

DOI: <http://dx.doi.org/10.18203/2320-1770.ijrcog20203865>

Original Research Article

## Pregnancy outcome in patients with intrahepatic cholestasis of pregnancy: an observational case control study

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**Received:** 16 July 2020

**Accepted:** 18 August 2020

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### ABSTRACT

**Background:** Intrahepatic cholestasis of pregnancy (IHCP) is the most common cholestatic liver disease, which may impact the foeto-maternal health. The present study is conducted to determine various factors including maternal and neonatal outcome in IHCP comparing with the controls.

**Methods:** In this prospective case control study, pregnancy with IHCP is compared with asymptomatic non-IHCP controls. Classical pruritus, icterus, elevated liver enzymes were considered in diagnostic criteria of IHCP. Dermatological lesion, acute or chronic liver disease, and other causes of pruritus were excluded from study.

**Results:** Out of 100 patients, 50 cases and 50 controls were included in this study. Incidence of IHCP was seen 3.914% of which 66% were primi presented maximum at 31-33 weeks. 86% of IHCP responded to medication. Mean value of ALT, AST and ALP was found significantly raised (p value-<0.001) in IHCP patients. 66% in IHCP and 64% in non-IHCP group had normal delivery and remaining 34% and 36 % had caesarean delivery respectively. There was no significant increase in foetal distress or low Apgar (<7 at 5 min) at birth or adverse neonatal or maternal outcome in IHCP group. However, there was a statistically high meconium stained liquor (MSL), neonatal jaundice, IUGR and NICU admission were noted in the IHCP group in comparison to non-IHCP group.

**Conclusions:** There is a significant incidence of IHCP in the obstetrical population. The biochemical changes, meconium stained liquor, neonatal jaundice, IUGR and NICU admission were significantly high in IHCP in pregnancy.

**Keywords:** Intrahepatic cholestasis of pregnancy, Total bile acid, Ursodeoxycholic acid

### 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%.<sup>1</sup> The incidence in Asians of Indian origin it is 1.24% and in other countries it varies from 0.25 to 1.5%.<sup>2,3</sup> It varies by population due to significant genetic influence. Incidence has declined since the 1970s.<sup>4-6</sup> 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.<sup>7,8</sup> 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.<sup>9-12</sup> Some drugs like synthetic estrogens, azathioprine etc. can trigger IHCP. It is also common in multiple pregnancies.<sup>13,14</sup>

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.

### **Aims and objectives**

Aim and objectives of the study was to study incidence, biochemical changes, maternal and neonatal outcome in pregnancy complicated by IHCP and compare with the non-IHCP controls.

### **METHODS**

The prospective cases control observational study was conducted from January 2018 to June 2019 at department of Obstetrics and Gynecology, Command Hospital, Kolkata, India. The study was initiated after obtaining approval from institutional ethical committee. All pregnant ladies  $\geq 20$  weeks gestation having symptoms suggestive of intrahepatic cholestasis of pregnancy during the study period was included in cases and all 20<sup>th</sup> 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 proforma. 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 20<sup>th</sup> non-IHCP patient 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 antepartum 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.

Indicated cases were treated with tablet ursodeoxycholic acid (10-20 mg/kg/day). Patients having signs of IUGR, oligohydramnios or with adverse USG findings were admitted, followed up and treated accordingly. Uncomplicated cases of IHCP were terminated at 37 completed weeks by priming of unfavorable cervix with dinoprostone gel 0.5 mg (if bishop's score  $<6$ ) followed by induction of labour with oxytocin drip as per labour room induction protocol. All labour were monitored and feto-maternal outcome were recorded and post-partum period were followed up till 6 weeks after delivery with sign of clinical or laboratory resolution of parameters.

### **Statistical analysis**

Maternal and fetal data were recorded, compiled and tabulated using Microsoft excel 2007. The statistical software SPSS version 20 has been used for analysis.

### **RESULTS**

The present study was conducted for the period of one and half years. A total no of 100 pregnant ladies (50 IHCP and 50 without IHCP) were included in this study. 3.914% 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 socio-economic group. 66% of cases were primigravida Table 1, 2, 3.

Onset of symptoms namely pruritus or icterus was presented at 31-33 weeks with mean POG of 31.48 weeks 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  $0.49 \pm 0.33$  and  $0.48 \pm 0.18$  and post-delivery were  $0.45 \pm 0.20$  and  $0.47 \pm 0.17$  respectively, which are not significant. Mean value of ALT, for pre-delivery and post-delivery were  $117.52 \pm 63.19$  and  $64.24 \pm 25.21$  respectively. Mean value of AST, for pre-delivery and

post-delivery were  $106.66 \pm 56.73$  and  $64.70 \pm 31.00$  respectively. Mean value of alkaline phosphatase (ALP),

for pre-delivery and post-delivery were  $224.86 \pm 62.29$  and  $120.58 \pm 38$  respectively Table 7, 8.

**Table 1: Distribution of age.**

Variables	Group		Total (%)	P value	Significance	
	Case (n=50) (%)	Control (n=50) (%)				
Age in years	21-25	13 (26)	15 (30)	28 (28)	0.656	Not significant
	26-30	28 (56)	25 (50)	53 (53)	0.547	
	31-35	5 (10)	10 (20)	15 (15)	0.157	
	36-40	4 (8)	0 (0)	4 (4)	0.057	
<b>Total</b>	50 (100)	50 (100)	100 (100)			

**Table 2: Socioeconomic status (SES).**

Variables	Group		Total (%)	P value	Significance	
	Case (n=50) (%)	Control (n=50) (%)				
SES	Upper	1 (2)	0 (0)	1 (1)	0.315	Not significant
	Upper middle	49 (98)	50 (100)	99 (99)		
<b>Total</b>	50 (100)	50 (100)	100 (100)			

**Table 3: Obstetric history.**

Variables	Group		Total (%)	P value	Significance	
	Case (n=50) (%)	Control (n=50) (%)				
Gravida	MULTI	17 (34)	28 (56)	45 (45)	0.027	Significant
	PRIMI	33 (66)	22 (44)	55 (55)		
<b>Total</b>	50 (100)	50 (100)	100 (100)			

**Table 4: Gestational age at onset of symptom (n=50).**

Minimum	Maximum	Mean	Median	Std. Deviation
26	38	31.48	31.00	3.16

**Table 5: Distribution according to pruritus (n=50).**

Variables	Group		Total (%)	P value	Significance	
	Case (n=50) (%)	Control (n=50) (%)				
Pruritus	Absent	0 (0)	48 (96)	48 (48)	<0.001	Significant
	Present	50 (100)	2 (4)	52 (52)		
<b>Total</b>	50 (100)	50 (100)	100 (100)			

**Table 6: Distribution of cases and control according to icterus (n=50).**

Variables	Group		Total (%)	P value	Significance	
	Case (n=50) (%)	Control (n=50) (%)				
Icterus	Absent	48 (96)	50 (100)	98 (98)	<0.495	Non significant
	Present	2 (4)	0 (0)	2 (2)		
<b>Total</b>	50 (100)	50 (100)	100 (100)			

A total 30 (60%) of patient in IHCP group (case) delivered at 36-38 weeks. 29 (58%) patients in Non-IHCP (Control) delivered at 38-40 weeks. 40 (80%) of cases were induced where as 17.07% of control required induction. 33 (66%) of cases and 32 (64%) of controls

had vaginal delivery and remaining 17 (34%) and 18 (36%) had caesarean delivery in respectively. 86% symptomatic cases relieved from symptoms with medication. Relief of symptom following delivery was 100% in cases.

**Table 7: Pre delivery biochemical data.**

Variables	Group						P value	Significance
	Case (n=50)			Control (n=50)				
	Mean	Median	Std. deviation	Mean	Median	Std. deviation		
<b>Hb</b>	11.03	10.80	0.95	11.11	10.95	0.88	0.417	NS
<b>PT</b>	10.41	10.40	1.61	10.68	10.60	0.67	0.444	NS
<b>INR</b>	1.04	1.10	0.11	0.94	1.10	0.32	0.315	NS
<b>Bilirubin</b>	0.49	0.40	0.33	0.48	0.50	0.18	0.543	NS
<b>SGPT</b>	117.52	92.00	63.19	41.94	41.00	9.58	<0.001	S
<b>SGOT</b>	106.66	86.00	56.73	45.44	45.00	9.32	<0.001	S
<b>ALP</b>	224.86	210.00	62.29	74.76	71.00	23.72	<0.001	S
<b>Protein</b>	6.90	6.90	0.39	6.87	6.90	0.41	0.693	NS

NS: Non significant, S: significant.

**Table 8: Post-delivery biochemical data.**

Variables	Group						P value	Significance
	Case (n=50)			Control (n=50)				
	Mean	Median	Std. deviation	Mean	Median	Std. deviation		
<b>Hb</b>	9.31	9.55	1.48	9.80	9.90	0.63	0.056	NS
<b>Bilirubin</b>	0.45	0.45	0.20	0.47	0.50	0.17	0.519	NS
<b>SGPT</b>	64.24	56.00	25.21	40.84	41.50	9.78	<0.001	S
<b>SGOT</b>	64.70	55.50	31.00	43.96	43.00	9.30	<0.001	S
<b>ALP</b>	120.58	113.50	38.38	71.26	65.00	22.31	<0.001	S
<b>Protein</b>	6.80	6.90	0.37	6.87	6.90	0.35	0.474	NS

NS: Non significant, S: significant.

**Table 9: Comparison of meconium-stained liquor (MSL).**

Variables		Group		Total (%)	P value	Significance
		Case (n=50) (%)	Control (n=50) (%)			
<b>MSL</b>	No	38 (76)	48 (96)	86 (86)	0.004	Significant
	Yes	12 (24)	2 (4)	14 (14)		
<b>Total</b>		50 (100)	50 (100)	100 (100)		

**Table 10: Comparison of neonatal jaundice.**

Variables		Group		P value	Significance
		Case (n=50) (%)	Control (n=50) (%)		
<b>Neonatal jaundice</b>	No	44 (88)	50 (100)	0.027	Significant
	Yes	6 (12)	0 (0)		
<b>Total</b>		50 (100)	50 (100)		

A total 12 (24%) in IHCP (case) and 2 (4%) in non-IHCP (control) had meconium stained liquor Table 9. 14% of cases and 4% of controls had fetal distress. 8% neonate in IHCP and 2% in Non-IHCP had Apgar <7 at 1 min. 4% neonate in IHCP had Apgar <7 at 5 min and all neonate in Control had Apgar >7 at 5 min.

A total 6 (12%) significant neonate in IHCP group (Case) had jaundice whereas none of the baby in control group had neonatal jaundice (Table 10). Mean value of birth weight of babies for cases was 2749.82±339.70 gm and 3115.00±416.43 gm respectively. 8% baby in IHCP

group (case) and 2% baby from control group had clinical sign of IUGR. 12% baby of IHCP group (case) and 6% baby of controls were admitted in NICU. In this study, none of the cases in both the group had antepartum, postpartum hemorrhage or required blood transfusion.

## 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.<sup>15</sup> 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.

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 (56%). 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.<sup>16,17</sup>

According to socioeconomic status, majority of cases and controls were from lower middle socio-economic status which was 98% in this study. Maximum cases were primigravida (66%). Study by Kant et al showed that frequency of IHCP in primigravida was significantly higher.<sup>18</sup>

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.<sup>19</sup> 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 4% 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.<sup>20</sup> Jaundice typically develops 1-4 weeks after the onset of pruritus.<sup>21</sup>

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  $117.52 \pm 63.19$  and non-IHCP (control) was  $41.94 \pm 9.58$ , and mean value of ALT (post-delivery) for cases was  $64.24 \pm 25.21$  and control was  $40.84 \pm 9.78$ . Mean value of AST (pre-delivery) for cases was  $106.66 \pm 56.73$  and control was  $45.44 \pm 9.32$ . Mean value of AST (post-delivery) for cases was  $64.70 \pm 31.00$  and control was  $43.96 \pm 9.30$ . Mean value of alkaline phosphatase (ALP) (pre-delivery) for cases was  $224.86 \pm 62.29$  and control was  $74.76 \pm 23.72$ . Mean value of alkaline phosphatase (ALP) (post-delivery) for cases was  $120.58 \pm 38.38$  and control was  $71.26 \pm 22.31$ . In Finnish studies the diagnostic laboratory criteria for the IHCP were BA  $\geq 6$  mol/L or ALT  $>40$  U/L or AST  $>35$  U/L.<sup>22,23</sup> Elevated serum BA level is the most sensitive indicator of IHCP, but serum ALT levels usually also rise in IHCP.<sup>20-25</sup> Kenyon et al concluded that alkaline phosphatase levels are usually elevated even more than in normal pregnancy.<sup>19</sup>

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.<sup>26,27</sup>

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.<sup>28</sup>

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 labor 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.<sup>29</sup>

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.<sup>30,31</sup>

Mean value of birth weight of babies for cases was  $2749.82 \pm 339.70$  gm and that of babies for control were  $3115.00 \pm 416.43$  gm. It was statistically significant. As per study by Kenyon et al, the average birth weight was significantly lower in the study group, which was in concordance with the higher gestational age in the control group (36.1 weeks versus 39.1 weeks).<sup>19</sup>

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%).<sup>32</sup> In this study, 4% of cases had Apgar  $<7$  at 5 min. Apgar score at 5 min was  $>7$  for all babies of controls. As per Joutsiniemi et al, Apgar scores at 5 min were significantly lower ( $p < 0.05$ ).<sup>33</sup> 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.<sup>1</sup>

No still birth and perinatal mortality occurred in this study. In some studies, perinatal mortality including stillbirths were 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 wks.<sup>27,34</sup>

## 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.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Maiti GD, Pal AR, Jose T, Saraswat M. Pregnancy outcome in patients with intrahepatic cholestasis of pregnancy: an observational case control study. *Int J Reprod Contracept Obstet Gynecol* 2020;9:3830-6.