33 weeks' gestation) results in improvement and some resolution of pruritus (21). Currently, there are no biomarkers for ICP in clinical use. The potential use of the predictive marker to determine whether pregnant women with pruritus will develop ICP is very interesting and should be explored in future prospective, robust studies.

This article had several limitations. First of all, it included retrospective and single-center data. Long-term follow-up of bile acid levels of the patients was not available due to its retrospective nature. Its strength is that it includes a large number of participants.

CONCLUSION

Exogenous progesterone supplementation early in pregnancy may lead to an increase in progesterone metabolites and thus earlier ICP in pregnancy. In this study, the relationship between exogenous progesterone intake and ICP was investigated. As a result, it was found that progesterone intake was significantly higher in the ICP group than in the control group. However, further studies are needed to investigate the relationship between adequate progesterone intake and dose and the risk of developing ICP.

Conflict of Interest

The authors have no conflicts of interest to declare.

Funding Statement

The authors received no funding for this work.

Acknowledgments

None.

Authors' Contributions

Concept: B.D.C., Design: B.D.C., G.D., Data Collection or Processing: B.D.C., G.D., Analysis or Interpretation: B.D.C., G.D., Literature Search: B.D.C., G.D., S.C., A.T.C., Writing: B.D.C., G.D., S.C., A.T.C.

Ethical Statement

Ethical permission required for the study was obtained by Ankara Etlik City Hospital Ethics Committee (Approval number: AEŞH-EK1-2023-732).

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