Evaluation of Plasma Lipid Levels in Intrahepatic Cholestasis of Pregnancy

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Abstract

Objective: To investigate the total cholesterol, triglyceride, LDL, VLDL, and HDL levels of pregnant women diagnosed with intrahepatic cholestasis of pregnancy and to examine the association with disease severity.

Material and Method: A total of 80 pregnant women, 40 of whom were diagnosed with intrahepatic cholestasis of pregnancy, and 40 age-matched controls, were prospectively enrolled in this study. Lipid levels were compared among the case and controls, and their association with disease severity was analyzed. Birth weight, birth week, and neonatal outcomes were studied.

Results: LDL and VLDL were significantly higher, and HDL levels were lower in the intrahepatic cholestasis of the pregnancy group than in the healthy pregnancies ($p<0.05$). Total cholesterol and triglyceride levels did not differ among the two groups. Birth weight, birth week, and 1-5-minute Apgar scores were lower, and the neonatal intensive care unit admission and the rate of primary cesarean section were higher in the group with intrahepatic cholestasis in pregnancy ($p<0.05$). In correlation analysis, a positive correlation was found between serum LDL and bile acids levels ($r=0.349$, $p=0.027$). LDL levels were significantly higher in severe disease than in mild disease ($p=0.009$)

Conclusion: There are significant changes in lipid homeostasis in intrahepatic cholestasis of pregnancy. Abnormal lipid levels, such as high LDL and VLDL levels, could have a role in the pathogenesis, and in particular high LDL levels may contribute to the prediction of disease severity.

Keywords: Bile acids, Cholesterol, Intrahepatic cholestasis of pregnancy, Triglycerides

Özet

Amaç: Çalışmamızın amacı, intrahepatik gebelik kolestazı tanılı gebelerde total kolesterol, trigliserid, LDL, VLDL, HDL düzeylerini araştırmak ve hastalık şiddeti ile ilişkisini incelemektir.

Gereç ve Yöntem: İntrahepatik gebelik kolestazı tanılı 40 ve benzer yaş grubunda 40 kontrol olmak üzere toplam 80 gebe prospektif olarak çalışmaya dahil edildi. Vaka ve kontrol grubu arasında lipid parametreleri karşılaştırıldı ve hastalık şiddeti ile ilişkisi analiz edildi. Doğum ağırlığı, doğumdaki gebelik haftası ve yenidoğan sonuçları incelendi.

Bulgular: İntrahepatik gebelik kolestazı tanılı grupta sağlıklı gebelere göre LDL, VLDL düzeyleri anlamlı olarak daha yüksek ve HDL düzeyleri daha düşük saptandı ($p<0,05$). Total kolesterol ve trigliserid seviyeleri iki grupta benzerdi. Gebelik kolestazı grubunda doğum haftası, doğum kilosu ve 1-5.dakika Apgar skorları daha düşük, yenidoğan yoğun bakıma yatış ve primer sezaryen oranları daha yüksekti ($p<0,05$). Korelasyon analizinde, serum LDL ile safra asiti seviyeleri arasında pozitif yönde korelasyon saptandı ($r=0,349$, $p=0,027$). LDL düzeyi, şiddetli hastalık grubunda hafif hastalık grubuyla karşılaştırıldığında anlamlı olarak yüksekti ($p=0,009$).

Sonuç: İntrahepatik gebelik kolestazında lipid homeostazında önemli değişiklikler meydana gelmektedir. LDL ve VLDL yüksekliği gibi anormal lipid düzeyleri gebelik kolestazı patogenezinde rol oynayabilir ve özellikle yüksek LDL kolesterol düzeyi kolestaz şiddetinin tahminine katkıda bulunabilir.

Anahtar Sözcükler: Gebeliğin intrahepatik kolestazı, Kolesterol, Safra asitleri, Triglseridler

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Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder characterized by elevated serum liver enzymes and bile acids and widespread pruritus that begins in the second and third trimester of pregnancy (1). The etiology of ICP is not clearly known. Autosomal inheritance, hypersensitivity to estrogen, hormonal changes, environmental factors, and dietary type may play a role in pathogenesis (2-4). Elevated aminotransferase and bile acid levels help diagnose ICP. It is associated with maternal conditions such as postpartum hemorrhage, preeclampsia, preterm delivery, and neonatal conditions such as a higher risk of meconium-stained amnion (1).

The higher prevalence of cholelithiasis is thought to be due to changes in lipid profiles in ICP (5-9). However, it is unclear whether dyslipidemia is the leading cause of ICP or a secondary consequence of liver dysfunction. It is more likely that lipid metabolism plays a role in the pathophysiology of cholestasis, as lipoproteins and their components generate oxidative stress and impair cell membrane fluidity and hepatobiliary transporter and receptor activity, thereby increasing the formation of cholestatic metabolites of placental steroid hormones (4, 10, 11).

This study aims to investigate low-density lipoproteins (LDL), very low-density lipoproteins (VLDL), the total cholesterol, triglycerides (TG), and high-density lipoproteins (HDL) levels of pregnant women diagnosed with ICP and to examine the association with disease severity.

Material and Method

This prospective study was conducted with 80 patients aged 18-42 between June 2019 and September 2019 at Zekai Tahir Burak Women's Health and Research Hospital, Gynecology and Obstetrics Department. Zekai Tahir Burak Hospital ethics committee approved the study (Decision number: 23/2019). The Declaration of Helsinki was followed, and all participants gave written informed consent.

80 pregnant women, 40 of whom were diagnosed with ICP, and age-matched 40 controls between 28 and 37 weeks gestation, were included in the study. Multiple pregnancies, fetal structural abnormalities, chronic liver disease, viral or nonviral hepatitis, diseases, conditions that block the bile ducts, such as cholelithiasis, hypertensive diseases such as preeclampsia, chorioamnionitis, chronic cardiac, renal, or pulmonary diseases were excluded from the study. ICP diagnosis was made with elevated serum bile acids higher than 10 mmol/L or elevated liver function tests and the presence of pruritus. Pruritus, characterized by exacerbations and abrasions due to nocturnal itching, was usually confined to the palms and feet without any known skin disease or rash. Ultrasonography of the upper abdomen was performed to rule out hepatobiliary disease. ICP patients were divided into 2 groups due to bile acid levels. At range of 10-40, mmol/L were defined as moderate ICP, whereas serum bile acids >40 mmol/L were defined as severe ICP. Maternal blood samples for TG, total cholesterol, aspartate transaminase (AST), alanine transaminase (ALT), LDL, VLDL, and HDL were obtained at diagnosis of cholestasis and measured with the Architect Autoanalyzer (Abbott Park, IL, USA). TBA concentrations were measured in millimoles per liter by a spectrophotometric method.

Statistical Analysis

SPSS (IBM SPSS Statistics 24) was used for statistical analysis. Means and standard deviations were used for descriptive variables. The independent-sample t-test was used for parametric distribution, and for nonparametric distribution, the Mann-Whitney U test was performed. The chi-square test was used to analyze the relationship between categorical data. The Spearman correlation test was performed to investigate the correlations. *P-value <0.05* indicates a significant difference.

Results

A total of 80 patients were enrolled in the study, 40 in the ICP group and 40 in the control group. Table I shows the maternal characteristics and laboratory parameters. When the groups were compared, no statistically significant differences were found in age, gravidity, parity, week of gestation at diagnosis (at the time of blood collection), and body mass index. LDL, VLDL, total bilirubin levels, ALT, and AST, were significantly higher in the ICP group than in healthy pregnancies (*p<0.05*). TG and total cholesterol levels didn't differ in the two groups (Table I).

Table I. Characteristics and laboratory parameters of case and control groups

	Intrahepatic cholestasis of pregnancy group (n=40)	Control group (n=40)	*p -value*
Age, year	32±5.9	30±4.6	*0.801*
Gravida (n)	2 [1-4]	2 [1-5]	*0.512*
Parity (n)	1[0-5]	0 [0-3]	*0.223*
Body mass index (kg/m^2)	30 [22-43]	25 [24-38]	*0.625*
Gestational week at diagnosis	32±2.1	31±1.9	*0.764*
Triglyceride (mg/dL)	262±109	255±114	*0.659*
Total cholesterol (mg/dL)	253±49	238±43	*0.164*
LDL (mg/dL)	165±40	145±29	***0.015***
VLDL (mg/dL)	63±28	52±15	***0.021***
HDL (mg/dL)	31±14	40±12	***0.002***
AST (U/L)	84±14	27±8	***0.024***
ALT (U/L)	120 ±23	36 ±11	***0.001***
Total bilirubin (mg/dL)	0.70 ±0.30	0.21± 0.14	***0.042***

mean ± standard deviation , median (min-max)
ALT, alanine transaminase; AST, aspartate transaminase; HDL, high-density lipoproteins; LDL, low-density lipoproteins; VLDL, very low-density lipoproteins
p < 0.05 considered statistically significant

Birth weight, birth week, and 1-5 minutes Apgar scores were lower in the ICP group, while rates of neonatal intensive care unit (NICU) admission and primary cesarean section rates were higher (*p<0.05*). The rate of meconium-stained amnion was found to be 17.5% in the ICP group and 5% in the control group, with no statistical difference between the groups (*p=0.067*) (Table II).

Table II. Comparison of pregnancy and neonatal outcomes of study groups

	ICP group (n=40)	Control group (n=40)	p-value
Apgar 1.min	7 [6-8]	8 [7-9]	**0.042**
Birth weight (gr)	2670±577	3050±640	**0.031**
Birth week	36±2.2	38±2.4	**0.043**
Apgar 1.min	7 [6-8]	8 [7-9]	**0.042**
Apgar 5.min	9 [7-10]	10 [9-10]	**0.036**
NICU admission	9/40 (22.5%)	2/40 (5%)	**0.045**
Primary CS rate	13/40 (32.5%)	4/40 (10%)	**0.014**
Meconium stained amnion	7/40 (17.5%)	2/40 (5%)	0.067

mean ± standard deviation, median (min-max), number (%),
CS, cesarean section; NICU, neonatal intensive care unit
Significant at $p < 0.05$

Correlation analysis revealed a positive correlation between LDL and serum bile acids (*r=0.349, p=0.027*) (Table III). A positive correlation was also detected between ALT, AST, and serum bile acids (*r=0.512, p=0.001; r=0.345, p=0.043*, respectively). There were 18 patients in the severe ICP group and 22 pregnant women in the mild ICP group. When comparing lipid levels between groups according to disease severity, LDL levels were significantly higher in severe disease than in mild ICP (*p=0.009*) (Table IV).

Table III. Correlation of laboratory characteristics and serum bile acid

ICP (n=40)	Serum bile acid	
	r[a]	*p-value*
LDL (mg/dL)	*0.349*	*0.027*
VLDL (mg/dL)	*0.192*	*0.241*
HDL (mg/dL)	*-0.158*	*0.332*
AST (U/L)	*0.345*	*0.043*
ALT (U/L)	*0.512*	*0.001*

ALT, alanine transaminase; AST, aspartate transaminase; HDL, high-density lipoproteins; Intrahepatic cholestasis of pregnancy; LDL, low-density lipoproteins; VLDL, very low-density lipoproteins
[a] Spearman's correlation coefficient
Significant at $p < 0.05$

Table IV. Comparison of lipid levels in groups with mild and severe ICP

	Mild ICP (n=22)	Severe ICP (n=18)	*p-value*
Total cholesterol (mg/dL)	232(133-310)	264 (177-336)	*0.192*
Triglyceride (mg/dL)	300 (184-480)	278 (119-664)	*0.505*
LDL (mg/dL)	147 (35-208)	190 (104-251)	*0.009*
VLDL (mg/dL)	65 (36-100)	60 (23-132)	*0.781*
HDL (mg/dL)	32 (21-67)	34 (8-60)	*0.227*

Median (min-max)
HDL, high-density lipoproteins; ICP, intrahepatic cholestasis of pregnancy; LDL, low-density lipoproteins; VLDL, very low-density lipoproteins
$p < 0.05$ considered statistically significant

Discussion

In this study, we investigated the lipid profile in ICP and its relationship to disease severity. Our results suggest that the lipid profile is impaired in ICP compared with healthy pregnancies and that abnormal lipid levels may have a role in the ICP pathogenesis. In particular, LDL levels might be related to disease severity.

Cholesterol is an essential structural element of the cell membrane and serves as a precursor of bile acids and steroid hormones. Bile acids have a toxic effect on the fetus, and their accumulation in the vascular bed of the placenta is thought to increase the risk of meconium-stained amnion and intrauterine exitus in cases with ICP (12, 13). Because of this relationship between total cholesterol and bile acid, attention has been focused on lipid levels in pregnant women with cholestasis, and there are conflicting results in the literature (7, 14). A recent study found that total cholesterol levels in pregnancies with cholestasis were significantly elevated than in the control group and increased during pregnancy (15). In our study, total cholesterol level was higher in ICP than healthy pregnancies, but this was not statistically significant. The mechanisms behind these changes in lipid metabolism remain unknown. The most likely cause is a disturbance of the hepatobiliary transport system (6, 16). It is not known whether ICP causes the changes in lipid metabolism or whether these changes are due to ICP. In a recent study, plasma LDL concentrations were found to be higher in cholestasis than in pruritis gravidarum patients, and the increase in bile acid levels from 28 weeks of gestation was probably due to an increase in LDL cholesterol (15). These data support our finding that LDL levels were significantly elevated in the group with severe ICP compared with those with mild ICP.

A recent study shows ICP may be part of metabolic disease (17). A growing body of research suggests that the farnesoid X receptor (FXR), the major bile acid receptor, may influence lipid metabolism. Bile acid is now recognized as a signaling molecule, and there is strong evidence that it modulates glucose and lipid balance via FXR (18). Activation of FXR inhibits endogenous bile acid production and lowers plasma levels of TG, cholesterol, and glucose (19). Cholestasis was associated with decreased FXR expression and activity (20). Increased levels of the 3-sulfated progesterone metabolite antagonize FXR in ICP pregnancies, as shown by another study (21). Consequently, decreased FXR activity could play a role in ICP and affect the maternal lipid profile. However, the relationship between ICP and imbalanced lipid profiles needs to be better understood and convoluted, and it could include additional findings such as intestinal flora changes in ICP (22). This close relationship between the bile acid receptor and lipid metabolism may be one of the reasons for the high lipid levels in ICP in our study.

In the current study, LDL and VLDL levels were significantly elevated, while HDL levels were significantly lower in the case group. High levels of cholesterol, especially elevated LDL and TG levels, are one of the main risk factors for atherosclerosis (23). LDL causes atherosclerosis by several mechanisms, such as cytotoxicity to smooth muscle cells. In placental atherosclerosis, there is a decrease in fetal blood flow, which can lead to fetal hypoxia, distress, and intrauterine loss, as well as a decrease in the transfer of oxygen nutrients in

the blood (24, 25). Similar to previous studies, the ratio of primary cesarean section and NICU acceptance were found to be higher, while 1 and 5-minute Apgar scores were lower in the case group (26, 27). An analysis of patients with ICP found an increased risk of meconium-stained amniotic fluid (OR 2.60) (26). The incidence of meconium-stained amniotic fluid was reported to range from 15% to 25% in the intrapartum period in a normal pregnancies and may be a potential indicator of fetal distress (1). Animal studies have shown that fetal colonic motility is increased due to high maternal bile acid, resulting in meconium in amniotic fluid (28). In a study of 713 women with bile acid levels of 40 micromol/L or more, researchers discovered that this group of patients had a higher preterm delivery risk and higher maternal age than healthy pregnancies (27). Although it was not statistically significant, the meconium-stained amniotic fluid rate increased in current study. The advantage of the current study is to evaluate the relationship between lipid profile and severe ICP. Although there are other publications showing worsening of the lipid profile in ICP, the main strength of our article lies in showing the association between high LDL levels and severe cholestasis. Our study's limitation is that apolipoproteins that may play a role in pathogenesis were not included in the lipid profile analysis. Further studies with larger lipid panels may help elucidate the relationship between bile acid and lipid metabolism.

Conclusion

In conclusion, we demonstrated that LDL and VLDL were higher in ICP than in healthy pregnancies suggesting abnormal lipid levels may play a role in the pathogenesis of ICP. There are significant changes in lipid homeostasis in ICP, and in particular, a high LDL cholesterol level may help predict the severity of the disease.

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