

TO STUDY THE OBSTETRIC OUTCOMES ASSOCIATED WITH HIGHER TOTAL SERUM BILE ACID LEVELS IN WOMEN DIAGNOSED WITH INTRAHEPATIC CHOLESTASIS OF PREGNANCY

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Abstract

Background: Intrahepatic cholestasis of pregnancy (IHCP) is a liver condition that is uniquely linked to pregnancy. It has been seen to impact both the mother and the fetus. An optimum fetomaternal outcome requires a thorough clinical and biochemical examination. The aim is to examine the obstetric outcomes associated with higher total serum bile acid levels in women diagnosed with intrahepatic cholestasis of pregnancy. **Materials and Methods:** Seventy individuals diagnosed with intrahepatic cholestasis of pregnancy were included in the study. The diagnosis was established by identifying the presence of pruritus, high levels of total serum bile acids, and elevated levels of serum transaminases. In addition to regular examinations, the patients had the following biochemical tests: AST, ALT, Alkaline phosphatase, Total serum bile acids, and Total serum bilirubin. **Result:** 42 patients, accounting for 60% of the total, had initial bile acid levels ranging from 10-40 $\mu\text{mol/L}$. Additionally, 25 patients, or 35.71% of the total, had values between 41-100 $\mu\text{mol/L}$. Only 3 patients, representing 4.29% of the total, had levels beyond 100 $\mu\text{mol/L}$. The majority of patients had elevated levels of alkaline phosphatase. The mean values for serum bilirubin, AST, ALT and ALP were 0.64 ± 0.12 , 109.43 ± 11.43 , 111.32 ± 12.65 , and 348.36 ± 13.63 , respectively. Meconium staining of the amniotic fluid was seen in 17 out of 70 newborns (24.29%). Birth asphyxia occurred in 5 neonates (7.14%). A total of 24 neonates (34.29%) needed admission to the Neonatal Intensive Care Unit (NICU). Additionally, 23 neonates (32.89%) were delivered preterm, before 37 weeks of gestation. **Conclusion:** We have shown that there is a substantial statistical association between the levels of bile acids in the blood and the occurrence of preterm, meconium staining of the amniotic fluid, and admission of newborns to the neonatal intensive care unit (NICU).

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP), commonly referred to as obstetric cholestasis (OC), is a distinct liver condition that occurs during pregnancy. It is characterized by itching in the palms and soles, without any visible skin rash, and elevated liver enzymes.^[1] The condition is often seen during the latter stages of the second and third trimester of pregnancy, however some studies have documented cases as early as 6 to 10 weeks after conception. The itching diminishes rapidly after childbirth, and the levels of serum bile acid and liver enzymes return to normal within 2–3 weeks after delivery. The prevalence ranges from 0.1 to 15.6% globally. The

prevalence of this condition is 0.1–1.5% in Central/Western Europe and North America, and 1.5–4% in Chile and Bolivia. In Finland, Sweden, Chile, and Portugal, the incidence of ICP is higher during the winter months. Twin pregnancies have a greater occurrence rate.^[2-7] Cholestasis is categorized as either intrahepatic or extrahepatic. Intrahepatic cholestasis mostly affects the small channels called bile canaliculi and the ducts inside the liver. Extrahepatic cholestasis refers to the obstruction or blockage of the ducts outside the liver, namely the extrahepatic ducts, the common hepatic duct, or the common bile duct. The development of ICP involves several elements, including genetic, hormonal, and environmental influences.^[8] Research has shown that mutations in the ABCB4 gene result in abnormalities

in the MDR3 protein in about 16% of individuals with ICP. These mutations result in impaired bile transport via the canaliculus. Hormonal variables are also a contributing component. Twin pregnancies, characterized by higher peak estrogen levels, have a higher occurrence of ICP compared to singleton pregnancies. Intrahepatic cholestasis of pregnancy (ICP) is often seen during the last trimester of pregnancy when the level of estrogen in the blood is at its peak. Cholestasis of pregnancy is very significant because of its strong association with a high occurrence of perinatal problems. These adverse effects include meconium-stained liquor, fetal distress, non-reassuring NST, reduced fetal movement, and premature birth. Administering ursodeoxycholic acid (UDCA) as a medication may lower levels of bile acid in pregnant women and lead to better outcomes for the fetus.^[9,10] Additionally, it alleviates itching and restores normal liver functioning in intrahepatic cholestasis of pregnancy (ICP). UDCA may reduce the transfer of bile acids via placenta.^[11-15]

MATERIALS AND METHODS

This was a retrospective and prospective study in which we studied the maternal and perinatal outcomes associated with increased levels of bile acids in pregnant women diagnosed with intrahepatic cholestasis of pregnancy. The study was conducted from February 2023 to February 2024 in the Department of Obstetrics & Gynaecology, ASCOMS hospital and CLDD hospital, Jammu, following approval from the institutional ethics committee. Seventy individuals diagnosed with intrahepatic cholestasis of pregnancy were included in the study. The diagnosis was established by identifying the presence of pruritus, high levels of total serum bile acids, and elevated levels of serum transaminases. The research excluded the following patients: Individuals afflicted with one or several medical conditions, such as those pertaining to the heart, cancer, blood disorders, and acute or chronic renal ailments. Patients with additional liver conditions such as viral hepatitis A, B, C, D, E and patients with cholelithiasis, bile duct lithiasis, cholangitis, various liver and biliary system abnormalities, alcohol addiction, HIV infection, and drug misuse. Individuals suffering from dermatological conditions characterized by pruritus and eruptions on the skin. Following the patient's agreement to participate, a comprehensive record of past events and experiences was collected. A comprehensive evaluation, including both general and obstetrical examinations, was performed on the patients. In addition to regular examinations, the patients had the following biochemical tests: Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase, Total serum bile acids, and Total serum bilirubin.

The UV technique with PSP (dry chemistry) was used to analyze aminotransferases, the PNPP method (dry chemistry) was used to analyze alkaline phosphatase, the enzyme assay calorimetry method was used to measure total blood bile acid levels, and the diphylline method (dry chemistry) was used to measure total serum bilirubin level.

Patients were administered ursodeoxycholic acid, antihistamines, and topical emollients based on studies and clinical evaluation. Patients were recommended to get repeat samples every 7-14 days, with the timing dependent on their symptoms and the severity of the condition. The decision for further treatment was made based on the deterioration of symptoms and the continuous monitoring of serum bile acid levels. Patients were regularly observed throughout their pregnancy via prenatal checkups, where the mother recorded the fetal movements on a daily basis. Additionally, serial sonography was performed to assess the well-being of the fetus. Starting from the 34th week of gestation, CTG was conducted twice a week. Corticosteroids were administered to enhance fetal lung maturation in cases of suspected preterm births occurring before to 34 weeks of gestation, whereas a vitamin K injection was given prior to delivery. To mitigate the higher likelihood of stillbirth in cases with IHCP, pregnancies were carefully monitored and managed by delivering the baby at an appropriate time. This was done by inducing labor around the 37th week of gestation or even earlier. The aim was to strike a balance between the potential harm caused by premature delivery due to medical intervention and the danger of fetal death. Nevertheless, these selections were personalized via meticulous patient counselling. Maternal and fetal outcomes were documented for each instance to assess the obstetric outcome. The received results were recorded and examined. Analyzed using binary logistic regression, this study examined the link between blood bile acid levels and transaminase levels, as well as the relationship between serum bile acid levels and fetal complications. The Chi-square approach was used to apply standard statistical methodologies. A p-value of less than 0.05 was determined to be statistically significant.

RESULTS

A total of 70 patients diagnosed with intrahepatic cholestasis of pregnancy were selected for inclusion in this research. Table 1 displays the demographic characteristics and clinical symptoms of the patients. All patients experienced pruritus, or itching, either across their whole body or just on their palms and soles. Most patients had sleeplessness due to the increased occurrence at night. [Table1]

Bile acid levels in the serum were measured in all of the patients. According to the data shown in [Table 2], 42 patients, accounting for 60% of the total, had initial bile acid levels ranging from 10-40 $\mu\text{mol/L}$.

Additionally, 25 patients, or 35.71% of the total, had values between 41-100 $\mu\text{mol/L}$. Only 3 patients, representing 4.29% of the total, had levels beyond 100 $\mu\text{mol/L}$. Patients with deteriorating symptoms, particularly those with serum bile acid levels over 40 $\mu\text{mol/L}$, were recommended to undergo serial estimate of their bile acid levels. Among the total of 70 individuals, only 25 underwent a further measurement of blood bile acid levels. 45 patients didn't have a repeat test owing to non compliance and improvement in symptoms. Subsequent measurements of S. bile acid levels revealed an increase in 16 patients, a decrease in 8 patients, and no change in 1 patient. After providing counseling, it was recommended to terminate the pregnancy in patients with rising levels. The method of termination was determined according to each patient's specific profile, either via the induction of labor or a cesarean section for other obstetric reasons. Patients exhibiting a decline or stable levels of serum bile acids were closely observed and had fortnightly treatment and check-ups, biochemical examinations, and CTG monitoring after being informed about the prognosis of their disease. Serial measurement of bile acid levels played a crucial role in determining the appropriate treatment for these individuals. Liver function tests were conducted for all the patients. The patients generally had serum bilirubin levels that were below the reference range, however there was a elevation of AST and ALT levels [Table 2]. The majority of patients had elevated levels of alkaline phosphatase. The mean values for serum bilirubin, AST, ALT and ALP were 0.64 ± 0.12 , 109.43 ± 11.43 , 111.32 ± 12.65 , and 348.36 ± 13.63 , respectively. [Table 3] displays the link between levels of S. bile acid and the occurrence of labor as well as the method of delivery. Among the total of 70 births, 39 were conducted by the vaginal route, 7 were planned caesarean sections, and 24 were unplanned

emergency caesarean sections. Among the 39 vaginal births, 3 of them were performed with instruments. [Table 4] includes references to indications for intervention. The majority of patients (82.05%) had induction of labor for IHCP, whereas 7.69% of patients had induction of labor due to premature rupture of membranes (PROM). Elective caesarean sections were performed on 7 patients, with the most prevalent reason being a prior cesarean delivery and a reluctance to attempt a vaginal birth in the current pregnancy (42.86%). Emergency caesarean sections were performed on 24 patients for diverse reasons, with the most frequent rationale being fetal distress in 45.83% of cases.

The average length of hospital stay for patients with S. bile acid levels ranging from 0 to 40 $\mu\text{mol/L}$ was 5.89 ± 1.32 days. For patients with levels ranging from 41 to 100 $\mu\text{mol/L}$, the average stay was 5.32 ± 1.53 days. Patients with levels over 100 $\mu\text{mol/L}$ had an average stay of 4.89 ± 1.02 days. The relationship between S. bile acid levels and the average duration of hospitalization for mothers was not statistically significant (p-value 0.21).

Meconium staining of the amniotic fluid was seen in 17 out of 70 newborns (24.29%). Birth asphyxia occurred in 5 neonates (7.14%). A total of 24 neonates (34.29%) needed admission to the Neonatal Intensive Care Unit (NICU). Additionally, 23 neonates (32.89%) were delivered preterm, before 37 weeks of gestation. The statistical analysis revealed a strong link between the levels of S. bile acid and the presence of meconium-stained liquor, admission to the neonatal intensive care unit (NICU), and preterm. The p-values associated with these correlations were <0.001 , 0.006, and 0.02, respectively. The correlation between S. bile acid levels and the mean Apgar score at 1 and 5 minutes, as well as birth asphyxia, was shown to be statistically negligible (p-values of 0.21, 0.34, and 0.16, respectively).

Table 1: demographic parameter of the participants

	Number	Percentage	P value
Age (yrs)			0.14
Below 25	18	25.71	
25-30	36	51.43	
30-35	12	17.14	
Above 35	4	5.71	
Socio-economic status (Modified Kuppuswamy scale)			0.43
I (Upper)	10	14.29	
II (Upper middle)	6	8.57	
III (Lower middle)	42	60	
IV (Upper lower)	11	15.71	
V (Lower)	1	1.43	
Area			0.36
Rural	24	34.29	
Urban	46	65.71	
Gravida			0.12
G1	36	51.43	
G2	18	25.71	
G3	12	17.14	
G4	2	2.86	
G5	2	2.86	

Table 2: Liver function tests

Initial S. bile acids (µmol/L)	Number	Percentage (%)
10-40	42	60
41-100	25	35.71
>100	3	4.29
Serial S. bile acids (µmol/L)		
10-40	8	32
41-100	16	64
>100	1	4
Total	25	100
Liver function tests		
	Reference value	Mean
S. bilirubin [mg/dl]	0.2-1.3	0.64 ± 0.12
AST (SGOT) [U/L]	17-59	109.43 ± 11.43
ALT (SGPT) [U/L]	21-72	111.32 ± 12.65
ALP [U/L]	38-126	348.36 ± 13.63

Table 3: S. bile acid in vaginal and caesarean patients

S. bile acid (µmol/L)	Total	Vaginal				Caesarean	
		Spontaneous		Induced		Elective	Emergency
		Normal	Instrumental	Normal	Instrumental		
0 - 40	42	10	1	11	1	3	17
41 - 100	25	4	0	10	1	3	7
>100	3	1	0	1	0	1	0
Total	70	14	1	22	2	7	24

Table 4: Induction of labour

Induction of labour	Number	Percentage
IHCP	32	82.05
PROM	3	7.69
Hypertensive disorders	1	2.56
Postdatism	1	2.56
GDM	1	2.56
IUD	1	2.56
Elective caesarean section	7	
Previous 1 CS with refusal of TOLAC	3	42.86
Caesarean delivery on maternal request	2	28.57
Transverse lie	1	14.29
Twin gestation with 1st twin breech	1	14.29
Emergency caesarean section	24	
Fetal distress	11	45.83
Previous 1 CS in labour with refusal of TOLAC	1	9.09
Previous 2 CS in labour	1	9.09
Placenta previa with APH	1	9.09
Primi breech in labour	2	18.18
Non progress of labour	1	9.09
Previous CS with twin in labour	1	9.09
Transverse lie in labour	1	9.09
Second stage arrest of labour	1	9.09
Previous CS with scar dehiscence	1	9.09
Twin gestation with 1st twin breech in labour	1	9.09
Previous CS with breech in labour	1	9.09
Twin gestation with cord prolapse	1	9.09

Table 5: Correlation of S. bile acid levels with fetal outcome

S. bile acid (µmol/L)	0 - 40	41 - 100	>100	Total=70	Percentage	P value
Meconium stained liquor	6	9	2	17	24.29	< 0.001
Birth asphyxia	2	2	1	5	7.14	0.14
NICU admission	11	12	1	24	34.29	0.006
Prematurity	11	11	1	23	32.89	0.02
IUD [0	-	1	1	1.43	-
Apgar Score						
At 1 min	7.14 ± 1.13	7.13 ± 1.17	7.23 ± 0.87	-		0.21
At 5 min	8.21 ± 1.14	8.24 ± 1.27	8.23 ± 0.87	-		0.21

DISCUSSION

The average age of the patients included in our research was 28.53 years. It was similar to previous research conducted by Joseph B et al.^[16] The majority

of the patients (60%) belonged to the lower middle-class category, as determined by the modified Kuppuswamy scale (2017), and lived in urban areas (65.71%). Previous writers have failed to include the socio-economic gradient and geographical location, thereby making a comparison of these demographic

data unfeasible. Our research found that 51.43% of the participants were primipara, while 48.57% were multiparous. According to research conducted by Joseph B et al,^[16] 68.3% of the participants were primipara (first-time mothers) and 31.7% were multiparous. In our research, pruritus was seen in all patients as their first complaint, whereas excoriation marks or rashes were observed in 45.33% of patients. In their research, Pegu B et al. discovered that the primary symptom of IHCP was pruritus, which affected 88% of the participants. This pruritus led to disrupted sleep in 35% of the participants and resulted in scratch marks in 73% of them.^[13] According to reports, itching may occur either before or after abnormal liver function tests, indicating the diverse character of this ailment. A study done by Alakananda et colleagues discovered that blood bile acids and liver enzymes were elevated in all patients.^[15]

Within our research, 42 individuals (60%) exhibited early bile acid levels ranging from 10-40 $\mu\text{mol/L}$, whereas 25 individuals (35.71%) displayed levels between 41-100 $\mu\text{mol/L}$. A mere 3 individuals (4.29%) showcased values beyond 100 $\mu\text{mol/L}$. Patients with deteriorating symptoms, particularly those with serum bile acid levels over 40 $\mu\text{mol/L}$, were recommended to undergo serial estimate of their bile acid levels.

Within the scope of our investigation Among the total of 70 births, 39 were conducted by the vaginal route, 7 were planned caesarean sections, and 24 were performed as emergency caesarean sections. Among the total of 39 vaginal births, 3 of them were performed with instruments. Pegu B et al discovered that the majority of patients had spontaneous labor, but a portion of them required induction. Several studies have shown favourable results when labor was induced at 37 or 38 weeks of gestation.^[17] Pregnancies impacted by IHCP have a greater rate of instrumental birth and caesarean delivery. This is because there is an increased incidence of meconium staining of liquor and induction of labor.

In research conducted by Sharma et al, it was found that 50% of the patients had a normal birth, 8.33% had an instrumental delivery, and 41.66% had a caesarean section.^[14] These results were similar to the findings of the study. In a study conducted by Pegu B et al, it was shown that 60.29% of patients had a normal birth, 8.82% had an instrumental delivery, and 30.8% had a caesarean section.^[13]

Our investigation revealed that Meconium staining of fluid was seen in 17 newborns, accounting for 24.29% of the cases. Birth asphyxia was identified in 5 neonates, representing 7.14% of the cases. Additionally, 24 neonates (34.29%) needed admission to the Neonatal Intensive Care Unit (NICU), while 23 neonates (32.89%) were delivered preterm, defined as being born before 37 weeks of gestation. The statistical analysis revealed a strong association between S. bile acid levels and meconium-stained liquor, NICU admission, and preterm, with p-values of <0.001, 0.006, and 0.02,

respectively. The correlation between S. bile acid levels and the mean Apgar score at 1 and 5 minutes, as well as birth asphyxia, was shown to be statistically negligible (p-values of 0.21, 0.34, and 0.16, respectively).

Alaknanda et al discovered that meconium-stained amniotic fluid was present in 29% of cases, NICU hospitalizations occurred in 21% of cases, and intrauterine mortality occurred in 2% of cases.^[15] In our research, the rate of preterm birth was 24.66%, whereas Alakananda et al,^[15] reported a rate of 23%. The logistic regression analyses of the data indicate that there is a positive correlation between increasing levels of bile acid and the occurrence of fetal problems such as meconium staining of liquor, and NICU hospitalizations for newborns. The fetal outcomes were examined in several investigations conducted by Kenyon AP et al,^[18] Glantz A et al,^[19] Singh G et al,^[20] Gupta A et al,^[21] Dang A et al,^[22] and Padmaja M et al.^[23]

According to Glantz A et al, there is a higher chance of negative effects on the baby if the level of bile acid in the mother's blood is over 40 $\mu\text{mol/l}$. However, if the maternal fasting serum bile acids are below 40 $\mu\text{mol/L}$, there is no increased danger to the fetus. Therefore, the authors indicate that mild IHCP does not pose a greater risk to the fetus. In our investigation, we observed a strong positive association between the amount of fasting bile acids in mothers and the presence of meconium staining in the amniotic fluid. This finding is consistent with the results published by Hani A et al (p value <0.001).^[24]

CONCLUSION

We have shown that there is a substantial statistical association between the levels of bile acids in the blood and the occurrence of preterm, meconium staining of the amniotic fluid, and admission of newborns to the neonatal intensive care unit (NICU). However, we did not discover any noteworthy association between serum bile acid levels and Apgar score, birth asphyxia, and average NICU stay. Estimating serial bile acid levels assisted in determining the appropriate course of action for these individuals.

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