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Original Research Article

A Prospective Study on Obstetric Outcome of Elevated Total Serum Bile Acid Levels in Women with Intrahepatic Cholestasis of Pregnancy

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Conflict of interest: Nil

Abstract:

Background: Intrahepatic cholestasis of pregnancy (IHCP) is a hepatic disorder associated specifically with pregnancy. It is found to affect both mother and fetus. It requires detailed clinical and biochemical evaluation for optimal feto-maternal outcome. Aim of this study to demographic profile, clinical features and obstetric outcome in patients with intrahepatic cholestasis of pregnancy and to assess correlation between serum bile acid levels and perinatal outcome.

Methods: This was a prospective study conducted on 150 pregnant women with IHCP who delivered at Department of Obstetrics and Gynaecology, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar from April 2023 to December 2023. The relationship between serum bile acid levels and fetal complications was analysed with binary logistic regression method.

Results: The incidence of IHCP at our centre was found to be 2.82%. We found that 59.94% patients had bile acid levels between 10-40 µmol/L, 36.6% patients bile acid levels between 41-100 µmol/L and 3.33% patients had bile acid levels >100 µmol/L. The correlation between serum bile acid levels with onset of labour and mode of delivery was not statistically significant (p-value 0.16 and 0.556 respectively). The correlation between serum bile acid levels with meconium stained liquor, NICU admission and prematurity was found to be statistically significant with p-value of <0.001, 0.007 and 0.018 respectively.

Conclusion: Symptomatic women should be subjected to estimation of serum bile acid levels so that appropriate treatment and timely intervention can be done to optimize obstetric outcome.

Keywords: Intrahepatic cholestasis of pregnancy, pruritis, serum bile acids, meconium stained liquor, ursodeoxycholic acid.

Introduction

Intrahepatic cholestasis (IHCP) of pregnancy is a hepatic disorder in the late second and early third trimester of pregnancy. It is characterized by maternal pruritis in absence of skin rash with increased serum bile acids and elevated serum aminotransferases. Overall incidence of IHCP is between 0.02% to 2.4% [1].

The etiopathophysiology of IHCP is still not clearly understood. The clinical symptoms and biochemical abnormality resolves after delivery. IHCP is associated with increased risk of adverse obstetrical outcomes, which includes stillbirth, meconium passage, respiratory distress syndrome and fetal asphyxia [1].

It is found that elevated serum bile acids levels in the fetal circulation plays significant role in fetal complications. Patients are classified as mild (S. Bile acids 10 – 40) or severe (S. Bile acids >40). Various studies have suggested that the risk of fetal complications is directly proportional to the increasing levels of serum bile acids [2,3].In view of limited studies on IHCP and its correlation with serum bile acids, the present study was conducted to study the clinical presentation and obstetric outcome in patients with IHCP. In our study, the correlation between serum bile acids and perinatal outcome was also assessed.

Material and Methods

This was a prospective study of maternal and perinatal consequences of elevated bile acid levels in pregnant women presenting with intrahepatic cholestasis of pregnancy, which was carried out from April 2023 to December 2023 in Department of Obstetrics & Gynaecology, Jawaharlal Nehru

Medical College and Hospital, Bhagalpur, Bihar. A total of 150 patients with intrahepatic cholestasis of pregnancy were included. Diagnosis was based on presence of pruritus, elevated total serum bile acid levels and serum transaminases. Patients with one or more medical diseases such as cardiologic, oncologic, hematologic, acute and chronic kidney diseases, patients having other liver disorders like viral hepatitis A, B, C, D, E, patients having cholelithiasis, bile duct lithiasis, cholangitis, other abnormalities of liver and biliary tract, alcohol addiction, HIV infection, substance abuse and patients with diseases of skin with itching and rashes were excluded in this study.

After informed consent, a thorough history was taken. Complete general and obstetrical examination was carried out on the patients. Besides routine investigations, the patients were also subjected to following biochemical tests) :

- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase
- Total serum bile acids
- Total serum bilirubin

Aminotransferases were analysed using UV with PSP (dry chemistry) method, alkaline phosphatase was analysed using PNPP, AMP (dry chemistry) method, total serum bile acid levels by enzyme assay calorimetry method, total serum bilirubin level by diphylline (dry chemistry) method.

Based on investigations and clinical assessment, patients were treated with ursodeoxycholic acid, antihistamines and topical emollients. Repeat samples were advised for patients after 7-14 days depending on symptoms and severity of disease. Decision regarding further management was based on worsening of symptoms and serial estimation of serum bile acid levels. Patients were monitored by regular antenatal visits with daily maternal recording of fetal movements, serial sonography for fetal well-being, twice weekly fetal cardiotocography (CTG) from 34 weeks of gestation. Steroid coverage was given for fetal lung maturity for suspected preterm deliveries before 34weeks of gestation and vitamin K injection was given before delivery. Given the increased risk of stillbirth in the setting of IHCP, pregnancies were actively managed by timely delivery, through induction of labor as recommended at around 37 weeks of gestation or earlier to balance the risk of iatrogenic preterm delivery against the risk of fetal mortality. However, these decisions were individualized with careful patient counselling.

Obstetric outcome was recorded in every case in terms of maternal and fetal outcome.

Results thus obtained were tabulated and analyzed. The relationship between serum bile acid levels and transaminases level, and that between serum bile acid levels and fetal complication was analysed with binary logistic regression method. Standard statistical methods were applied, according to Chi-square method, p-value< 0.05 was considered to be significant.

Results

150 patients with intrahepatic cholestasis of pregnancy were included in this study. The overall incidence of intrahepatic cholestasis of pregnancy recorded at our hospital was found to be 2.82%. Table 1 shows the demographic profile and clinical presentation of the cases. All the patients presented with complaints of pruritus/itching either on whole body or palms and soles. It was more at night time which resulted in insomnia in many patients. Excoriation or rashes were observed in 68 (45.33%) patients whereas clinical jaundice was seen only in 3 (2%) patients.

Table 1: Demographic profile and clinical features of cases

Categories	Number	Percentage (%)
Age(yrs)		
≤ 25	40	26.66%
26-30	77	51.33%
31-35	28	18.66%
>35	5	3.33%
Socio-economic status (Modified Kuppuswamy scale)		
I (Upper)	20	13.33%
II (Upper middle)	14	9.33%
III (Lower middle)	89	59.33%
IV (Upper lower)	22	14.67%
V (Lower)	5	3.33%
Locality		
Rural	53	35.33%
Urban	97	64.67%
Gravida		
G1	76	50.66%

G2	36	24%
G3	28	18.66%
G4	5	3.33%
G5	5	3.33%
Clinical features		
Pruritus	150	100%
Excoriation/Rash	68	45.33%
Jaundice	3	2%

Table 2: Showing initial and serial serum bile acid levels and LFTs

Initial S. bileacids (µmol/L)	**Number**	**Percentage (%)**
10-40	90	59.94%
41-100	55	36.66%
>100	5	3.33%
Total	150	100%
Serial S. bileacids (µmol/L)		
10-40	16	30.77%
41-100	34	65.38%
>100	2	3.85%
Total	52	100%
Liver function tests	**Reference value**	**Mean**
S. bilirubin [mg/dl]	0.2-1.3	0.625± 0.325
AST(SGOT) [U/L]	17-59	108.46 ± 41.08
ALT (SGPT)[U/L]	21-72	110.20±38.40
ALP[U/L]	38-126	350.2±175.34

Serum bile acid levels were estimated in all the patients. As seen in table 2, ninety (59.94%) patients had initial bile acid levels between 10-40 µmol/L, 55 (36.6%) patients between 41-100 µmol/L and only 5 (3.33%) patients had levels >100 µmol/L.

Serial estimation of serum bile acid levels were advised for patients with worsening symptoms, especially with bile acid levels > 40 µmol/L. Out of 150 patients, only 52 patients had repeat estimation of serum bile acid levels. Ninety-eight patients did not have repeat test either because of high cost of test or due to non-compliance or their symptoms improved. Repeat S. bile acid levels were found to be increasing in 33 patients, decreasing in 14 and remained same in 5 patients. In patients with increasing levels, termination of pregnancy was advised after counselling. Mode of termination was decided based on individual patient's profile, either by induction of labour or caesarean section for other obstetric indications. Patients with decreasing or same S. bile acid levels were monitored and followed up with regular antenatal visits, biochemical studies and CTG monitoring after explaining prognosis of the condition. So, serial bile acid level estimation helped in deciding management of these patients. Liver function tests were monitored for all the patients. Serum bilirubin was usually within reference value for the patients, with mild increase in AST and ALT (table 2). Alkaline phosphatase was increased in majority of the patients. Mean S. bilirubin, AST, ALT, ALP values were 0.625 ± 0.325, 108.46 ± 41.08, 110.20 ± 38.40 and 350.2 ± 175.34 respectively. In 87 (58%) patients, LFTs were within normal limits, whereas they were deranged in 63 (42%) patients.

After starting pharmacotherapy, LFTs were repeated in 63 patients in whom the values were abnormal initially. In 54 (85.71%) patients values improved and deteriorated in 11 (14.29%) patients. Symptoms improved in 133 (88.67%) patients after starting pharmacotherapy. Eleven (7.33%) patients showed no signs of improvement and worsening of symptoms was seen only in 6 (4%) patients.

Table 3: Correlation of S. bile acid levels with onset of labour and mode of delivery

S. bile acid (□mol/L)	**Total**	**Onset of labour and mode of delivery**					
		Vaginal				**Caesarean**	
		Spontaneous		**Induced**		**Elective N(%)**	**Emergency N(%)**
		Normal N(%)	**Instrumental N(%)**	**Normal N(%)**	**Instrumental N(%)**		
0-40	90	21(23.23%)	2(2.22%)	27(30%)	3(3.33%)	6(6.7%)	31(34.44%)
41-100	55	10(18.2%)	0	18(32.72%)	1(1.82%)	9(16.36%)	17(30.90%)

>100	5	2(40%)	0	1(20%)	0	1(20%)	1(20%)
Total	150	33(22%)	2(1.33%)	46(30.67%)	4(2.67%)	16(10.67%)	49(32.67%)

Table 3 shows correlation between S. bile acid levels with onset of labour and mode of delivery. Out of 150 deliveries, 85 were vaginal deliveries, 16 were elective caesarean sections and 49 were emergency caesarean sections. Out of 85 vaginal deliveries, 6 were instrumental vaginal deliveries.

In majority patients, induction of labour was done for IHCP (82.19%), followed by PROM in 9.59% patients. Elective caesarean section was done in 16 patients, most common indication being previous 1 caesarean delivery with refusal for trial of labour in present pregnancy (43.75%). Emergency caesarean section was done in 49 patients for various indications, most common indication being fetal distress in 25 (51.02%) patients. Mean hospital stay of patients (in days) with S. bile acid levels 0-40, 41-100, >100 µmol/L was 5.74 ± 5.43, 5.49 ± 3.24, 5.00± 2.55 respectively. The correlation between S. bile acid levels with mean hospital stay of mother was statistically insignificant (p-value 0.908). There were 141 uneventful deliveries without any complication. One patient needed ICU care post-operatively and 8 patients had PPH which was medically managed. No surgical intervention was required in these 8 patients. The correlation between S. bile acid levels with maternal complications during delivery was statistically insignificant (p-value 0.422).

There were 158 neonates born to 150 mothers as there were 8 twin pregnancies. There were 2 intra-uterine fetal deaths. Out of 156 live births, 102 (65.38%) neonates were normal and did not have any complications, while 54 (34.62%) neonates had one or more problems as seen in table 4.

Table 4: Correlation of S. bile acid levels with fetal outcome

S. bile acid(µmol/L)	0-40	41- 100	>100	Total	P value
Meconium stained liquor [Number (%)]	13(35.14%)	20 (54.05%)	4(10.81%)	37(24.67%)	<0.001
Apgar Score					
At1 min	7.12 ±1.03	7.11 ±1.15	7.20±0.84	-	0.983
At5 min	8.18 ±1.06	8.20 ±1.25	8.20±0.84		0.993
Birthasphyxia [Number(%)]	7(53.84%)	5(38.46%)	1(7.7%)	13(8.3%)	0.830
NICUadmission[Number(%)]	24 (44.44%)	26(48.15%)	4(7.41%)	54 (34.6%)	0.007
Prematurity[Number(%)]	23(45.1%)	24 (47.06%)	4(7.84%)	51 (34%)	0.018
IUD [Number(%)]	1(50%)	-	1(50%)	2(1.27%)	-

Meconium staining of liquor was seen in 37 (24.67%), birth asphyxia in 13 (8.3%) neonates, 54 (34.6%) required NICU admission and 51 (34%) were born prematurely (<37 weeks). The correlation between S. bile acid levels with meconium stained liquor, NICU admission and prematurity was found to be statistically significant with p-value of <0.001, 0.007 and 0.018 respectively. Correlation of S. bile acid levels with mean Apgar score at 1 and 5 minutes and birth asphyxia was found to be insignificant (p-value 0.983, 0.993 and 0.830 respectively). Regarding birth weight of neonates, 110 had birth weight >2500 gm, out of these 17 were preterm and 93 were term babies. Forty eight were low birth weight babies (<2500 gm), out of these 32 were preterm and 16 were term babies. Low birth weight for these 16 term babies was attributed to gestational hypertension in 3, uteroplacental insufficiency in 5, placenta previa in 2, multiple gestation in 1, polyhydramnios in 1 and idiopathic in 4 babies. No baby weighed <1000 gm.

Discussion

In our study, the incidence was of 2.82%. The incidence was found to be 2.73% by Pegu B et al [4], 2.4% by Sharma et al [5] and 2.59% by Alakananda et al [6]. The mean age of patients in our study was 27.85 years. It was comparable to a recent study by Joseph B et al [7]. Majority of the patients belonged to lower middle class group (59.3%) according to modified Kuppuswamy scale (2017) and resided in urban locality (64.67%). Other authors have not taken into account the socio-economic scale and locality, so we could not compare these demographic data. In our study, 50.66% (n = 76) were primipara and 49.34% (n = 74) were multiparous.

In a study by Joseph B et al [7], 68.3% were primipara and 31.7% were multiparous. In our study, pruritus was seen in 100% patients which was their presenting complaint, excoriation marks or rashes were seen in 45.33% patients. Pegu B et al [4] in their study found that main symptom of IHCP were pruritus (88%) which cause disturbed sleep (35%) and scratch marks (73%). It has been reported that itching may be presented either before or after abnormal liver function test and this may reflect the heterogeneous nature of this condition.

Study conducted by Alakananda et al found serum bile acids and liver enzymes were raised in 100% cases 6. In our study, 59.94% (n=90) patients had bile acid levels between 10-40 µmol/L, 36.6%

(n=55) patients had levels between 41-100 µmol/L and only 3.33% (n=5) patients had levels >100 µmol/L. In our study 40.66% (n=61) had spontaneous labour, in 47.33% (n=71) patients induction of labour was done and for 16 (10.67%) patients elective caesarean section was done before onset of labour for various indications. Pegu B et al found that most of the patients went into labour spontaneously and some of them needed induction [4]. Some studies have reported good outcomes with a policy of induction of labour at 37 or 38 wks gestation. Many clinicians in the UK have adopted this practice as the IUDs appear to cluster at later gestations [2].

Rate of instrumental delivery and caesarean delivery is higher in pregnancies affected by IHCP due to increased incidence of meconium staining of liquor and induction of labour. In our study, 85 patients (56.7%) had vaginal delivery and 65 patients (43.3%) underwent caesarean section. Out of 85 deliveries, 6 (4%) were instrumental deliveries. Maximum number of caesarean sections were done for 49.1% (n=27) patients with serum bile acid levels 41-100 µmol/L. Comparable results were seen in a study by Sharma et al 5, where normal delivery occurred in 50% patients, instrumental delivery in 8.33% patients and caesarean section in 41.66% patients. Pegu B et al [4] found that normal delivery occurred in 60.29% patients, instrumental delivery in 8.82% and caesarean section in 30.8% patients.

In our study the incidence of PPH was found to be high in women with IHCP i.e. 5.3% (n = 8) which was comparable to Alakananda et al study with 6% cases of PPH 6. Other studies did not mention about maternal ICU stay. In our study, only 1 (0.67%) patient had to stay in ICU for observation.

Even though IHCP is benign to the mother, it is associated with increased fetal complications. In our study we found association with perinatal complications, including meconium-stained amniotic fluid in 24.6%, NICU admissions in 32.7% and there were 2 (1.3%) unbooked cases who presented with intrauterine fetal death. In comparison, Alaknanda et al found meconium-stained amniotic fluid in 29%, NICU admissions in 21% and intrauterine death in 2% cases [6]. The incidence of preterm delivery in our study was 24.66% compared to 23% in study by Alakananda et al [6]. Logistic regression analyses of the data for fetal complications suggested that meconium staining of liquor, green placenta, NICU admissions for neonates increased as levels of bile acid increased. Fetal outcome in different studies by Kenyon AP et al [8], Glantz A et al [9], Singh G et al [10], Gupta A et al [11], Dang A et al [12], Padmaja M et al [13] and Alaknanda et al [6] is seen in table 6.

Glantz A et al reported increased adverse fetal outcome if serum bile acid was >40 µmol/l and no increase in adverse outcomes if the maternal fasting serum bile acids were below 40 µmol/L, leading the authors to suggest there is no increased risk to the fetus with mild IHCP [9]. In our study also, we found that patients having serum bile acid level >40 µmol/l seem to have more fetal complications (p value 0.0007). Hani A et al [14] reported that significant positive correlation was seen between maternal fasting bile acids level and meconium staining of amniotic fluid (P value <0.001) which was found in our study also (p value <0.001).

However, in spite of high incidence of meconium staining, Apgar score is usually normal. It shows that meconium staining of amniotic fluid seen in IHCP is not due to fetal distress; instead it is because of bile acids as bile acids are suggested to increase colonic motility and meconium. Mean birth weight was 2.6±0.4 kg which is appropriate for gestational age. It indicates that birth weight is not affected by IHCP. Similar to our study, other studies also did not find any significant maternal adverse outcome whereas association with poor perinatal outcome was significant correlating with increasing serum bile acid levels.

Conclusion

The incidence of cholestasis of pregnancy is high in the Indian population. Serum bile acid levels are increased in cholestasis of pregnancy. Poor perinatal outcome is associated with derangements in serum bile acid levels and liver function tests. Proper monitoring during antenatal period and termination of pregnancy at term improves the perinatal outcome.

In our study, significant statistical correlation has been found between serum bile acid levels and prematurity, meconium staining of liquor and NICU admission of neonates. Though, we did not found any significant correlation between serum bile acid levels and Apgar score, birth asphyxia and average NICU stay. Serial bile acid levels estimation helped in deciding management ofthese patients. We recommend that symptomatic patients should be subjected to estimation of serum bile acid levels and liver transaminases, so that appropriate treatment can be provided and timely intervention can be done to optimize obstetric outcome.

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