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Are Postprandial Bile Acid Levels Helpful in Predicting Perinatal Complications in Patients with Intrahepatic Cholestasis of Pregnancy?

Gebelik Kolestazlı Gebelerde Safra Asit Seviyeleri Perinatal Komplikasyonları Tahmin Etmede Yardımcı mıdır?

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ABSTRACT

Purpose: To determine the outcomes of Iintrahepatic cholestasis of pregnancy and the role of postprandial serum bile acid levels in the prediction of perinatal complications.

Material and Methods: This retrospective study consisted of 103 patients with intrahepatic cholestasis of pregnancy between January 2008 and June 2013. Maternal age, obstetric history, pregnancy outcome, maternal and neonatal complications, ursodeoxycholic acid treatment during pregnancy and serum laboratory tests were retrieved from patients' medical records. Receiver operating characteristic analysis was used to evaluate the performance of fasting and postprandial serum bile acid levels to predict perinatal complications.

Results: Gestational diabetes and preterm delivery occurred more frequently in patients with intrahepatic cholestasis of pregnancy patients. The rate of primary cesarean delivery was more common in in patients with intrahepatic cholestasis of pregnancy patients. The rate of growth-restricted infants was higher in the patients who received ursodeoxycholic acid. Nenoatal intensive care unit admissions and overall neonatal complications, as well as spontaneous preterm deliveries, were similar among in patients with intrahepatic cholestasis of pregnancy regardless of ursodeoxycholic acid therapy. In the receiver operating characteristic analysis, the area under curve values for postprandial and fasting bile acids to predict neonatal complications were 0.64 and 0.70, respectively.

Conclusion: Intrahepatic cholestasis of pregnancy patients increases certain perinatal complications, such as preterm deliveries and neonatal morbidity. Postprandial serum bile acid levels are inferior to fasting serum bile acid levels in the prediction of obstetric complications. ursodeoxycholic acid does not seem to improve perinatal outcomes.

Key words: Pregnancy Complications, Intrahepatic Cholestasis, Postprandial Bile Acids

ÖZET

Amaç: Gebelik kolestazlı gebelerin gebelik sonuçlarının ve postprandial serum safra asit seviyelerinin perinatal komplikasyonları ile ilişkisinin değerlendirilmesi.

Materyal ve Metod: Bu retrospektif çalışma Ocak 2008 ve Haziran 2013 arasında gebelik kolestazı tanısı alan 103 hastayı içermektedir. Hastaların yaşları, obstetrik hikayeleri, gebelik sonuçları, maternal ve neonatal komplikasyonları, ursedeoksikolik asit tedavisi ve serum labaratuar testleri hastaların medikal kayıtlarından elde edildi. Receiver operating karakteristik analizleri açlık ve postprandial safra asitleri seviyelerinin perinatal komplikasyonları tahmin etme gücünü değerlendirmek için kullanıldı.

Bulgular: Gestasyonel diyabet ve preterm doğum intrahepatik kolestazlı gebelerde daha sıklıkla izlendi. Primer sezeryan oranı intrahepatik kolestazlı hastalarda daha yaygındı. Gelişme geriliği oluşan fetusların oranı ursodeoksikolik asit kullanan kadınlarda daha yüksekti. Ursodeoksikolik asit kullanımından bağımsız olarak intrahepatik kolestazlı tüm gebelerde neonatal yoğun bakım ihtiyacı ve spontan preterm doğumların dahil olduğu tüm neonatal komplikasyonların görülme oranı benzerdi. Receiver operating karakteristik analizinde postprandial ve açlık safra asit seviyelerinin gebelik kompliksayonlarını tahmin etme gücü sırasıyla 0,64 ve 0,70 idi.

Sonuç: Gebelik kolestazı preterm doğum ve neonatal morbiditi gibi perinatal komplikasyonları kesin olarak arttırmaktadır. Postprandial safra asit seviyesi açlık safra asit seviyesine göre obstetik komplikasyonları tahmin etmede daha değersiz bulunmuştur ve ursodeoksikolik asit tedavisi perinatal sonuçların üzerinde etkili bulunamamıştır.

Anahtar kelimeler: Gebelik komplikasyonları, intrahepatik kolestaz, postprandial safra asitleri

INTRODUCTION

Intrahepatic cholestasis (ICP) is a pregnancy-specific liver disorder that typically presents after the second trimester. The chief symptom of ICP is maternal pruritus and it is usually accompanied by elevated serum transaminases and fasting serum bile acid as the laboratory finding[1]. The importance of this disorder is its association with preterm delivery, preeclampsia, fetal distress, meconium staining and stillbirth[1,3]. The cause of ICP is heterogeneous and multiple factors have been implicated in the pathophysiology. Genetic predisposition and environmental and hormonal influences have been studied as etiological factors in the literature[1,3].

The overall prevalence of ICP varies significantly among different nations and ethnic groups. In the United Kingdom, the overall prevalence is 0.7% and it is 1.5% in Sweden and other Scandinavian countries. The prevalence is the highest in parts of South America, specifically in Chile, where the reported prevalence is as high as 15.6%[1]. Although a relatively benign condition for the mother, ICP poses several risks to the fetus. Morbidity usually results from iatrogenic prematurity due to worsening liver function of the mother[3,4]. The active management of ICP consists of close fetal surveillance and delivery at term, which aims to protect the fetus from the potential risk of stillbirth, even by facing the risks of prematurity[5]. Elevated fasting serum bile acid levels are of both diagnostic and prognostic importance[3]. However to the best of our knowledge no study has previously examined the role of postprandial bile acid levels in ICP.

The present study aimed to evaluate five years of experience of a tertiary maternal/fetal medicine center and to determine the outcomes of ICP and the role of postprandial serum bile acid levels in the prediction of perinatal complications.

MATERIALS and METHODS

This retrospective study consisted of recorded cases of ICP at the maternal fetal medicine clinic of Dr Zekai Tahir Burak Womens Health, Research and Training Hospital between January 2008 and June 2013. ICP was defined as pruritus, otherwise unexplained elevated liver enzyme levels and elevated serum bile acid levels[6]. Patients without complete laboratory workups for diagnosis or who were lost to follow up were excluded from the study. Patients with chronic cholestatic liver disease were not included in the study. However, asymptomatic patients who tested positive for hepatitis B or C were not excluded from the study. During this period, 103 cases of ICP were included in the study. 69 patients with ICP were excluded from the study due to above-mentioned reasons. Three controls per case were randomly selected from the remaining births at our institution by using a random table. The study was approved by the local ethics committee.

The following clinical and demographic data were obtained by reviewing the patients' medical records: maternal age, obstetric history, pregnancy outcome and maternal and neonatal complications

and ursodeoxycholic acid (UDCA) treatment during pregnancy. Patients received UDCA 15 mg/kg per day when UDCA therapy commenced. Indication of UDCA therapy in our perinatology department was presence of maternal pruritic symptoms, severely elevated serum bile acids (> 40 µmol/l) presence of hyperbilirubinemia or diagnosis at 2nd or early third trimester. Evaluated biochemical values included serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) ,fasting and postprandial serum bile acids. Serum laboratory tests were typically obtained at the time of presentation and weekly thereafter until delivery.

Among fetal complications, fetal distress was defined by repetitive severe variable decelerations, repetitive late decelerations or fetal bradycardia of less than 110 beats per minute lasting 3 minutes or longer, requiring emergent delivery. Intrauterine growth restriction (IUGR) was defined as estimated fetal weight below the tenth percentile associated with fetal Doppler abnormalities.

Deliveries occurring prior to 37 weeks of gestation were recorded as preterm deliveries. Spontaneous preterm delivery was defined as deliveries due to spontaneous preterm labor in the absence of medical conditions necessitating delivery. Preeclampsia was defined as persistent elevation of blood pressure after 20 weeks of gestation, with additional systemic features. Gestational diabetes was defined as one abnormal result in 75 gr or two abnormal results in 100 gr oral glucose tolerance tests that exceeded the threshold for diagnosis.

Statistical analysis was performed using SPSS version 17 (Statistical Package for the Social Sciences, Chicago, IL). Student's t test was performed for parametric variables between groups, and a Chi-square test was performed for nonparametric variables between groups. A paired samples t test was performed to evaluate differences in serum bile acid levels after UDCA therapy. Receiver operating characteristic (ROC) analysis was used to evaluate the performance of fasting and postprandial serum bile acid levels to predict perinatal complications. The neonatal complications screened for ROC analysis included low Apgar scores at 1 or 5 minutes, IUGR, deliveries before 34th gestational weeks and NICU admission. The Youden index (sensitivity + specificity - 1) was used to detect optimal cut-off for fasting and postprandial bile acids. P values less than 0.05 were considered as significant.

RESULTS

The demographic characteristics of the patients are shown in Table 1. Advanced maternal age, nulliparity and preterm deliveries were more common in the ICP patients.

Pregnancy complications of the ICP patients and the control group were shown in Table 2. Gestational diabetes and preterm delivery occurred more frequently in the ICP patients. The rates of primary cesarean delivery and cesarean delivery for probable fetal distress were also more common in the ICP patients. Cholelithiasis was more common in the ICP patients. However, the rates of seropositivity for hepatitis B and C were similar. The rates of low birth weight infants and neonatal intensive care admissions were higher in the ICP group.

The outcomes of ICP patients who received and did not receive UDCA were shown in Table 3. The disease was diagnosed at an earlier gestational age in the patients who received UDCA compared to those who did not. In addition, the number of weeks that elapsed from diagnosis to delivery was greater in the patients who received UDCA. There was a higher rate of improvement in pruritic complaints in the patients who received UDCA. NICU admissions and overall neonatal complications, as well as spontaneous preterm deliveries, were similar in the two groups. The rate of growth-restricted infants was higher in the patients who received UDCA. Serum ALT and AST levels declined within weeks in the patients who received UDCA but remained relatively steady in those who did not receive UDCA (Figures 1 and 2). Changes in the fasting and postprandial bile acid

serum levels of the ICP patients who received and did not receive UDCA were shown in Figure 3. Both fasting and postprandial levels were higher in the patients who received UDCA. The decrease in fasting and postprandial bile acids following treatment was significant in the patients who received UDCA. ROC curves for fasting and postprandial serum bile acids for the prediction of neonatal complications were shown in Figure 4. The area under curve (AUC) values for postprandial and fasting bile acids were 0.70 and 0.64, respectively. Best cutoff for predicting neonatal complications was 38 µmol/l for fasting and 24 µmol/l for postprandial serum bile acids.

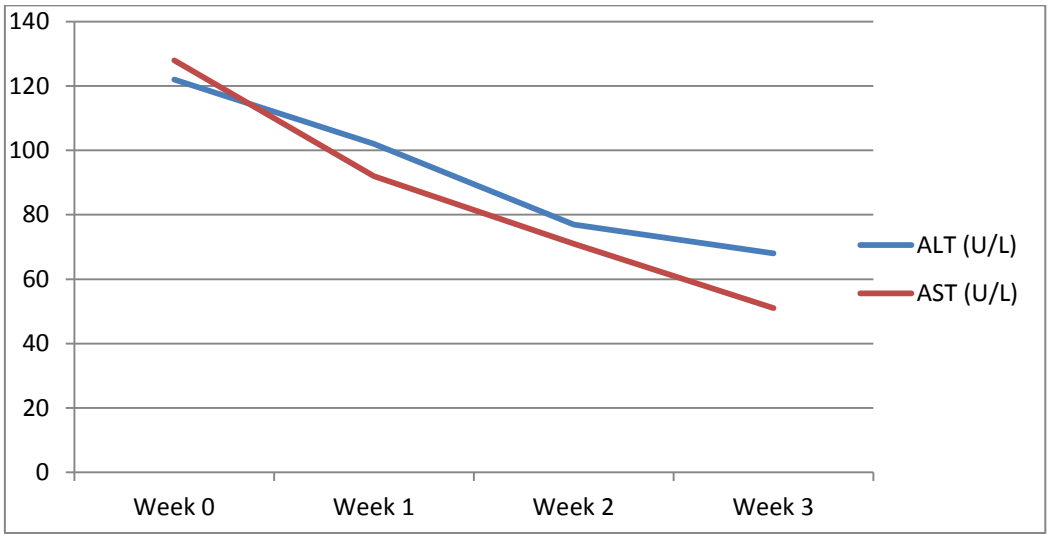

Figure 1. Serum alanine amino transferase (ALT), aspartate amino transferase (AST) levels in patients receiving ursodeoxycholic acid.

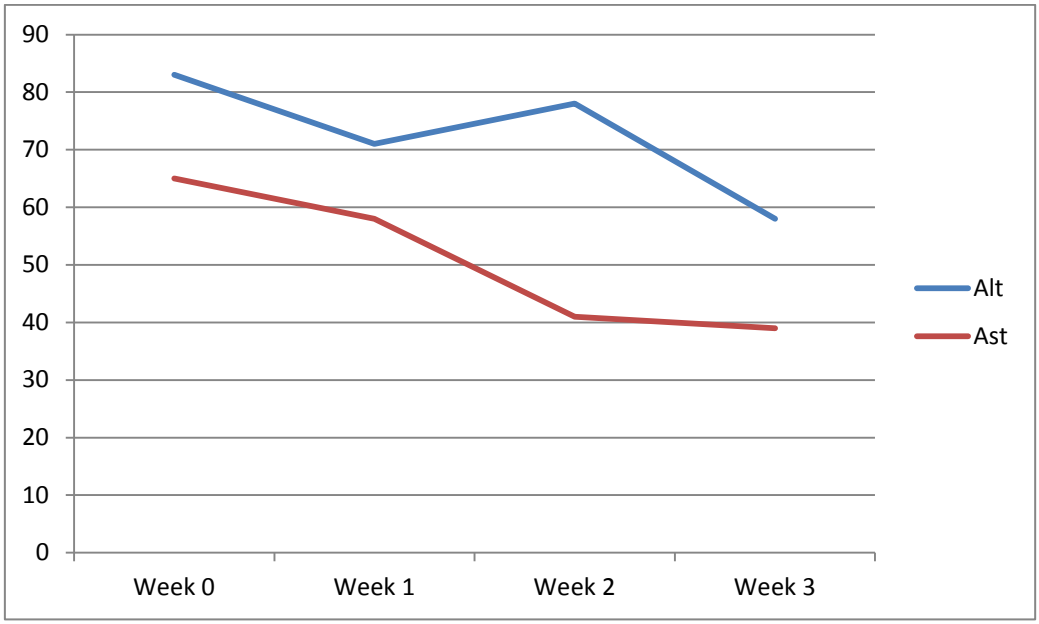

Figure 2. Serum alanine amino transferase (ALT), aspartate amino transferase (AST) levels in patients not receiving ursodeoxycholic acid.

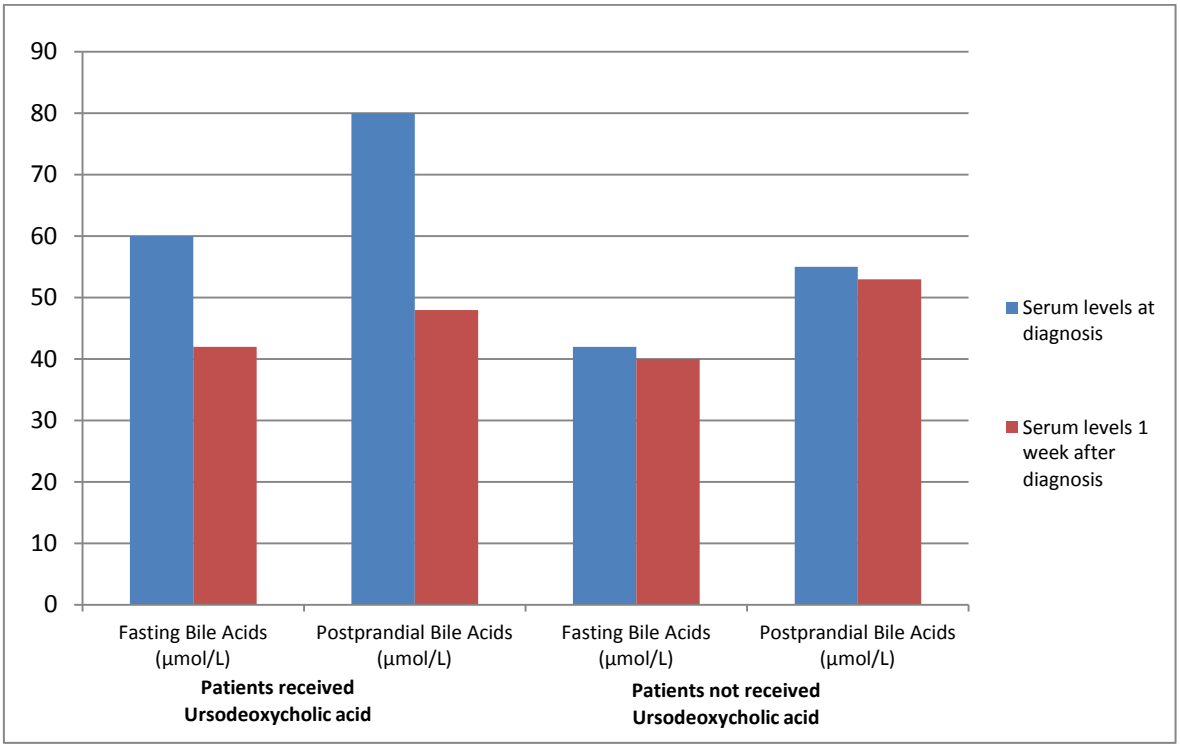

Figure 3. Serum bile acid profile of patients with intrahepatic cholestasis of pregnancy.

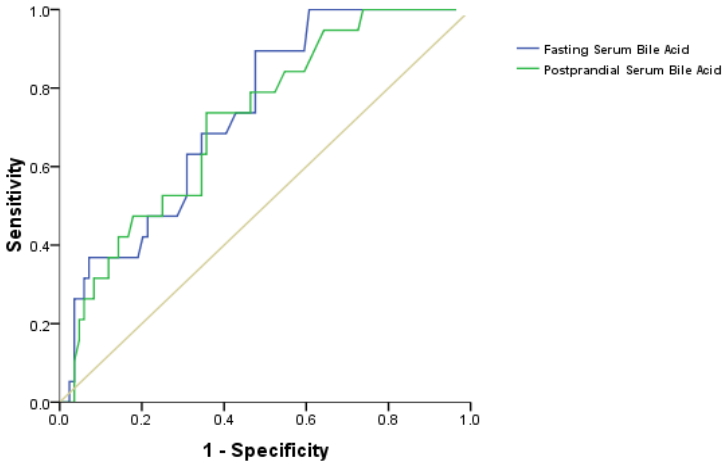

Figure 4. Receiver operating characteristic *curves* of fasting and postprandial serum bile acid levels to predict neonatal complications.

Table 1. Clinical data of patients with ICP * and control group.

Characteristics	ICP (n = 103) (%)	Control (n = 309) (%)	p
Maternal age (years)			
< 19	2 (1,9 %)	36 (11,7 %)	< 0,01
19-35	88 (85,4 %)	254 (82,2 %)	
> 35	13 (12,6 %)	19 (6,1 %)	
Gestational age (weeks)			
< 36	47 (45,6 %)	33 (10,7 %)	< 0,01
37-40	56 (54,4 %)	236 (76,4 %)	
> 41		40 (12,9 %)	
Parity			
0	61 (59,2 %)	117 (37,9 %)	
1-3	42 (40,8 %)	187 (60,5 %)	< 0,01
≥ 4	0	5 (1,2 %)	
Body mass index			
20 - 25	18 (17,5 %)	109 (35,3 %)	
25 - 30	48 (46,6 %)	131 (42,4 %)	< 0,01
> 30	37 (35,9 %)	69 (22,3 %)	
Birthweight (grams)			< 0,01
< 2500	28 (27,2 %)	20 (6,5 %)	
2500-4000	74 (71,8 %)	272 (88 %)	
> 4000	1 (0,2 %)	17 (5,5 %)	
Male fetus	45 (43,7 %)	162 (52,8 %)	0,11

Data expressed as number (%), * ICP: intrahepatic cholestasis of pregnancy

Table 2. Comparision of pregnancy complications in patients with ICP [a] and control group.

Characteristics	ICP (n = 103) (%)	Control (n = 309) (%)	p
GDM b	12 (11,7 %)	16 (5,2 %)	0,02
IUGRc	9 (8,7 %)	14 (4,5 %)	0,11
Preeclampsia	4 (3,9 %)	9 (2,9 %)	0,62
Preterm Delivery	47 (45,6 %)	33 (10,7 %)	< 0,01
Delivery < 34 weeks	16 (15,5 %)	9 (2,9 %)	< 0,01
Hepatitis B seropositivity	4 (3,9 %)	13 (4,2 %)	0,89
Hepatitis C seropositivity	2 (1,9 %)	2 (0,6 %)	0,25
Cholelithiasis	11 (10,7 %)	15 (4,9 %)	0.04
Cesarean delivery	23 (53,5 %)	46 (34,8 %)	< 0,01
Primary Cesarean delivery	51 (56,7 %)	91 (34,0 %)	< 0,01
Birth weight<2500	21 (32,8 %)	9 (6,8 %)	< 0,01
NICU d admission	14 (21,9 %)	9 (6,8 %)	0,02
Perinatal mortality	1 (1,0 %)	2 (0,6 %)	0,74
Cesarean indications			0,03
Non-progrressive labor	14 (21,9 %)	30 (22,7 %)	
Fetal distress	31 (48,4 %)	39 (29,5 %)	
Repeat cesarean delivery	13 (20,3 %)	41 (31,1 %)	
Malpresentation	6 (9,4 %)	13 (9,8 %)	
Fetal macrosomia	0	9 (6,8 %)	

Data expressed as number (%), a ICP: intrahepatic cholestasis of pregnancy, b GDM: gestational diabetes mellitus, c IUGR:Intrauterine growth restriction, d NICU: neonatal intensive care unit

Table 3. Comperative analysis of clinical data of ICP patients according to Ursodeoxycholic acid theraphy

	Patients received Ursodeoxycholic acid. (n = 48)	Patients not received Ursodeoxycholic acid. (n = 55)	p
Gestational age at Delivery (weeks)	35,4 ± 3,06	36,2 ± 2,39	0,21
Gestational age at Diagnosis (weeks)	32,4 ± 4,46	34,5 ± 3,27	<0,01
Pregnancy prolongation (weeks)	3,09 ± 4,78	1,68 ± 3,02	0,08
Fasting serum bile acid at diagnosis (µmol/L)	60,0 ± 56,6	41,9 ± 37,1	0,06
Postprandial serum bile acid at diagnosis(µmol/L)	80,9 ± 73,5	55,3 ± 55,9	0,05
ALT a before therapy (U/L)	122 ± 100	83,2 ± 587,	0,02
ALT normalization during follow-up(U/L)	38 (78,7 %)	28 (50,9 %)	<0,01
Patients with pruritus at onset	28 (58,3 %)	30 (54,5 %)	0,70
Improvement in pruritic symptoms	25 (52,1 %)	9 (16,4 %)	<0,01
Spontaneous preterm birth	9 (18,8 %)	7 (12,7 %)	0,40
IUGR b	7 (14,6 %)	2 (3,6 %)	0,05
NICU c admission	12 (25,0 %)	7 (12,7 %)	0,11
Overall neonatal complications	15 (31,2 %)	9 (16,4 %)	0,08

Data expressed as number (%), mean ± SD, a ALT: alanine aminotransferase, b IUGR:Intrauterine growth restriction, c NICU: neonatal intensive care unit

DISCUSSION

The findings of this study suggest that patients receiving UDCA had a longer latency period. In addition, UDCA treatment significantly reduced pruritic complaints in ICP patients. In contrast, the rate of IUGR was higher in patients who received UDCA. However, no beneficial effects of the UDCA treatment were observed in terms of pregnancy complications. A meta-analysis of nine randomized controlled trials including 454 patients was conducted in 2012[7]. In addition to the resolution of maternal pruritus and normalization of laboratory parameters, the authors reported fewer preterm deliveries, less frequent respiratory distress in the newborn and fewer neonates in the ICU as a result of UDCA treatment. However, in a Cochrane review, conducted in 2013, that investigated the effectiveness of therapy, the authors concluded that UDCA therapy was not effective in preventing perinatal morbidity or spontaneous preterm delivery, although maternal pruritic complaints and serum liver enzymes improved significantly[8]. It is still debated whether UDCA is helpful in preventing perinatal complications, as some conclusions of these two recent meta-analyses are contradictory. As stated previously, our results revealed that treatment with UDCA did not positively influence perinatal outcome. However, this data might reflect clinicians' decisions rather than the effectiveness of the therapy. The patients in our groups were not homogenous or randomly selected. The patients who received UDCA were diagnosed at an earlier gestation time and had higher levels of fasting bile acids. Therefore, the present data might suggest a higher rate of complications in patients with more severe disease rather than the ineffectiveness of UDCA therapy. The higher rate of IUGR in the patients receiving UDCA also supports this hypothesis.

The overall neonatal complication rate was higher in the ICP patients, who had a higher rate of preterm deliveries and very early preterm deliveries, as well as low birth weight infants and NICU admissions. Moreover, cesarean delivery rates and primary cesarean deliveries were higher in the ICP patients. There were also more cases of cesarean deliveries due to suspected fetal distress in the ICP patients. Women with ICP had higher

rates of cholelithiasis and gestational diabetes as well. Increased cesarean delivery rate, preterm deliveries, and cholelithiasis in patients with ICP have been reported previously[2,9-12]. The association between ICP and GDM was recently stated in a large Swedish cohort, which is in agreement with our data[2].

An important finding of the present study concerns postprandial bile acid levels. To the best of our knowledge, no study has previously examined the relationship between postprandial bile acid levels and obstetrical complications. In the present study, postprandial bile acid levels were inferior to fasting bile acids in predicting perinatal morbidity. ROC analysis revealed that the AUC curve for postprandial bile acids was 0.64. The AUC for fasting bile acids was 0.70, slightly higher than postprandial bile acids. In human, fasting serum bile acid concentrations are generally low in the peripheral circulation and in response to a meal, peripheral venous levels of serum bile acids increase several fold[13-15]. Low fasting bile acid levels are presumed to be the consequence of an increased hepatic absorption of bile acids, whereas elevated postprandial bile acids are presumed to occur due to increased intestinal absorption of bile acids and thus, an elevated portal venous load to the liver[15,16]. Serum postprandial bile acid levels in ICP was investigated by laatikainen [17]. In this unique study postprandial serum bile acid were highly elevated in patients with ICP and increased more than the control group. Thus the author have concluded that postprandial serum bile acids might be of value in the confirmation of diagnosis of ICP. In the present study, However, the median increase of serum bile acid was 1.6-fold one hour following a meal, which was similar to the physiological elevation in healthy subjects. The present data suggest that no specific serum biochemical pattern of postprandial bile acid characterizes ICP and that there is no strong relationship between postprandial bile acid and perinatal complications. Therefore, we conclude that the preliminary data provided by the findings of this study suggest that postprandial serum bile acids do not predict perinatal complications better than fasting serum bile acid levels.

Our study has several limitations. First, the retrospective design of the study might limit the validity of the findings, for reasons that are inherent in all retrospective studies. In addition, patients with higher levels of fasting bile acids in our cohort had a higher rate of iatrogenic preterm deliveries. Such variances in management of patients with ICP limit the ability to interpret the influences of certain clinical features and management strategies on perinatal outcome. However, to the best of our knowledge, the present study is the first to examine the relationship between postprandial serum bile acid level and perinatal outcome.

The findings of the present study confirm the previous data in the literature that have suggested that ICP increases certain perinatal complications, such as preterm deliveries and neonatal morbidity. Moreover, our results show that postprandial serum bile acid levels are inferior to fasting serum bile acid levels in the prediction of obstetric complications. UDCA does not seem to improve perinatal outcomes, although these latter findings still need to be confirmed by future studies.

Declaration of interest

None of the authors has a financial relationship with a biotechnology manufacturer, a pharmaceutical company, or any other commercial entity that has an interest in the subject matter or materials discussed in this article.

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