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Maternal and fetal outcome in intrahepatic cholestasis of pregnancy at tertiary care institute: A prospective study

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Abstract
Introduction: Intrahepatic cholestasis of pregnancy (IHCP) is characterized by pruritus of the hand and sole with abnormal liver function test and bile acid metabolism. IHCP occurs in the second and third trimesters of pregnancy and usually resolves after delivery. The overall prevalence is about 1.2 to 1.5%. This study was conducted to assess the fetomaternal outcome according to maternal serum bile acids levels and its correlation with liver function tests in patients with IHCP.
Methods: This hospital based analytical observational case control study enrolled 44 subjects with IHCP and 44 normal healthy pregnant controls. The subjects were assessed for demographic parameters, obstetric history, liver function tests including Bile acids. Outcome was measured as various parameters related to delivery and maternal and fetal complications.
Results: Study groups were matched for age (0.52). Frequency of primipara was higher in IHCP (p=0.01). Serum bilirubin (p=0.002), liver enzymes (p<0.0001 for all) and Bile acids (p=0.001) were significantly elevated in IHCP subjects compared to controls. Further, frequency of preterm birth was higher in IHCP (p=0.013). Fetal complications (p=0.01) and birth weight (p=0.03) were higher in IHCP subjects.
Conclusions: IHCP is associated with higher risk of complications in infants and to lesser extent in mothers.

Keywords: Fetal complications, fetal outcome, intrahepatic cholestasis of pregnancy (IHCP), maternal outcome, obstetric, pregnancy

Introduction
Intrahepatic cholestasis of pregnancy (IHCP) is a pregnancy-specific liver disease characterized by pruritus without any skin rash, abnormal liver function, and altered bile acid metabolism. The incidence is about 1.2 to 1.5% of cases of pregnancy [1]. IHCP cases are almost double in Asian women compared to European women. The highest incidence of IHCP (4%) was found in indigenous women from Chile and Bolivia [2]. Increased frequency of pruritus at night, involving the palms and soles without any skin lesion is particularly suggestive of IHCP. The serum bile acid level is sensitive and specific markers for IHCP. Serum aminotransferases more than two times of normal level and elevated alkaline phosphatase (ALP) levels are seen in IHCP but it is not specific for cholestasis. Total bilirubin concentrations rarely exceed 5 mg/dl [3].
Maternal bile acids get accumulated in the fetus and amniotic fluid by crossing the placental barrier, which carries significant risk for the fetus. The maternal complication associated with IHCP has increased risks of preterm prelabour rupture of membrane (PT PROM), severe pruritus with dyslipidemia and deranged coagulation profile, post-partum hemorrhage and operative delivery [4].
In the Indian population, there is a lack of data indicating the association of various risk factors for IHCP with feto-maternal outcomes and the correlation of maternal serum bile acid with variables of liver function test. Hence, this study was done to assess feto-maternal outcomes in association with the severity of IHCP so that we can improve obstetrical outcomes without jeopardizing the perinatal outcomes, in addition, to find out the correlation of liver function test (LFT) with serum bile acids (BA) in patients with IHCP. This study was done planned to know prevalence, fetal and maternal outcome in IHCP in our North Indian Population.

Material and Methods

This case–control study was conducted over a period of 1 year in the department of obstetrics and gynecology at Fortis Escorts Hospital Faridabad with the collaboration of the department of biochemistry after approval from research and ethical committee of the institute. Patients with diagnosis of IHCP were recruited in the case group (n = 44) whereas apparently healthy pregnant women with singleton pregnancy were included in the control group (n = 44). Informed consent was obtained from all participants.

All patients underwent testing for complete hemogram, liver function test (total and conjugated serum bilirubin), aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), serum bile acids, urine routine, and microscopy test. Viral markers and ultrasonography of hepatobiliary system and pancreas were also done in all patients to exclude any other pathology. Dermatology consultation was also taken wherever required. Diagnosis of IHCP was made in pregnant women with complaints of itching and deranged liver enzymes (serum transaminases), alanine transaminase (ALT/SGPT > 40 IU/L)/aspartate transaminase (AST/SGOT > 35 IU/L), or serum bile acids >14 µmol/L.

All confirmed cases of IHCP were advised to take ursodeoxycholic acid (UDCA) 10–15 mg/kg/day, with a maximum dose of 300 mg 8 hourly by oral route. Fetal surveillance was done in confirmed cases with weekly biophysical profile till delivery. All women in the case group received three doses of 10 mg Vitamin K by intramuscular route. An elective termination of pregnancy was done at 37–38 weeks of gestation in all except those induced or had spontaneous labor before this gestation. Incidence of meconium-stained liquor, preterm delivery, mode of delivery, and any complication during labor and delivery were also noted. Fetal outcome such as Apgar score, need of intensive care, and neonatal jaundice in both the groups was also observed. All women were followed up till 6–8 weeks postpartum with liver function test. Total numbers of deliveries in that time period were also noted to find out the prevalence of disease.

Exclusion Criteria

Other causes of pruritis, history, clinical features or lab investigations suggestive of viral hepatitis, any other associated complication of pregnancy.

Statistical Analysis

Sample size was calculated using PS (power and sample size calculator vs 3.1.2 using 5% alpha error and 80% power of study. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD or median and range depending on distribution of data. Qualitative variables were compared using Chi-Square test/ Fisher's exact test. Quantitative variables were compared using student's t test. p value of <0.05 was considered statistically significant and analysis was done using statistical package for Social Sciences (SPSS) version 21.0.

Results

Age distribution of study subjects was compared using Chi square test. Two study groups were found to be age matched on this analysis (p=0.52). Further mean age was also compared using student's unpaired t- test. No significant difference was observed in two groups (p=0.4) indicating that two groups were age matched (Table 1)

Table 1: Distribution of patients according to age

Groups	IHCP		Control		P- value
Age in years	No	%	No	%	
21-25	5	11.3	8	18.8	0.52
26-30	22	50	16	36.36	
31-35	12	27.2	16	36.36	
36-40	5	11.7	4	9.09	
Total	44	100	44	100	
Mean±S.D	29.88±4.35		29.70±4.35		0.4

Most of the patients had onset of symptoms after 28 weeks. Maximum (59.09%) patients had onset of pruritus at 32-36 weeks (Figure 1).

Various liver function test parameters were compared between two study groups. Significantly higher levels of Bilirubin (p=0.0003 using Fischer exact test for assessing frequency distribution and p=0.002 using Student's Unpaired t Test for comparing mean). Serum AST, ALP, ALT (p<0.0001 using Fischer exact test for assessing frequency distribution and p<0.0001 using Student's Unpaired t Test for comparing mean) were found in ICP group compared to controls. 40.90% and 43.18% patients had AST in the range of 100-200 and ALT in the range of 0-100 respectively. Comparison of bile acid levels was performed in two study groups significantly higher levels were noted in IHCP compared to controls (Table 2).

Table 2: Laboratory parameters in study subjects.

Parameters		IHCP		Control		p value
		No.	%	No.	%	
Bilirubin (mg/dl)	0.2-0.6	29	65.90	42	100	0.0003
	0.6-1.0	14	31.81	1	0	
	1-1.4	1	2.27	1	0	
	Mean ± SD	0.8±0.07		0.4±0.03		0.002
S.AST (IU/L)	0-100	13	29.54	40	90.9	<0.0001
	100-200	18	40.90	2	4.5	
	200-300	9	20.40	0	0	
	≥300	4	9.09	2	4.5	
	Mean ± SD	245.3±137.2		39.2±16.1		<0.0001
S.ALT (IU/L)	0-100	19	43.18	43	97.72	<0.0001
	100-200	15	34.09	0	0	
	200-300	8	18.18	0	0	
	≥300	2	4.54	1	2.28	
	Mean ± SD	190.3±107.2		39.3±9.3		<0.0001
S.ALP (IU/L)	0-200	7	15.90	42	94.6	<0.0001
	200-400	16	36.36	2	5.4	
	400-600	17	38.63	0	0	
	≥600	5	11.36	0	0	
	Mean ± SD	378.5±116.3		127.2±12.3		<0.0001
S. bile acid (µMol/L)	≤10	0		35		
	≥10	44		09		
	Mean ± SD	32±7.3		15±3.2		0.001

Present study showed that frequency of primipara females was significantly higher in the IHCP group compared to the control group. Subjects were found to be having preterm delivery in IHCP group compared to control group, but the difference failed to reach statistical significance (p =0.14). Gestational age at delivery was found to be 36.63±2.57 weeks in IHCP subjects (Table 3)

Table 3: Obstetric parameters in study subjects.

Parameters		IHCP		Control		P value
		No.	%	No.	%	
Parity	P1	35	79.54	22	50	0.01
	P2	06	13.63	16	36.36	
	P3	03	06.8	06	13.63	
GA at delivery (in weeks)	<37	11	25	06	13.6	0.013
	37-40	33	75	38	86.36	
Mode of delivery	Vaginal	19	43.48	24	54.54	0.14
	LSCS	25	56.81	20	45.46	
Intra-partum complications	Meconium	04	09.09	01	02.27	0.6
	Preterm delivery	11	25	05	11.36	
	Abruption	0	0.00	01	02.27	
	Fetal distress	11	25	06	13.63	
	Adherent placenta	0	0.00	01	02.27	

Table 4: Neonatal outcome parameters in study subjects.

Parameters		IHCP		Control		P value
		No.	%	No.	%	
Uneventful		15	34.09	31	70.4	0.01
IUD		0	0.0	0	0	0.5
Still birth		0	0.0	0	0	0.5
Preterm		11	25	05	11.36	0.4
Fetal distress		11	25	06	13.63	0.4
NICU stay		03	6.81	01	02.7	0.3
Meconium		04	9.09	01	02.7	0.2
Birth weight(kg)	1.5-2.5	10	22.72	03	06.8	
	2.6-3.5	31	70.45	35	79.54	0.07
	≥3.6	03	06.81	06	13.6	
Birth weight (in kg) (mean ± SD)		3.3±0.48		3.11±0.33		0.03

Frequency of meconium stained liquor, preterm delivery and fetal distress was found to be higher in subjects with IHCP. Overall intra-partum complication rate was found to be significantly higher in subjects with IHCP. Perinatal outcome in infants was also found to be comparable in both groups. Frequency of low birth weight deliveries was higher in IHCP group; though mean birth weight was found to be higher in (Table 4).

Discussion

In present study authors assessed maternal and fetal outcome in intra-hepatic cholestasis of pregnancy and tried to assess the various risk factors associated with IHCP, maternal and fetal outcome and its association with various risk factors of IHCP. Authors recruited 44 subjects with IHCP and 44 normal control subjects. Age distribution in two groups was comparable in present study. Mean age of IHCP subjects in present study was found to be 29.88 years. Brouwers *et al*. also performed similar study on subjects with intrahepatic cholestasis. In a prospective population-based study by Geenes *et al.* to assess outcome in severe IHCP, mean age was 29.6 (±6.3) years. Both the studies were in accordance to present study with mean age also similar to population of present study [5]. In a study by Shoballi *et al*. with similar objectives also the age of IHCP subjects was found to be 29.18±3.54 and those of the controls was 29.86±4.37 years [6]. Maximum subjects in present study showed onset of symptoms (pruritis) at 32-36 week of pregnancy. IHCP is characterized by pruritus starting in the second or third trimester of pregnancy and disappearing after delivery [7-9]. In a study by Brouwers *et al*., the diagnosis was established at 33rd to 36th week suggesting similar timing for onset of pruritis as the present study. Further the disease presenting late in course of pregnancy was found to be milder in severity [10]. In present study various parameters of liver damage including total bilirubin, direct bilirubin, aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase were found to be significantly elevated. Further frequency of subjects with higher level of these markers was also found to be significantly higher in IHCP group compared to controls. In a study by Brouwers *et al*., bilirubin and all liver enzymes including AST, ALT, ALP, GGT, and LDH were found to be elevated. Surprisingly these parameters were highest in subjects with moderate severity of IHCP. Further while all other parameters were significantly different, GGT failed to reach the significance [10]. Geenes *et al*. reported that peak level of all these parameters was found to be reached in 36th week [5]. Shobailli *et al*. also found that the mean levels of enzymes were significantly higher in IHCP group compared to controls.6 Present study showed that frequency of primipara females was significantly higher in the IHCP group compared to the control group, contrary to normal belief that IHCP is more common in multiparous women with advanced maternal age [11]. Present study was also contrary to various other studies done by Geenes *et al*. where no significant difference was found to exist between parity of IHCP subjects and control subjects [5]. Also, in a study by Shobailli *et al*., difference in mean parity failed to reach statistically significant difference [6]. But in a similar study in an Indian setting by Arbinder *et al*. from same found that frequency of primipara was significantly higher in IHCP group compared to controls indicating possibly different presentation of IHCP in north India. The difference can be attributed to socio-demograhic factors including preferences of the pregnant females for different hospital set up [12]. Gestational age at delivery was found to be 36.63±2.57 weeks in IHCP subjects and was significantly less compared to controls 37.24±1.9 in a study by Shobailli *et al*. [6] In a study by Shemer *et al*. though maximum pregnancies were terminated only after achieving full term, significantly higher frequency of moderate preterm births were noted compared to non IHCP group [13]. Preterm delivery frequency was also significantly higher in a study by Arbinder *et al*. [12] Shobaili *et al*. noted significantly higher rate of meconium stained liquor in IHCP subjects similar to present study while no significant difference was noted in rate of IUD [6]. Geenes *et al*. noted significantly higher rate of stillbirth in IHCP group, their findings regarding 5 min APGAR score were also similar to present study, while neonatal unit admission were found to be higher than controls [5]. Shemer *et al*. found no significant difference in two groups regarding frequency of neonatal death or meconium aspiration, rather contrary to most studies they noted increased rate of large for gestational age babies [13]. Arbinder *et al*. noted significantly higher rate of meconium stained liquor while no significant increase in IUGR or fetal distress was noted [12]. Comparison of bile acid levels was performed in two study groups significantly higher levels were noted in IHCP subjects. Bile acid has been noted as one of the most sensitive markers for IHCP by many authors and has also been performed and observed to be raised in ICP subjects compared to control subjects [6, 12, 14, 15]. Further levels of bile acids are said to be indicative of severity of ICP with increasing levels suggesting higher associated risk [6, 8]. In contrast to the favourable prognosis

for mothers, IHCP poses significant risk for the fetus. The major complications are premature deliveries in 19 to 60%, stillbirths in 0, 4 to 4, 1% and fetal distress in 22 to 33% of cases [9, 15, 16]. The mechanism for poor perinatal outcome remains unclear. Because high bile salt levels were found to be associated with more frequent occurrence of fetal distress, this might be of great relevance for fetal prognosis. Autopsies show signs of acute, lethal anoxia with petechial bleeding in pleura, pericardium and adrenal glands, but no signs of chronic anoxia [17, 18]. Fetuses of women with ICP have adequate birth weights for gestational age and normal Doppler umbilical artery velocimetry, suggesting that chronic placental insufficiency is not the primary cause of fetal death. Bile acids have been shown to induce vasoconstriction of human placental chorionic veins, and myometrial sensitivity to oxytocin [19, 20]. None of present study subjects showed post-partum hemorrhage or placental abruption.

Conclusion

Itching over whole body was the predominant presenting complaints of cholestasis of pregnancy. Diagnosis of IHCP should be supported by bile acids in women with normal liver enzymes to decrease the cost of investigations obviously after excluding other etiologies of itching. There was no correlation found between cholestasis of pregnancy with preterm labor and meconium-stained liquor in the present study. Early termination of pregnancy between 36 and 37 weeks can be considered in women with bile acids >40 μmol/L and in noncompliant patient. Early Key Message:

1. Pruritus all over the body rather than over extremities may be the first complaints of IHCP.
2. Raised bile acids are the definitive diagnostic test but in places where bile acid test is not routinely available diagnosis should be supported by raised liver enzymes.
3. Bile acids levels should be considered in cases of normal liver enzymes when all other causes of pruritus have been excluded.
4. Early termination of pregnancy at 37–38 weeks is advised in whom liver enzymes/bile acids and symptoms gets resolved with UDCA whereas earlier induction can be advocated in cases with intense itching and persistently raised liver enzymes/bile acids for favorable fetal outcome

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