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*Original Article*

# Maternal and fetal outcome in intrahepatic cholestasis of pregnancy at tertiary care institute of North India

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## ABSTRACT

**Objectives:** Intrahepatic cholestasis of pregnancy (IHCP) is the most common reversible form of hepatic disease in pregnancy. The risk of sudden intrauterine infant death is major threat as none of the fetal monitoring proved effective for its prevention. This study was conducted to know the prevalence of IHCP along with fetal and maternal outcome in North Indian population.

**Material and Methods:** This case–control study was conducted over a period of 6 months. One hundred pregnant patients were recruited in each group. Patients with IHCP were included in case group whereas apparently healthy pregnant women with singleton pregnancy were included in control group. Bile acids were done only once at the time of initial visit whereas liver enzymes were done at initial visit and subsequently weekly for total 3 times. All cases of IHCP were started on ursodeoxycholic acid (UDCA) with a dose of 10–15 mg/kg/day throughout pregnancy and three doses of 10 mg Vitamin K by intramuscular route were also given. Fetal and maternal outcomes were compared between both the groups. Total numbers of deliveries in that time period were also noted to find out the prevalence of disease. The tests of two or more proportions were done using Fisher's exact test and Chi-square test. $P < 0.05$ was considered statistically significant.

**Results:** The prevalence of IHCP was 4.08% in our population, however, women from urban area had higher incidence of cholestasis than rural population. History of recurrent disease was found in 30% of women. Out of 100, 96% presented with itching and only 57–58% had raised liver enzymes levels. In 89% of patients (89/100), bile acids levels were >14 μmol/l. During follow-up, SGOT and SGPT levels were significantly improved over 2-week interval while on treatment with UDCA; however, levels were still on higher side. There was no correlation found between cholestasis of pregnancy with preterm labor and meconium-stained liquor in the present study. Comparable results were found in terms of respiratory distress syndrome and NICU admission, whereas significant high incidence of neonatal jaundice found in the control group.

**Conclusion:** Itching over whole body was the predominant presenting complaints of cholestasis of pregnancy. Diagnosis should be supported by bile acids in women with normal liver enzymes to decrease the cost of investigations. Early termination of pregnancy between 36 and 37 weeks can be considered in women with bile acids >40 μmol/L and in non-compliant patients on UDCA treatment.

**Keywords:** Intrahepatic cholestasis of pregnancy, Liver disease, Pruritus during pregnancy, Ursodeoxycholic acid

## INTRODUCTION

Intrahepatic cholestasis of pregnancy (IHCP) is the most common cause of liver disease in pregnancy. It has a variable incidence due to geographical variation; factors such as advanced age, multiple pregnancy, family history, and history of cholestasis in previous pregnancy have shown increased prevalence in these patients.[1,2]

Etiology of cholestasis in pregnancy has not been well understood. In general, it coincides with rising estrogen levels in the second half of pregnancy and following ovarian hyperstimulation syndrome in early pregnancy.[3] Familial clustering of disease in the first-degree relatives favors genetic susceptibility, mutation of *ABCB4* (also called *MDR3*) (adenosine triphosphate-binding cassette, subfamily B, member 4) gene is primarily involved in a subtype of progressive familial intrahepatic cholestasis.[4,5]

Clinically, it presents with itching predominantly over palms and sole, without any primary skin lesion with raised liver enzymes and bile acids. Preterm labor, HELLP syndrome, acute fatty liver of pregnancy, and postpartum hemorrhage are some of the reported maternal complications in these patients.[6-8] There are no specific antenatal fetal monitoring tests to predict sudden intrauterine fetal deaths.[9] Therefore, termination of pregnancy is recommended near 36–37 weeks of gestation to avoid perinatal mortality with expectant management beyond this gestation.[10,11] This study was

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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 6 months from June 2012 to December 2012 in the department of obstetrics and gynecology 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 ($n$ = 100) whereas apparently healthy pregnant women with singleton pregnancy were included in the control group ($n$ = 100). 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. Among liver function test; bile acids were done only once at the time of initial visit whereas rest of them were done for 3 times; difference in the levels of liver enzymes in the 1st and 3rd week of testing was also noticed. 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.

### Statistical analysis

The tests of two or more proportions were done using Fisher's exact test and Chi-square test. *P*-values were taken from two sample tailed tests. $P < 0.05$ was considered statistically significant. A multivariate logistic regression analysis was done to assess the independent factors which were associated with cholestasis of pregnancy.

## RESULTS

There was no statistical difference found in age and parity of patients between both the groups; however, women from urban area had higher incidence (68%) of cholestasis than rural population. History of recurrent cholestasis has been found in 30% of multiparous women. Out of 100 cases, 65% of them have had itching all over the body followed by legs and arms in 20% and itching was confined to abdomen only in 11%. Raised SGPT levels were detected in 57% and 58% had raised SGOT levels. In 89% of patients (89/100), bile acids levels were >14 μmol/l. Three had bile acids <14 μmol/l whereas samples could not be processed for eight patients.

None of them had jaundice at the time of presentation and afterwards. Ultrasonography of liver, pancreas, and gallbladder was normal in 80% of cases and could not be done in three patients and rest of them had mild hepatomegaly. Diagnosis of IHCP was made only on the basis of raised liver enzymes and bile acids without any complaints of itching in 4% of patients after excluding other causes.

During follow-up, SGOT and SGPT levels were significantly improved over 2-week interval while on treatment with UDCA, however, levels were still on higher side [Table 1]. Among cases, 88 patients took UDCA 300 mg 3 times a day, 30 required other modalities such as use of antihistaminic drugs in 4 cases and local emollients by 26 cases.

There were two intrauterine deaths between 36 and 38 weeks in whom no treatment was taken. Serum bile acid levels were >45 and 42 μmol/L and serum SGOT/PT levels were 458 IU/L and 398 IU/L, respectively. Induction of labor was done in 64.6% versus 18.8% patients in cases and control, respectively. There was a significant difference found in rate of total cesarean section 34% versus 24% in the case and control groups, respectively. There was no significant difference found in preterm birth, meconium-stained liquor, birth weight, sex preponderance, and need of neonatal intensive care between both the groups. There was statistically significant difference noted in neonatal jaundice, although more in the control group [Table 2]. There was no significant difference found in rate of postpartum hemorrhage with 5% and 4% in cases and control, respectively. In 79% of cases, itching got relieved within 1 week and persisted for >1 week in 17% of cases.

## DISCUSSION

Intrahepatic cholestasis is a pregnancy-induced disease with variable incidence of 0.2–2% with as high as 20–22% in

**Table 1:** Changes in liver enzymes over a period of 2 weeks while on treatment.

| Liver enzymes | Week 1 | Week 2 | Week 3 | Paired sample | Paired difference | | *P* value |
|---|---|---|---|---|---|---|---|
| | | | | | Mean and standard deviation | df | |
| SGOT (*n*=58%) | 176.01 | 139.2 | 111.2 | SGOT 1 and 3 | 64.8±157.5 | 38 | 0.014 |
| SGPT (*n*=57%) | 208.3 | 173.0 | 138.3 | SGPT 1 and 3 | 70.25±160.6 | 40 | 0.008 |

multiple pregnancies.[12,13] Although there is no well-defined etiology of IHCP; variable incidence has been reported due to difference in population susceptible to genetic predisposition, environmental factors, and increase in sex hormone synthesis may affect its incidence.

Its diagnosis has been made by presence of itching, deranged liver enzymes (serum transaminases), especially ALT/SGPT than AST/SGOT which may rise from 2- to 30-fold of pregnancy-specific range and raised bile acids predominantly conjugated cholic and chenodeoxycholic acid (>10 μmol/L). Levels of serum bile acids may vary according to analytical methods used, fasting status, gestational age at diagnosis, and population studied. It is a reversible disease but can reoccur in subsequent pregnancy and while taking oral contraceptive pills. There are various etiological factors of raised bile acids which are supposed to be excluded before diagnosing it as pregnancy induced cholestasis.[14] Major concern is of adverse perinatal outcome with rising levels of bile acids as all antenatal monitoring test proved futile for its prevention.

The present study revealed higher prevalence (4.08%) of IHCP in our population which is explained by referral of all patients from peripheral center with diagnosis of cholestasis of pregnancy. Women from urban area had higher incidence of cholestasis than rural population that may due to geographical variation and influence of environmental factors. Mean age at presentation was 29 years in a study by Morton and Laurie[15] while age of participants in the present study was in the range of 22–35 years. History of cholestasis in previous pregnancy was 30% in the present study whereas it was reported in 44%–14.9% of multiparous women in other studies.[15,16] Gestational age at presentation was in the range of 14–40 weeks[15] while in the present study, it was in the range of 32–39 weeks.

Itching over palm and sole are typical symptoms of IHCP. However, the present study contraindicates this statement as 65% of the cases described pruritus predominantly over whole body than over palms and soles. Patients with chronic liver disease also present with pruritus, however, it has been reported mainly over back and abdomen but rarely over extremities.[14]

This study revealed positive test results either raised liver enzymes or bile acids in all 100 cases whereas as Morton and Laurie[15] reported normal liver enzymes and bile acids in initial test in 21% (40/183) of study population which were raised in 21 (52%) cases over a period of 9–90 days. They did not exclude patient with various medical disorders and dermatological disease such as eczema, psoriasis, and urticaria from the study population. Hence, only 54% of women were chosen for treatment with UDCA whereas in the present study, 88% took this treatment although all were qualified for it. UDCA therapy improved pruritus in 62.5% of cases by Morton and Laurie[15] whereas 66% got relief in the present study.[15] Their study had 29% (56/193) of cases with a history of allergy to some medications whereas patient with such history was excluded from the present study. Improvement of itching and dearranged liver function has been observed with UDCA in this study which is also supported by Kong *et al*.[17] Whereas, Morton and Laurie[15] reported increase in liver function test over a period of time even with UDCA treatment which might be explained by inclusion of various medical disorders which leads to raised liver enzymes or bile acids.

The present study did not found any significant difference in preterm birth between both the groups that may be

**Table 2:** Comparisons of obstetric outcome between both the groups.

| Obstetrical outcome | Case (*n*-100) | Control (*n*-100) | *P* value |
|---|---|---|---|
| Preterm birth | 24% | 28% | 0.62 |
| Birth weight (g) | 2.74 | 2.64 | |
| Intrauterine fetal death | 02% | 00 | |
| Induced labor | 62% | 19% | <0.001 |
| Mode of delivery, *n* (%) | | | |
| Vaginal delivery | 63% | 74% | |
| Forceps delivery | 03% | 02% | |
| Elective cesarean | 12% | 00 | |
| Emergency cesarean | 22% | 24% | 0.350 |
| Meconium stained liquor | 09% | 09% | |
| Fetal distress | 14% | 05% | |
| Perinatal outcome | | | |
| Respiratory distress | 00 | 00 | |
| Jaundice | 01% | 07% | 0.033 |
| NICU admission | 02% | 03% | |

explained by the beneficial effect of UDCA treatment which is also supported in a meta-analysis by Kong *et al*.[17] Although, preterm birth was reported in 4/21, 19.0% of cases with severely raised bile acids (≥100 μmol/L) even on treatment by Brouwers *et al*.[16] However, majority (84%) of preterm birth in this entity were reported to be of iatrogenic in origin.[18] Therefore, it is difficult to say bile acids as a sole precursor of spontaneous preterm labor as most of the study included patients with IHCP only, whereas we included general population as a control and found similar rate of preterm labor in both the groups.[16-18]

There is no well-defined suggested mechanism to correlate raised bile acids with the risk of meconium-stained liquor; stimulation of colonic motility and fetal distress is the proposed theory to link with meconium-stained amniotic fluid in cholestasis of pregnancy. There was no significant difference found in incidence of meconium-stained liquor between both the groups in the present study whereas Kong *et al*.[17]also did not find any beneficial effect of UDCA treatment on meconium-stained liquor similar to Brouwers *et al*.[16] who have reported higher incidence of meconium stained liquor (10/21, 47.6%) in severely raised bile acids (≥100 μmol/l) even on UDCA treatment. Insignificant difference in meconium aspiration syndrome in our study may be due to timely delivery in all patients and large percentage of patients who took UDCA treatment.

There is a risk of intrauterine fetal demise probably due to sudden fetal arrhythmia and spasm of chorionic surface vessels. In the present study, intrauterine fetal demise occurred in two patients who did not received UDCA treatment and had bile acids >40 mmol/l. Surprisingly, Morton and Laurie[15] did not report any still birth in 10 patients with bile acids of >40 mmol/l. Whereas, Kong *et al*.[17] were not successful in determining role of UDCA treatment in prevention of intrauterine fetal death as incidence of intrauterine death was too rare to conduct analysis. Brouwers *et al*.[16] reported perinatal death (2/21, 9.5%) in severely raised bile acids (≥100 μmol/L) and none in mild and moderate IHCP group. Composite of adverse perinatal outcomes was not effectively reduced with the *UDCA* treatment as reported by Chappell *et al*.[19]

In the present study, rate of emergency cesarean section was comparable between both the groups. However, there was a statistically significant difference in induced labor when compared between both the groups (61.6% vs. 18.8%). High incidence of fetal distress in the case group is explained by induced labor associated adverse events as there was no significant difference seen in either meconium-stained liquor or neonatal respiratory distress syndrome in both the groups, that is also explained by timely termination of pregnancy with high standard of antepartum care and immediate decision of cesarean section in the present study which is also supported by Puljic *et al*.[10] However, favorable fetal outcome in terms of decreased in fetal distress and neonatal respiratory distress syndrome, NICU admission has been reported with the use of *UDCA* treatment than with placebo.[17] There were more cases of jaundice in the control group as compared to cases (7% vs. 1%, $P < 0.033$) in the present study which may be explained by therapeutic effect of UDCA in neonatal jaundice.

For accurate diagnosis of pregnancy-induced cholestasis and to differentiate it from other causes of pruritus and raised liver enzymes; raised serum autotaxin activity has been found highly sensitive and specific diagnostic test.[20] Due to non-availability of this test worldwide; it is prudent to consider liver enzymes first for the diagnosis as bile acid test are also costly with limited availability although, it can be used in cases where liver enzymes are normal as revealed by the present study.

Pros of this study is being prospective case–control study, exclusion of all confounding factors leading to raised liver enzymes and bile acids with good sample size. Outcome of fetus is also included in the present study. Limitation of the present study is the need of large sample size and multicentric study to exclude effects of regional and genetic variation in laboratory test such as liver enzyme and total bile acids on fetal outcome.

## 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 non-compliant 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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**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent.

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**Conflicts of interest**

There are no conflicts of interest.

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