

AN OBSERVATIONAL STUDY OF PREGNANCY OUTCOMES IN PATIENTS WITH INTRAHEPATIC CHOLESTASIS OF PREGNANCY IN A TERTIARY CARE HOSPITAL

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Abstract

Background: The present study has been conducted to study the incidence, biochemical changes, maternal and neonatal outcome in IHCP with pregnancy and also to compare with non-IHCP normal pregnancy. **Materials and Methods:** The prospective cases control observational study was conducted from September 2022 to August 2023 at department of Obstetrics and Gynaecology, Nalanda Medical College and Hospital, Patna, Bihar, India. The study was initiated after obtaining approval from institutional ethical committee. All pregnant ladies ≥ 20 weeks' gestation having symptoms suggestive of intrahepatic cholestasis of pregnancy during the study period was included in cases and all 20th non IHCP patients attending OPD are included in controls. Each patient was subjected to investigations of complete blood count, liver function test (ALT, AST and Alkaline phosphatase) and viral markers (HBsAg, HCV and HAV). **Results:** The present study was conducted for the period of one year. A total no of 100 pregnant ladies (50 IHCP and 50 without IHCP) were included in this study. 3.91% was the incidence of IHCP was during the study period. Demographic profiles were adjusted in both groups. 66% of cases were in the age group of 26-30 years, maximum cases belonging to lower middle socioeconomic group. 66% of cases were primigravida. **Conclusion:** In the present study, there is a significant incidence of IHCP found in the obstetrical population commonly affecting primigravida with common presentation of pruritus at 31-33 weeks POG.

INTRODUCTION

Intrahepatic cholestasis of pregnancy (IHCP) is the most common cholestatic liver disease during pregnancy. It is characterized by pruritus in absence of a skin rash, with onset in the second or third trimester of pregnancy, elevated serum aminotransferases and bile acid levels and spontaneous relief of signs and symptoms after delivery. Incidence overall of IHCP is between 0.02% to 2.4%.^[1] The incidence in Asians of Indian origin it is 1.24% and in other countries it varies from 0.25 to 1.5%.^[2,3] It varies by population due to significant genetic influence. Incidence has declined since the 1970s.^[4-6] The etiology of IHCP is unclear. Result of insufficient liver capacity to metabolize high amounts of placenta-derived sex steroids during pregnancy is thought to be a cause.^[7,8] The familial occurrence and mutations in the many genes like multidrug resistance protein 3 (MDR3) and ABCB11 gene and gene products (foresaid X receptor and transporting ATPase encoded by ATP8B1) have

association with IHCP.^[9-12] Some drugs like synthetic estrogens, azathioprine etc. can trigger IHCP. It is also common in multiple pregnancies.^[13,14]

The present study has been conducted to study the incidence, biochemical changes, maternal and neonatal outcome in IHCP with pregnancy and also to compare with non-IHCP normal pregnancy.

MATERIALS AND METHODS

The prospective cases control observational study was conducted from September 2022 to August 2023 at department of Obstetrics and Gynaecology, Nalanda Medical College and Hospital, Patna, Bihar, India. The study was initiated after obtaining approval from institutional ethical committee. All pregnant ladies ≥ 20 weeks' gestation having symptoms suggestive of intrahepatic cholestasis of pregnancy during the study period was included in cases and all 20th non IHCP patients attending OPD are included in controls. All recruited patients are interviewed and written consent from patients for

participation in the study was obtained and detailed clinical examination was recorded in the structured Performa. Each patient was subjected to investigations of complete blood count, liver function test (ALT, AST and Alkaline phosphatase) and viral markers (HBsAg, HCV and HAV).

Diagnostic criteria the diagnosis of IHCP is based on

- Pruritus without skin lesion.
- Elevated serum transaminases (ALT >40 U/L or AST >35 U/L).
- Spontaneous relief of signs and symptoms (e.g., pruritus and jaundice) within two to three weeks after delivery.
- Absence of other dermatological or medical causes of pruritus.

Inclusion Criteria

Pregnancy with pruritus due to IHCP developing after 20 weeks of gestation. All 20th non-IHCP patients in ANC OPD were included in this study.

Exclusion Criteria

Pregnancy <20 weeks; dermatological lesion with pruritus; acute or chronic liver disease, infective hepatitis; other dermatological causes of pruritus were excluded from the study.

Outcome definition and parameters: Maternal outcome

- Onset and severity of symptoms namely pruritus, icterus.
- Medication and response to medication
- Gestational age of termination and mode of delivery.
- Any ante partum or post-partum complication.
- Blood transfusion
- Biochemical changes during follow-up.
- Fetal outcome
- Meconium stained liquor.
- Period of gestation on delivery.
- Birth asphyxia.
- Live born/ perinatal death/ still born/ IUD.
- Birth weight.
- APGAR score at 1 minute and 5 minutes.
- NICU admission.
- Neonatal Jaundice.

RESULTS

The present study was conducted for the period of one year. A total no of 100 pregnant ladies (50 IHCP and 50 without IHCP) were included in this study. 3.91% was the incidence of IHCP was during the study period. Demographic profiles were adjusted in both groups. 66% of cases were in the age group of 26-30 years, maximum cases belonging to lower middle socioeconomic group. 66% of cases were primigravida Table 1, 2, and 3

Onset of symptoms namely pruritus or icterus was presented at 31-33 weeks with mean POG of 31.48 wee up's Table 4. All 50 (100%) cases presented with pruritus versus 2 (4%) in control and only 2 (4%) cases presented with icterus Table 5, 6.

Mean value of total bilirubin (pre-delivery) for both groups were 0.49±0.33 and 0.48±0.18 and post-delivery were 0.45±0.20 and 0.47±0.17 respectively, which are not significant. Mean value of ALT, for pre-delivery and post-delivery were 117.52±63.19 and 64.24±25.21 respectively. Mean value of AST, for pre-delivery and post-delivery were 106.66±56.73 and 64.70±31.00 respectively. Mean value of alkaline phosphatase (ALP), for pre-delivery and post-delivery were 224.86±62.29 and 120.58±38 respectively Table 7, 8.

NS= Not significant

S=Significant

Table 1 shows the distribution of patients according to age. Out of 110 patients 14 patients (25.45%) in case and 16 patients (29.09%) in control were in the age between 21-25 years, 29 patients (52.72%) in case and 26 patients (47.27%) were in the age between 26-30 years, 7 patients (12.72%) in case and 13 patients (23.63%) in control were in the between 31-35 years, 5 patients (9.09%) in case and 0 patients in control were in the age between 36-40 years. Maximum no. patients (50%) were in the age between 26-30 years and least no. of patients (4.54%) was in the age between 36-40 years [Table 1].

Table 2 shows the distribution of patients according to age. Out of 110 patients 29 patients (52.75%) in case and 31 patients (56.36%) in control have received primary education, 10 patients (18.18%) in case and 8 patients (14.54%) in control have received secondary education, 16 patients (29.09%) in case and 16 patients (29.09%) in control has graduated. Most patients have received primary education and least patients have received secondary education. Equal number patients have graduated. Maximum no. of patients has received primary education only (54.54%) and least no. of patients (16.36%) has received secondary education [Table 2].

Table 3 shows the distribution of patients according to socio-economic factors. Out of 110 patients 27 patients (49.09%) in case and 30 patients (54.54%) from lower class, 8 patients (14.54%) in case and 7 patients (12.72 %) from lower middle class, 13 patients (23.63%) in case and 12 patients (21.81%) in control from upper middle class, 7 patients (13.72%) in case and 6 patients (12.72%) in control from higher class with p value of 0.21 [Table 3].

Table 4 shows the distribution of patients according to obstetric history. Maximum cases were primigravida (55.45%). I this study no. of patients in primigravida was significantly higher as compare to multigravida [Table 4].

Table 1: Distribution of patients according to age

Variable	Case	Control	Total	P value	Significance
21-25 years	14(25.45%)	16(29.09%)	30(27.27%)	0.656	NS
26-30 years	29(52.72%)	26(47.27%)	55(50%)	0.547	NS

31-35 years	7(12.72%)	13(23.63%)	20(18.18%)	0.157	NS
36-40 years	5(9.09%)	0(0.00%)	5(4.54%)	0.057	NS
Total	55(100%)	55(100%)	110(100%)	--	--

Table 2: Distribution of patients according to education

Education	Case	Control	Total	P value	Significance
Primary	29(52.75%)	31(56.36%)	60(54.54%)	0.315	NS
Secondary	10(18.18%)	8(14.54%)	18(16.36%)		
Graduate	16(29.09%)	16(29.09%)	32(29.09%)		
Total	55(100%)	55(100%)	110(100%)	--	--

Table 3: Distribution of patients according to socio-economic factors

Socio-economic factors	Case	Control	Total	P value	Significance
Lower class	27(49.09%)	30(54.54%)	56(51.81%)	0.215	NS
Lower middle class	8(14.54%)	7(12.72%)	15(13.63%)		
Upper Middle class	13(23.63%)	12(21.81%)	25(22.72%)		
Higher class	7(13.72%)	6(12.72%)	13(11.81%)		
Total	55(100%)	55(100%)	110(100%)	--	--

Table 4: Obstetric history

Variable	Case	Control	Total	P value	Significance
Multigravida	19(35.54%)	30(54.54%)	49(44.54%)	0.027	S
Primigravida	36(65.45%)	25(45.45%)	61(55.45%)		
Total	55(100%)	55(100%)	110(100%)	--	--

Table 5: Distribution of patients according to pruritus

Pruritus	Case	Control	Total	P value	significance
Absent	0(0.00%)	50(90.90%)	50(45.45%)	<0.001	S
Present	55(100%)	5(9.09%)	60(54.54%)		
Total	55(100%)	55(100%)	110(100%)	--	--

Table 6: Distribution of patients according to icterus

Icterus	Case	Control	Total	P value	significance
Absent	51(92.75%)	55(100%)	106(96.36%)	<0.495	NS
Present	4(7.27%)	0(0.00%)	4(3.63%)		
Total	55(100%)	55(100%)	110(100%)	--	--

Table 7: Comparison of meconium-stained liquor (MSL)

MSL	Case	Control	Total	P value	significance
No	40(72.72%)	50(90.90%)	90(81.81%)	0.004	S
Yes	15(27.27%)	5(9.09%)	20(18.18%)		
Total	55(100%)	55(100%)	110(100%)	--	--

Table 8: Comparison of neonatal jaundice

Neonatal jaundice	Case	Control	Total	P value	significance
No	47(85.45%)	55(100%)	102(92.72%)	0.027	S
Yes	8(14.54%)	0(0.00%)	8(7.27%)		
Total	55(100%)	55(100%)	110(100%)	--	--

DISCUSSION

IHCP is multifactorial including genetics and environmental influences. Incidence varies in different parts of the world. IHCP usually manifests in the third trimester of pregnancy.^[15] The levels of Bile acids, liver transaminases and alkaline phosphatase are usually higher. A total no of 100 antenatal cases (50 IHCP and 50 without IHCP) included in this study.

Table 1 shows the distribution of patients according to age. Out of 110 patients 14 patients (25.45%) in case and 16 patients (29.09%) in control were in the age between 21-25 years, 29 patients (52.72%) in case and 26 patients (47.27%) were in the age between 26-30 years, 7 patients (12.72%) in case and 13 patients (23.63%) in control were in the between

31-35 years, 5 patients (9.09%) in case and 0 patients in control were in the age between 36-40 years. Maximum no. patients (50%) were in the age between 26-30 years and least no. of patients (4.54%) was in the age between 36-40 years.

Table 2 shows the distribution of patients according to education. Out of 110 patients 29 patients (52.75%) in case and 31 patients (56.36%) in control have received primary education, 10 patients (18.18%) in case and 8 patients (14.54%) in control have received secondary education, 16 patients (29.09%) in case and 16 patients (29.09%) in control has graduated. Most patients have received primary education and least patients have received secondary education. Equal number patients have graduated. Maximum no. of patients has received primary education only

(54.54%) and least no. of patients (16.36%) has received secondary education.

Table 3 shows the distribution of patients according to socio-economic factors. Out of 110 patients 27 patients (49.09%) in case and 30 patients (54.54%) from lower class, 8 patients (14.54%) in case and 7 patients (12.72 %) from lower middle class, 13 patients (23.63%) in case and 12 patients (21.81%) in control from upper middle class, 7 patients (13.72%) in case and 6 patients (12.72%) in control from higher class with p value of 0.215.

Table 4 shows the distribution of patients according to obstetric history. Maximum cases were primigravida (55.45%). In this study no. of patients in primigravida was significantly higher as compare to multigravida.

Incidence of IHCP in this study (3.914%) was higher than that in the nation-wide study (overall incidence 1.03%- comparable to South Asia statistics of 0.8-1.4%). Incidence was highest in cases of age group 26-30 years (50%). As per study by Pathak et al and Heinonen et al, risk factors for IHCP are family history, biliary disease prior IHCP, multiparity, multifetal gestation and maternal age greater than 35 years.^[16,17]

According to socioeconomic status, majority of cases and controls were from lower middle socio-economic status which was 51.81% in this study. Maximum cases were primigravida (55.45%). Study by Kant et al showed that frequency of IHCP in primigravida was significantly higher.^[18]

As per study by Kenyon et al most common symptom of IHCP was pruritus, which typically appears in the third trimester and starts in the palms and soles.^[19] Usually 80% of patients have symptoms after 30 gestational weeks and the condition presents in the late second and third trimester of pregnancy. In this study, onset of symptom found maximum at 31-33 weeks POG and earliest was at 26 weeks. All the cases (100%) were suffering of pruritus. Only 7.27% of cases were suffering from jaundice. Other studies showed that mild jaundice with serum levels of conjugated bilirubin observed in 10 to 15% of cases.^[20] Jaundice typically develops 1-4 weeks after the onset of pruritus.^[21]

There were statistically significant increase in mean value of liver enzymes including ALT, AST, alkaline phosphatase in all IHCP case in both pre and post-delivery samples in comparison to non-IHCP controls with ALT (pre-delivery) for IHCP (case) were 117.52 ± 63 ,^[19] and non-IHCP (control) was 41.94 ± 9.58 , and mean value of ALT (post-delivery) for cases was 64.24 ± 25 ,^[21] and control was 40.84 ± 9.78 . Mean value of AST (pre-delivery) for cases was 106.66 ± 56.73 and control was 45.44 ± 9.32 . Mean value of AST (post-delivery) for cases was 64.70 ± 31.00 and control was 43.96 ± 9.30 . Mean value of alkaline phosphatase (ALP) (pre-delivery) for cases was 224.86 ± 62.29 and control was 74.76 ± 23.72 . Mean value of alkaline phosphatase (ALP) (post-delivery) for cases was 120.58 ± 38.38 and control was 71.26 ± 22.31 . In Finnish studies the

diagnostic laboratory criteria for the IHCP were BA ≥ 6 mol/L or ALT >40 U/L or AST >35 U/L.^[22,23] Elevated serum BA level is the most sensitive indicator of IHCP, but serum ALT levels usually also rise in IHCP.^[20-25] Kenyon et al concluded that alkaline phosphatase levels are usually elevated even more than in normal pregnancy.^[19]

In this study, 60% of cases delivered at 36-38 weeks and 58% of controls delivered at 38-40 weeks. In other studies, induction of labour at 37-38 weeks of gestation done with the aim of reducing the risk of intra uterine fetal demise as many deaths occur after 37 weeks of period of gestation.^[26,27]

In this study, 80% of cases and 17.07% of controls were induced. 66% of cases and 64% of controls had vaginal delivery. 32% of cases and 34% of controls had LSCS. Chappell et al also reported planned early termed delivery not to increase caesarean section rate significantly.^[28]

In another study, caesarean section, which was around 10% both for women with and without IHCP, did not increase, when labor was induced? Caesarean section with spontaneous onset of labour in gestational weeks 37-39 was around 10%, as per Germain et al increased bile acid levels might have enhanced uterine contractility through activation of the oxytocin receptor pathway, which is also reflected by the decreased amount of oxytocin that is required to stimulate contractions in women with IHCP.^[29]

In this study, 86% cases relieved from symptoms after medication. All the cases relieved from symptoms following delivery. Bacq et al concluded in their meta-analysis that UDCA therapy might reduce maternal symptoms, fetal distress, and the need for NICU treatment might decrease.^[30,31]

In this study, 14% of cases and 10% of controls had preterm delivery. 24% of IHCP cases and 14% of normal pregnancy had meconium stained liquor. It was statistically significant. 14% of cases and 4% of controls had fetal distress. 12% baby of IHCP cases had neonatal jaundice and it was significant. 8% baby of cases and 2% baby of controls were IUGR. 12% baby of cases and 6% baby of normal pregnancies were admitted in NICU. In the study by Williamson et al, preterm delivery (19-60%), meconium staining of amniotic fluid (27%), fetal bradycardia (14%), fetal distress (22-41%) and fetal loss (up to 0.4-4.1%).^[32] In this study, 4% of cases had Apgar 7 for all babies of controls. As per Joutsiniemi et al, Apgar scores at 5 min were significantly lower ($p < 0.05$). 33 There was no antepartum hemorrhage, postpartum hemorrhage or blood transfusion.

As per Brouwers et al, postpartum hemorrhage was present in 7.4% of all cases.^[1] No still birth and perinatal mortality occurred in this study. In some studies, perinatal mortality including stillbirths was reduced to 3.5% or less with more recent active management, which includes treatment with UDCA, intensified fetal monitoring and planned deliveries at gestation 37-38 weeks.^[27,34]

CONCLUSION

In the present study, there is a significant incidence of IHCP found in the obstetrical population commonly affecting primigravida with common presentation of pruritus at 31-33 weeks POG. The biochemical changes, meconium stained liquor and neonatal jaundice were significantly increase with IHCP in pregnancy. 86% cases relieved from symptoms after medication during antenatal period and all cases symptomatically recovered following delivery.

Though there was no significant adverse neonatal or maternal outcome found in the present study, a significant meconium stained liquor (MSL), neonatal jaundice; IUGR and NICU admission were noted in the IHCP group in comparison to non-IHCP group.

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