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Original Research Article

Maternal and perinatal outcome in cholestasis of pregnancy: a study in tertiary care hospital in North India

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ABSTRACT

Background: Intrahepatic cholestasis of pregnancy (IHCP) is the most common pregnancy related liver disorder. It typically presents with troublesome itching and can lead to complications for both mother and fetus. Thus, authors aimed to assess risk factors associated with IHCP as well as maternal and fetal outcome in pregnancy associated with IHCP in north Indian population.
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

Cholestasis can be defined as an interruption in the flow of bile due to obstruction of bile ducts or excretory failure of hepatocytes with accumulation of bile constituents in the blood.[1] In this condition, bile cannot flow from liver to the duodenum.

Obstetric cholestasis is a liver disorder unique to pregnancy, which typically presents with pruritus. However, pruritus is common in pregnancy and the diagnosis of obstetric cholestasis is confirmed by finding abnormal liver function.[2] Intrahepatic cholestasis of pregnancy or obstetric cholestasis is the most common pregnancy related liver disorder and is characterized by pruritus, elevated serum-aminotransferases and bile-acid level with onset in second or third trimester of pregnancy and spontaneous relief of symptoms within second or third week after delivery. It typically presents with troublesome itching and can lead to complications for both mother and fetus.[3]

Its prevalence varies between populations as well as within population over time and between seasons. Prevalence has seasonal cycles and it may be more prevalent in the winters.[4] Variable incidence of IHCP has been noted in Indian population with paucity of data on comparison of various fetal risks with normal pregnant

subjects. There is lack of data indicating association of various risk factors for IHCP with maternal and fetal outcome in north Indian population. Hence this study was done to assess risk factors associated with IHCP as well as maternal and fetal outcome in pregnancy associated with IHCP in north Indian population as primary outcome. The secondary outcome is to find out an association between risk factors for IHCP and maternal and fetal outcome.

METHODS

This hospital based analytical observational case control study was carried out in Department of Obstetrics and Gynaecology, Asian Institute of Medical Sciences, Faridabad for a period of one year. Study population was divided into group 1 which comprised of pregnant females clinically diagnosed with IHCP as defined by otherwise unexplained pruritus combined with elevated bile acids and/or transaminases in the late second and third trimester of pregnancy and group 2 included normal healthy pregnant females without any obvious complaints as controls. Eligible subjects were enrolled in the study only after obtaining informed written consent and were subjected to detailed history taking (including demographic and obstetric history), clinical examination and all routine biochemical analysis including liver function tests, hepatitis viral markers (HBsAg, anti-HCV) and hepatobiliarysonography. When indicated, additional investigations to identify the etiology of liver disease were done. Patients with intrahepatic cholestasis of pregnancy received ursodeoxycholic acid (10-15 mg/kg body weight). All study subjects received careful weekly outpatient clinical monitoring. The study groups were followed up through the pregnancy till 3 weeks post-partum. Demographic data and pregnancy outcome measures were collected by the delivery team. If a subject had two abnormalities, such as low birth weight (LBW) and preterm delivery, each was considered an independent outcome and the subject was included in both categories.

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 or Mann Whitney U 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	18.18	0.52
26-30	22	50	16	36.36	
31-35	12	27.2	16	36.36	
36-40	5	11.3	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).

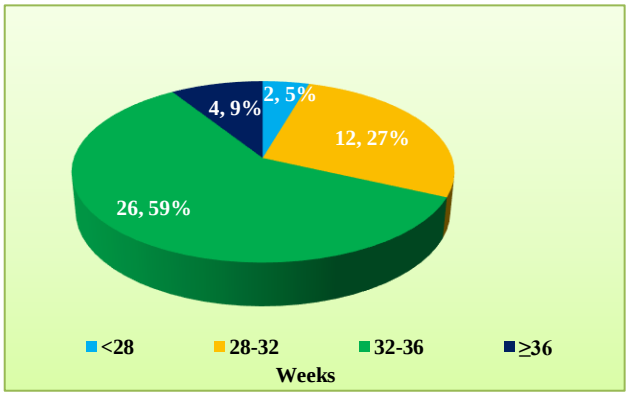

Figure 1: Onset of pruritis in study subjects.

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

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	0.07
	2.6-3.5	31	70.45	35	79.54	
	≥3.6	03	06.81	06	13.6	
Birth weight (in kg) (mean±SD)		3.3±0.48		3.11±0.33		0.03

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).

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 Shobailliet 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

Authors concluded that IHCP mothers are at risk of preterm delivery, induced labour and LSCS. Though intrapartum complications are higher there is no significant increase in postpartum complications. Fetus is at higher risk of preterm delivery, meconium stained liquor, fetal distress and lower APGAR score but not statistically significant. Significant association between elevated T. bilirubin, AST, ALT and ALP was noted with ICP. Thus, IHCP is associated with higher risk of complications in infants and to lesser extent in mothers. In this study categorization into mild, moderate and severe IHCP was not done as well as long term follow up is needed usually to reach a conclusion.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of Asian Institute of Medical Sciences, Faridabad, Haryana, India

REFERENCES

1. Van Wettere AJ. Histologic patterns of hepatotoxic injury. Comprehensive Toxicol. 2018;2:97-136.
2. Kenyon AP, Piercy CN, Girling J, Williamson C, Tribe RM, Shennan AH. Pruritus may precede abnormal liver function tests in pregnant women with obstetric cholestasis: a longitudinal analysis. BJOG. 2001;108(11):1190-2.
3. Ghosh S, Chaudhuri S. Intra-hepatic cholestasis of pregnancy: a comprehensive review. Indian J Dermatol. 2013;58(4):327.
4. Pusl T, Beuers U. Intrahepatic cholestasis of pregnancy. Orphanet J Rare Dis. 2007;2:26.
5. Geenes V, Chappell L, Seed P, Steer P, Knight M, Williamson C. Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: A prospective population-based case-control study. Hepatol. 2014;59(4):1482-91.
6. Al Shobaili H, Hamed H, Al Robaee A, Alzolibani A, Amin A, Ahmad S. Obstetrical and fetal outcomes of a new management strategy in patients with intra-hepatic cholestasis of pregnancy. Arch Gynecol Obstet. 2010;283(6):1219-25.
7. Reyes H. Review: intrahepatic cholestasis. A puzzling disorder of pregnancy. J Gastroenterol Hepatol. 1997;12:212-6.
8. Lammert F, Marschall H, Glantz A, Matern S. Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management. J Hepatol. 2000;33(6):1012-21.
9. Bacq Y, Sapey T, Bréchot MC, Pierre F, Fignon A, Dubois F. Intrahepatic cholestasis of pregnancy: a French prospective study. Hepatol. 1997;26(2):358-64.
10. Brouwers L, Koster M, Page-Christiaens G, Kemperman H, Boon J, Evers I, et al. Intrahepatic cholestasis of pregnancy: maternal and fetal outcomes associated with elevated bile acid levels. Am J Obstet Gynecol. 2015;212(1):100.e1-7.
11. Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. Hepatol. 2004;40:467-74.
12. Dang A, Agarwal N, Bathla S, Sharma N, Balani S. Prevalence of liver disease in pregnancy and its outcome with emphasis on obstetric cholestasis: An Indian scenario. J Obstet Gynecol India. 2010;60(5):413.
13. Wikström Shemer E, Marschall H, Ludvigsson J, Stephansson O. Intrahepatic cholestasis of pregnancy and associated adverse pregnancy and fetal outcomes: a 12-year population-based cohort study. BJOG. 2013;120(6):717-23.
14. Wikström Shemer E, Thorsell M, Marschall H, Kaijser M. Risks of emergency cesarean section and fetal asphyxia after induction of labor in intrahepatic cholestasis of pregnancy: A hospital-based retrospective cohort study. Sexual Reproductive Healthcare. 2013;4(1):17-22.
15. Geenes V, Chambers J, Khurana R, Shemer E, Sia W, Mandair D, et al. Rifampicin in the treatment of severe intrahepatic cholestasis of pregnancy. Eur J Obstet Gynecol Reprod Bio. 2015;189:59-63.
16. Cavazos-Rehg PA, Krauss MJ, Spitznagel EL, Bommarito K, Madden T, Olsen MA, et al. Maternal age and risk of labor and delivery complications. Maternal Child Health J. 2015;19(6):1202-11.
17. Heinonen S, Kirkinen P. Pregnancy outcome with intrahepatic cholestasis. Obstet Gynecol. 1999;94(2):189-93.
18. Laatikainen T, Tulenheimo A. Maternal serum bile acid levels and fetal distress in cholestasis of pregnancy. Int J Gynaecol Obstet. 1984;22:91-4.
19. Zimmermann P, Koskinen J, Vaalamo P, Ranta T. Doppler umbilical artery velocimetry in pregnancies complicated by intrahepatic cholestasis. J Perinat Med. 1991;19:351-5.
20. Simpson LL. Maternal medical disease: risk of antepartum fetal death. Semin Perinatol. 2002;26:42-50.

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