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Evaluation of perinatal outcomes according to fasting bile acie level in pregnant women diagnosed with intrahepatic cholestasis

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Abstract

Objective: This study aimed to determine perinatal outcomes based on fasting bile acid concentrations in pregnant women diagnosed with intrahepatic cholestasis of pregnancy (ICP) and to assess pregnancy management according to fasting bile acid levels.

Methods: This study is carried out with 160 patients who were diagnosed with Intrahepatic Cholestasis of Pregnancy and gave birth in the same clinic. The patients were divided into two groups based on their fasting bile acid concentrations: Group 1 (54 patients), with levels between 10 and 40 micromol/liter, defining mild ICP according to the literature, and Group 2 (106 patients), with levels above 40 micromol/liter, defining severe ICP. The birth weeks, delivery methods, indications for cesarean section if applicable, birth weights, 1st and 5th minute APGAR scores, neonatal intensive care unit admission, presence of meconium-stained amniotic fluid at birth, and fetal death data of both groups were recorded and compared.

Results: Patients with severe ICP were found to have statistically higher ALT and total bilirubin values than patients with mild ICP. (p<0.001, p<0.001 respectively). The presence of meconium was significantly higher in group 2 patients compared to patients group 1 patients (26.4% and 9.3%, respectively; p=0.011).

It was found that the weeks of diagnosis of cholestasis and weeks of labor were significantly greater in the patients with meconium in the amniotic fluid compared to the group without meconium (34,9±3,4; 33,0±3,5; p=0,002 ve 38,1±0,9; 36,9±1,5 respectively; p<0,001). Group 2 patients were found to have significantly higher incidence rates of ALT values above 75 and AST values above 130 compared to group 1 patients (p<0,001).

Conclusion: Intrahepatic cholestasis of pregnancy causes unpredictable fetal complications. The patients with values of bile acid above 40 and ALT values above 75 and/or having meconium stained amniotic fluid during labor should evaluated carefully due to the association with poor perinatal outcomes.

Keywords: Bile acids, itching, intrahepatic cholestasis of pregnancy, newborn, intensive care

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is typically characterized by pruritus, abnormal serum fasting bile acid concentrations (≥10µmol/L) and elevated liver function tests (LFTs), which usually develop in the late second and/or third trimester, with rapid resolution of symptoms and laboratory findings after delivery. Physical examination does not reveal any skin lesions, but scratch marks and itchy nodules secondary to scratching may be seen. Itching may be more common on the palms of the hands and soles of the feet; it is typically worse at night. Maternal outcomes of ICP are generally benign. However, it carries significant risks for the fetus as maternal bile acids cross the placenta. The main complications include amniotic fluid with meconium, spontaneous or iatrogenic preterm delivery, low APGAR scores, respiratory distress syndrome of the newborn and consequent neonatal intensive care unit hospitalization and fetal death.[1]

The aim of this study was to determine whether the perinatal outcomes (preterm delivery, birth weight, APGAR scores, presence of meconium amniotic fluid, neonatal intensive care unit hospitalization and fetal death) of patients with mild ICP (ASA: 10-40µmol/L) and severe ICP (ASA≥40µmol/L) are different, to evaluate postpartum infant well-being and to examine ICP in terms of epidemiological, etiological, clinical and obstetric management according to the results obtained.

Methods

This retrospective study consisted of 160 patients with fasting bile acids >10 micromol/liter and diagnosed as “Intra-

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hepatic Cholestasis of Pregnancy" with fasting bile acids >10 micromol/liter who presented to the perinatology outpatient clinic of the University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital Clinic with the complaint of itching in the second and third trimesters between January 1, 2017 and January 1, 2023 and delivered their babies in our clinic. Ethics committee approval was obtained from T.C. Health Sciences University Şişli Hamidiye Etfal Training and Research Hospital SUAM Clinical Research Ethics Committee with the approval letter dated 16.05.2023 and numbered 3937 and our study was conducted in accordance with the Helsinki Declaration rules.

Information about the patients was obtained from the hospital electronic data environment and patient files. Patients with fasting bile acid concentration below 10 micromol/liter, whose information could not be accessed clearly in the hospital electronic data environment, who were hospitalized at the time of diagnosis but whose delivery did not take place in our clinic, who had elevated LFTs due to preeclampsia and/or HELLP; Patients diagnosed with viral hepatitis, autoimmune hepatitis, acute fatty liver of pregnancy or acute liver pathology, multiple pregnancy, congenital disease in the baby, or any skin pathology that may cause pruritus were not included in the study. Data at the time of initial diagnosis were taken into consideration in patients diagnosed with ICP.

Data of 160 eligible patients were analyzed retrospectively. The gestational week of the patients was determined according to the last menstrual date or ultrasonographic measurements in the early weeks of pregnancy. Ursodeoxycholic acid (UDCA) was started at a dose of 10-15mg/kg/day when fasting bile acid concentrations were elevated and ICP was diagnosed. Patients were followed up according to fasting bile acid concentrations by repeating biophysical profile, non-stress test (NST), LFTs and bile acid concentrations when necessary. In addition to demographic data such as age, gravida, parity, and abortion, fasting bile acid concentration, AST/ALT, total bilirubin levels, and the week of ICP diagnosis were recorded. Patients were divided into two groups as 54 patients with fasting bile acid concentrations between 10-40 micromol/liter and 106 patients with fasting bile acid concentrations above 40 micromol/liter. The first group was defined as mild GIC and the second group as severe GIC in accordance with the literature. The birth weeks, mode of delivery, indication for cesarean section, birth weight, 1st and 5th minute APGAR scores, neonatal intensive care unit hospitalization, presence of meconium amniotic fluid at the time of delivery and fetal loss data were recorded.

The APGAR score includes neonatal respiration, heart rate, muscle tone, laryngeal reflex to nasogastric probe and skin color.

Birth before 37 weeks of gestation was defined as preterm delivery, birth weight below 2500 g was defined as low birth weight (LBW), birth weight below 1500 g was defined as very low birth weight (VLBW), and prolonged, variable and recurrent late deselerations, loss of variability or category 3 NST were defined as fetal distress.

SPSS (Statistical Package for the Social Sciences) 25.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as number and percentage, and continuous measurements were summarized as mean and standard deviation (median and minimum-maximum where necessary). Chi-square test was used for comparisons of categorical expressions. Shapiro-Wilk test was used to determine whether the parameters in the study showed normal distribution. Mann whitney u test was used for the parameters that did not show normal distribution. The cut off value was determined by examining the area under the ROC curve of AST and ALT values based on the fasting bile acid variable of the patients in the study. Statistical significance level was taken as 0.05 in all tests.

Results

The study included 160 patients diagnosed with "Intrahepatic Cholestasis of Pregnancy". Of these patients, 54 had a bile acid concentration of 10-40 micromol/liter (mild) and 106 had a bile acid concentration over 40 micromol/liter (severe). Demographic data, laboratory findings, perinatal outcomes and delivery information are summarized in Table 1. In comparison of these findings, parity, gestational age at diagnosis,AST, ALT, Total bilirubin at diagnosis and meconium staining status was satatistically different between the groups (Table 2).

The diagnostic test performances of ALT and AST laboratory values evaluated with mild ICP and severe ICP in the study are shown in Table 3. Accordingly, it was observed that the sensitivity of the ALT value was 65.33% and the sensitivity of the AST value was 47.41%; the best diagnostic test performance was found to be the ALT value with a sensitivity of 65.33% (Table 3). Among the patients included in the study, those with severe GIC were found to have a significantly higher frequency of ALT value above 75 and AST value above 130 compared to patients with low fasting bile acids ($p<0.001$ and $p=0.013$, respectively) (Table 3).

Table 1. Maternal demographic data, laboratory findings, perinatal outcomes, delivery information, neonatal intensive care hospitalization, presence of meconium and fetal loss findings

	Mean±SD	
Age	29.6±5.7	
Gravidity	2.28±1.4	
Parity	0.95±1.0	
Abortion	0.32±0.8	
Gestational age at diagnosis	33.4±3.6	
AST [U/L]	111.5±99.9	
ALT [U/L]	121.8±103.9	
Total bile acids at diagnosis [☪mol/L]	51.8±33.4	
Total bilirubin at diagnosis[☪mol/L]	1.5±4.8	
Gestational age at delivery	37±1.5	
Birth weight	2939±479.5	
1 min Apgar score	7.41±1.2	
5 min Apgar score	8.91±0.9	
	(n)	(%)
Mild cholestasis (Total bile acids < 40 ☪mol/L)	54	33.8
Severe cholestasis (Total bile acids > 40 ☪mol/L)	106	66.2
Mode of delivery		
Vaginal	91	56.9
Casarean section	69	43.1
Fetal distress	18	19.7
Neonatal unit admission		
Yes	68	42.5
No	92	57.5
Meconium staining		
Yes	33	20.6
No	127	79.4
Perinatal mortality		
Yes	-	-
No	160	100

Table 2. Comparison of demographic data, laboratory findings, birth findings and perinatal outcomes by groups

	Mild cholestasis (Total bile acids < 40 ☪mol/L) (n=54) Mean±SD	Severe cholestasis (Total bile acids > 40 ☪mol/L) (n=106) Mean±SD	p
Age	29.3±6.3	29.8±5.5	0.427
Gravidity	2.02±1.2	2.41±1.4	0.085
Parity	0.72±0.9	1.07±1.07	0.041*
Abortion	0.30±0.8	0.33±0.9	0.543
Gestational age at diagnosis	34.3±2.8	32.9±3.8	0.038*
AST[U/L]	90.8±68.4	122.1±111.5	0.041*
ALT[U/L]	84.1±69.0	140.9±113.3	<0.001*
Total bilirubin at diagnosis[☪mol/L]	1.2 ± 0.4	1.9 ± 1.0	<0.001*
Gestational age at delivery	37.5±1.4	37.0±1.5	0.063
Birth weight	2959.3±505.0	2928.8±468.1	0.681
1 min Apgar score	7.40±1.3	7.42±1.2	0.921
5 min Apgar score	8.98±0.9	8.89±0.9	0.498
	n (%)	**n (%)**	**p**
Mode of delivery			
Casarean section	32 (59.3)	59 (55.7)	0.664**
Vaginal	22 (40.7)	47 (44.3)	
Fetal distress	7 (13.0)	11 (10.4)	0.589
Neonatal unit admission			
Yes	20 (37.7)	48 (45.3)	0.318
No	34 (63.0)	58 (54.7)	
Meconium staining			
Yes	5 (9.3)	28 (26.4)	0.011**
No	49 (90.7)	78 (73.6)	
Perinatal mortality			
Yes	-	-	1.000
No	54 (100)	106 (100)	

Table 3. ALT and AST cut-off findings for mild and severe ICP

	ALT [U/L]	AST [U/L]	p
AUC 95%-CI (%)	0.687 (0.609-0.758)	0.597 (0.517-0.674)	
Cut-off	>75	>130	
Sensitive(%)95%-CI (%)	65.33 (54.3-73.2)	47.41 (36.5-56.2)	
p	<0.001**	0.042	
	Mild cholestasis (Total bile acids < 40 ☪mol/L) (n=54)	**Severe cholestasis (Total bile acids > 40 ☪mol/L) (n=106)**	
	n (%)	**n (%)**	
ALT [U/L]			
≤ 75	36 (66.7)	38 (35.8)	<0.001*
> 75	18 (33.3)	68 (64.2)	
AST [U/L]			
≤ 130	40 (74.1)	57 (53.8)	0.013*
>130	14 (25.9)	49 (46.2)	

Cholestasis diagnosis week and birth week findings according to the presence of meconium are summarized in Table 4. It was found that the group with meconium in the amniotic fluid was born at later weeks and ICP diagnosis was made later. There was no significant difference in preterm delivery for mild and severe ICP (Table 5). Preterm delivery rate was significantly higher in those with fasting bile acids above 100 micromol/liter (p<0.001) (Table 6).

Table 4. Cholestasis diagnosis week and birth week findings according to the presence of meconium

	Meconium stained amniotic fluid (n=33)	Clear amniotic fluid (n=127)	p
	Mean±SD	Mean±SD	
Gestational age at diagnosis	34.9±3.4	33.0±3.5	0.002*
Gestational age at delivery	38.1±0.9	36.9±1.5	<0.001*

Table 5. Comparison of preterm delivery for mild and severe ICP

	Preterm birth	Term birth	p
	n (%)	n (%)	
Mild cholestasis	15 (31.3)	39 (34.8)	
Severe cholestasis	33 (68.7)	73 (65.2)	0.662*

Table 6. Comparison of those with bile acid concentrations below and above 100 micromol/liter in terms of preterm delivery

	Total bile acids < 100 ✂<mol/L	Total bile acids >100 ✂<mol/L	p
	(n=148)	(n=12)	
	n (%)	n (%)	
Preterm birth	38 (25.7)	10 (83.3)	<0.001*
Term birth	110 (74.3)	2 (16.7)	

Discussion

Intrahepatic cholestasis of pregnancy causes unpredictable fetal complications. Although many studies have described the mechanism of ICP related symptoms, the pathophysiology of fetal complications and fetal death is still unclear. Therefore, there is a need for markers and methods that can predict these adverse neonatal outcomes and help to determine the timing of delivery. In this study the patients with values of bile acid above 40 and ALT values above 75 and/or having meconium stained amniotic fluid during labor should evaluated carefully due to the association with poor perinatal outcomes. Our findings may help to determine the timing of delivery, which may predict adverse neonatal outcomes.

In the present study, no fetal death was observed in 12 patients with bile acid concentrations above 100 micromol/liter. We think that the reason for this is that in our center, UDCD treatment was started at the time of diagnosis, antenatal follow-up was performed more frequently, and the timing of delivery was determined in a planned manner rather than spontaneous delivery. According to our study, the delivery rates of patients with bile acid concentrations above 100 micromol/liter before 37 weeks were significantly higher than those with concentrations below 100 micromol/liter, and the fact that the deliveries of patients diagnosed with ICP were at early weeks (median delivery week=37.1) and cesarean section rates (56.9%) support this situation. ICP is usually diagnosed in the second and third trimesters. According to the study by Çelik et al. the gestational week at presentation was 35 weeks (range 29-39) in the mild ICP group and 32 weeks (range 27-36) in the severe cholestasis group and the difference between the two groups was found to be significant.[2] Similarly in our study, the earliest diagnosis was made at 21 weeks and the mean diagnostic week was 33-34 weeks, while the diagnostic week was significantly earlier in patients with fasting bile acid concentration above 40 micromol/liter in parallel with the study by Kawakita et al..[3]

There are some studies in the literature investigating perinatal outcomes according to AST and ALT values. According to a study by Ekiz et al. ALT values above 95 IU/L were found to be associated with fetal complications.[4] Serum aminotransferase levels increased with increasing severity of ICP in our study in accordance with many studies in the literature. The frequency of ALT levels above 75 IU/liter and AST levels above 130 IU/liter in patients with severe ICP is higher than in patients with mild ICP. Accordingly, it is concluded that ALT is more sensitive than AST in determining the diagnosis and severity of ICP.

In our study, no significant finding was found between the two groups in terms of birth week, birth weight, mode of delivery and APGAR scores. According to the results of a study by Jhirwal et al. including 152 patients, no difference was found between patients diagnosed with mild and severe ICP in terms of mode of delivery and APGAR scores in parallel with our study, whereas the birth week was found to be earlier and the birth weight was found to be lower with a mean of 2000 grams especially in patients with severe ICP.[5] In our study, the mean birth weight was 2900 grams in both groups formed according to bile acid concentration and this was correlated with no increase in preterm delivery. The diagnosis or severity of ICP does not constitute an indication for cesarean section and according to the results of our study, there was no significant difference in cesarean section rates according to the severity of ICP. According to the study conducted by Çelik et al., different from our study, it was observed that the infant birth weights of patients with severe ICP were lower than the group with mild ICP due to the early delivery week, but no significant difference was found

in cesarean section rates according to the severity of ICP in parallel with the results of our study.[3]

Preterm labor results in lower birth weight babies and preterm labor may increase the risk of neonatal morbidity and require intensive care. In our study, no significant difference was found between mild and severe GIC patients in terms of preterm delivery and birth weight, and no significant difference was found between both patient groups in terms of intensive care unit admission. However, not only these two factors are important in the need for intensive care hospitalization, but also transient respiratory distress of the newborn due to the effect of high bile acids on the lung of the fetus due to the early diagnosis week may be the reason for intensive care hospitalization. According to the results of a large-scale meta-analysis conducted by Ovadia et al., intensive care hospitalization rates of infants of patients diagnosed with GIC increased significantly compared to healthy pregnant women.[6] In the study by Çelik et al. comparing the neonatal intensive care of two groups as mild and severe GIC, it was found that the intensive care hospitalization rate of the infants of patients diagnosed with severe GIC increased significantly between the two groups.[3] However, since intensive care hospitalization of infants was evaluated multifactorial, the rate of intensive care hospitalization according to bile acid concentrations alone may not have been significant in our study.

Kawakita et al. and Çelik et al. found an increased likelihood of amniotic fluid with meconium in severe GIC. Relaxation of the anal sphincter and peristalsis due to increased vagal stimulation associated with fetal stress may cause meconium passage. According to the results of our study, we think that increased bile acid concentration may cause fetal stress and lead to meconium stained amniotic fluid. According to the results of a large-scale meta-analysis by Ovadia et al., the timing of delivery is recommended between 37-39 weeks for patients with a bile acid value of 10-40micromol/liter, between 36-38 weeks for patients with a bile acid value of 40-100 micromol/liter, and at the latest 36 weeks for patients with a bile acid value above 100 micromol/liter.[6] In our study evaluating the perinatal outcomes of patients with mild and severe GIC, the only finding found to be perinally significant was the presence of meconium amniotic fluid. The median mean gestational age at delivery was found to be 38 weeks in patients with meconium-amniotic amniotic fluid and the median mean gestational age at delivery was found to be 37 weeks in patients without meconium-amniotic amniotic fluid. We think that these results may give an idea in terms of planning the timing of delivery. We think that the timing of delivery should not exceed 37 weeks, especially in patients with severe GIC, which is a finding consistent with the literature.

The biggest limitation of our study is that it was evaluated retrospectively. Patients whose all information could not be accessed from the hospital data system had to be excluded from the study and therefore the number of patients was limited. Since UDCA was started in all our patients at the time of diagnosis, our study cannot determine the perinatal outcomes of patients who did not receive UDCA treatment.

Conclusion

Intrahepatic cholestasis of pregnancy causes unpredictable fetal complications. The fact that fetal morbidity and mortality cannot be predicted by any marker makes the management of the disease very difficult. In the severe group with fasting bile acid concentrations above 40 micromol/liter and in patients with delayed delivery time, amniotic fluid with meconium was observed. The patients with values of bile acid above 40 and ALT values above 75 and/or having meconium stained amniotic fluid during labor should evaluated and followed up carefully due to the association with poor perinatal outcomes.

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