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## ORIGINAL RESEARCH

# Intrahepatic Cholestasis of Pregnancy: Prevalence and Feto-maternal Outcome in a Prospective study in a Tertiary care center

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**ABSTRACT**

**Background: Maternal physiology undergoes a number of transient and persistent changes throughout pregnancy. Nearly all maternal tissues change in some way during pregnancy.The prevalence of IHCP varies significantly across all ethnic groups. In the world, 0.2–2% of pregnant women experience it. Increased risks of post-partum haemorrhage, LSCS, severe pruritus with dyslipidemia, altered coagulation profile, and premature prelabour rupture of membrane are some of the complications associated to IHCP, so this study was conducted with an aim to assess the incidence of intra hepatic cholestasis among pregnant women and to assess the feto-maternal outcome pregnancy complicated by intra hepatic cholestasis.**

**Methods: After receiving approval from the research and ethical committee of the institute, this hospital-based prospective study was carried out among pregnant women with a diagnosis of intra hepatic cholestasis who were recruited over a period of 2 years in the department of Obstetrics and Gynaecology. A complete hemogram, liver function tests (total and conjugated serum bilirubin), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), serum bile acids, urine routine, and microscopy test were performed on all patients. Ursodeoxycholic acid (UDCA) 10-15 mg/kg/day, with a maximum dose of 300 mg 8 hours a day, was indicated for oral administration to all confirmed patients of IHCP.**

**Results: The incidence of Intra Hepatic cholestasis among pregnant women was 3.88%.The mean age of pregnant women was 27.11±5.82 years. Around two third of pregnant women (69.0%) were diagnosed with Intra Hepatic cholestasis between 33-36 weeks of gestational age.Three fourth of the pregnant women with Intra Hepatic cholestasis had deranged total bilirubin (76.8%), Aspartate Aminotransferase (79.8%), and Alanine Aminotransferase (73.2%).The Pre-eclampsia and Postpartum haemorrhage were observed as complications among 22.0% and 14.3% of pregnant women with Intra Hepatic cholestasis respectively. The Apgar score at 1 minute and at 5 minutes was <7 in 12.5% and 8.3% of neonates born to pregnant women with Intra Hepatic cholestasis respectively.**

**Conclusion: Hepatic dysfunction in pregnancy is typically caused by intrahepatic cholestasis. In terms of higher incidence of lower segment caesarean sections and discomfort from pruritus, maternal morbidity has increased.**

**Keywords: Pregnancy, Intrahepatic cholestasis, preeclampsia, liver function test, low birth weight**

## INTRODUCTION

Maternal physiology undergoes a number of transient and persistent changes throughout pregnancy. Nearly all maternal tissues change in some way during pregnancy. Moreover, the hepatobiliary system experiences a number of alterations that can be seen clinically and biochemically. One such liver condition that is specific to pregnancy is intrahepatic cholestasis of pregnancy (IHCP) [1, 2, 3].

The prevalence of IHCP varies significantly across all ethnic groups. In the world, 0.2–2% of pregnant women experience it. Comparing Asian women to European women, IHCP instances are almost two times as common in Asia. Indigenous women from Chile and Bolivia had the highest rate of IHCP (4%) [4,5].

Increased risks of post-partum haemorrhage, LSCS, severe pruritus with dyslipidemia, altered coagulation profile, and premature prelabour rupture of membrane are some of the complications associated to IHCP. IHCP is linked to a higher risk of adverse perinatal outcomes, including stillbirth, meconium-stained amniotic fluid, and spontaneous preterm birth [6,7,8].

Due to this wide variation in incidence and feto-maternal outcomes among different ethnic groups of several countries, so this study was conducted with an aim to assess the incidence of intra hepatic cholestasis among pregnant women and to assess the feto-maternal outcome in pregnancy complicated by intra hepatic cholestasis.

## MATERIALS AND METHODS

After receiving approval from the research and ethical committee of the institute, this hospital-based prospective study was carried out among pregnant women with a diagnosis of intra hepatic cholestasis who were recruited over a period of 2 years from September 2020 to August 2022 in the department of Obstetrics and Gynaecology with the collaboration of the department of Paediatrics and Biochemistry. Informed consent was obtained from all participants before enrolling into the study.

A complete hemogram, liver function tests (total and conjugated serum bilirubin), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), serum bile acids, urine routine and microscopy test were performed on all patients. Bile acids were only tested once during the initial visit, although the other liver function tests were repeated three times; a difference in the levels of liver enzymes between the first and third testing weeks was also noted. To rule out any other pathology, all patients underwent hepatobiliary system and pancreatic ultrasonography as well as viral markers testing (HBsAg). Where necessary, dermatology consultations were also obtained. Pregnant women with itchiness and abnormal serum bile acids (and elevated transaminases) were diagnosed with Intra Hepatic cholestasis of pregnancy .

Ursodeoxycholic acid (UDCA) 10-15 mg/kg/day, with a maximum dose of 300 mg 8 hours a day, was indicated for oral administration to all confirmed patients of IHCP. In confirmed cases, foetal surveillance was carried out with a weekly biophysical profile till birth. Except for individuals who were induced or went into labour spontaneously before this gestation, all pregnancies were terminated electively between 37 and 38 weeks. Furthermore, observed were the occurrence of meconium-stained liquor, preterm births, the mode of delivery, and any complications during labour or delivery. Neonatal jaundice and foetal outcomes like the Apgar score and requirement for intensive care were also noted. Liver function tests were performed on all women up to 6–8 weeks after giving birth. To determine the prevalence of disease, the total number of deliveries during that time period were also recorded. The

collected data was entered in the MS excel sheet. The variables were presented as frequency and percentages.

## RESULTS

In our study, during the defined period 168 pregnant women were diagnosed with Intra Hepatic cholestasis. Also, during that period of a total of 4319 deliveries were conducted in the department of Obstetrics and Gynaecology. So, the incidence of Intra Hepatic cholestasis among pregnant women was 3.88%.As the itching was diagnostic for the Intra Hepatic cholestasis, so all pregnant women presented with the itching symptom and raised bile acid levels (>4.08 μg/mL). Among the 20.4% (34/168) of pregnant women the jaundice was present when they were diagnosed with Intra Hepatic cholestasis (Table 1). The mean age of pregnant women was 27.11±5.82 years. Around two third of pregnant women (69.0%) were diagnosed with Intra Hepatic cholestasis between 33-36 weeks of gestational age. Only 4.8% and 5.4% of pregnant women were diagnosed with Intra Hepatic cholestasis at <28 weeks and >36 weeks of pregnancy respectively.

**Table 1: Baseline characteristics of the pregnant women with Intra Hepatic cholestasis**

| Variables | Frequency | % |
|---|---|---|
| **Age group (in years)** | | |
| <26 | 59 | 35.1 |
| 26-30 | 65 | 38.7 |
| 31-35 | 35 | 20.8 |
| >35 | 9 | 5.4 |
| **Age (in years) [mean±SD]** | 27.11±5.82 | |
| **Gravida** | | |
| 1 (primigravida) | 68 | 40.5 |
| >1 (multigravida) | 100 | 59.5 |
| **Gestational age at onset of symptoms** | | |
| <28 weeks | 8 | 4.8 |
| 28-32 weeks | 35 | 20.8 |
| 33-36 weeks | 116 | 69.0 |
| >36 weeks | 9 | 5.4 |

The laboratory investigation was carried among pregnant women at the time they were diagnosed with Intra Hepatic cholestasis and it was found that in around three fourth of the pregnant women with Intra Hepatic cholestasis have deranged total bilirubin (76.8%), Aspartate Aminotransferase (79.8%), and Alanine Aminotransferase (73.2%). Alkaline phosphatase was deranged in 44.6% of pregnant women. 3.0% of pregnant women were having HBsAg positive and blood glucose (hypoglycaemia) was seen in 10.1% of pregnant women with Intra Hepatic cholestasis (Table 2).

**Table 2: Laboratory investigations of the pregnant women with Intra Hepatic cholestasis**

| Variables | Frequency | % |
|---|---|---|
| **Liver function test** | | |
| **Total bilirubin (mg/dL)** | | |
| Deranged | 129 | 76.8 |
| Within normal limit | 39 | 23.2 |
| **Aspartate Aminotransferase (U/L)** | | |
| Deranged | 134 | 79.8 |
| Within normal limit | 34 | 20.2 |

| | | |
|---|---|---|
| **Alanine Aminotransferase (U/L)** | | |
| Deranged | 123 | 73.2 |
| Within normal limit | 45 | 26.8 |
| **Alkaline phosphatase (U/L)** | | |
| Deranged | 75 | 44.6 |
| Within normal limit | 93 | 55.4 |
| **Coagulation profile** | | |
| Deranged | 12 | 7.1 |
| Within normal limit | 156 | 92.9 |
| **Seropositive for Hepatitis B (HBsAg)** | | |
| Yes | 5 | 3.0 |
| No | 163 | 97.0 |
| **Blood glucose (mg/dL)** | | |
| Deranged | 17 | 10.1 |
| Within normal limit | 151 | 89.9 |

The pregnant women with Intra Hepatic cholestasis were followed till the perinatal period for the maternal outcome. In our study the mode of delivery in 73.2% of pregnant women was lower segment caesarean section (LSCS). The delivery was term in 84.5% of pregnant women and it was post-term in 4.2% of pregnant women. The mean gestational age of pregnant at the time of delivery was 37.26±3.98 weeks. The Pre-eclampsia and Postpartum haemorrhage were observed as complications among 22.0% and 14.3% of pregnant women with Intra Hepatic cholestasis respectively (Table 3).

**Table 3: Maternal outcome among pregnant women with Intra Hepatic cholestasis**

| Maternal outcome | Frequency | % |
|---|---|---|
| **Mode of delivery** | | |
| Vaginal delivery | 45 | 26.8 |
| Lower segment caesarean section | 123 | 73.2 |
| **Mode of labour in vaginal delivery (n=45)** | | |
| Induced at preterm | 14 | 44.4 |
| Induced at term | 17 | 37.8 |
| Spontaneous | 14 | 44.4 |
| **Gestational age at delivery** | | |
| Preterm (<37 weeks) | 20 | 11.9 |
| Term (37-41 weeks) | 142 | 84.5 |
| Post term (>41 weeks) | 7 | 4.2 |
| **Gestational age (in weeks) [mean±SD]** | 37.26±3.98 | |
| **Complications** | | |
| Pre-eclampsia | 37 | 22.0 |
| Postpartum haemorrhage | 24 | 14.3 |

The pregnant women with Intra Hepatic cholestasis were followed till the perinatal period for the foetal outcome. Among 37.5% of pregnant women the meconium-stained liquor was noticed. The Apgar score at 1 minute and at 5 minutes was <7 in 12.5% and 8.3% of neonates born to pregnant women with Intra Hepatic cholestasis respectively. Also, deranged total bilirubin was observed in 3.0% of neonates. NICU admission was indicated in 42.9% of neonates and mean NICU stay for neonates was 11.24±4.83 days (Table 4).

**Table 4: Perinatal outcome among pregnant women with Intra Hepatic cholestasis**

| Perinatal outcome | Frequency | % |
|---|---|---|
| **Meconium-stained liquor** | | |
| Yes | 63 | 37.5 |
| No | 105 | 62.5 |
| **Apgar score at 1 minute** | | |
| <7 | 21 | 12.5 |
| 7 or more | 147 | 87.5 |
| **Apgar score at 5 minutes** | | |
| <7 | 14 | 8.3 |
| 7 or more | 154 | 91.7 |
| **Low birth baby (<2500 grams)** | | |
| Yes | 53 | 31.5 |
| No | 115 | 68.5 |
| **Total Bilirubin (mg/dL)** | | |
| Deranged | 5 | 3.0 |
| Within normal limit | 163 | 97.0 |
| **NICU admission** | | |
| Yes | 72 | 42.9 |
| No | 96 | 57.1 |
| **NICU stay (in days) [mean±SD]** | 11.24±4.83 | |

## DISCUSSION

Intrahepatic cholestasis is a pregnancy-induced illness with a variable prevalence of 0.2-2% and as high as 20-22% in multiple pregnancies [9,10]. Although there is no known cause of IHCP, its occurrence has been observed to vary due to population differences that are vulnerable to genetic predisposition, environmental factors, and an increase in the synthesis of sex hormones (oestrogen and progesterone).

In our study, during the defined period 168 pregnant women were diagnosed with Intra Hepatic cholestasis. As the itching was one the diagnostic criteria for the Intra Hepatic cholestasis, so all pregnant women presented with the itching symptom. The mean age of pregnant women was 27.11±5.82 years. According to Shukla et al., there is no significant correlation between maternal age and IHCP [11].

According to the current study, primigravidae and multigravidae had an incidence of IHCP of about 40.5% and 59.5%, respectively. Pillarisetty et al., found an elevated risk of IHCP in a multifetal pregnancy but no association between IHCP and multigravida in their study [12].

The most effective pharmaceutical for the treatment of IHCP is ursodeoxycholic acid, which also lowers bile acid levels in the blood and prevents unfavourable perinatal outcomes [13]. In the current study, 94.6% of IHCP patients received ursodeoxycholic acid, and 5.4% of the remaining patients underwent pregnancy termination since their symptoms persisted after 37 weeks of gestation.

At 33–36 weeks of pregnancy, about 69.0% of pregnant women had an IHCP diagnosis. Preterm births occurred in 11.9% of pregnant women in the current study, compared to a nationwide preterm birth incidence of 8–12% [11].

In our study, lower segment caesarean sections were employed for delivery in 73.2% of pregnant women (LSCS). The choice to do emergency LSCS, which was also supported by Puljic et al., was taken in order to offer standard antenatal care and to minimize adverse perinatal outcomes in about 37.5% of pregnant patients with meconium-stained liquid [6].

Due to concurrent medical disorders such preeclampsia and uncontrolled gestational diabetes mellitus, 44.4% and 37.8%, pregnant women who delivered vaginally (n=45) needed to be induced at preterm and term, respectively. The myometrium's enhanced expression and sensitivity of oxytocin receptors is assumed to be the cause of the nearly 13.3% (6/45) pregnant women who experienced spontaneous preterm labour [14].

Among these, 11.9% of pregnant women with IHCP had a termination of pregnancy with a gestation period of less than 37 weeks, and only 0.5% (n=1) experienced a termination of pregnancy with a gestation period of lesser than 32 weeks. Deranged serum bile acid was the cause of the induction of labour at or before 37 weeks of POG. The unfavourable perinatal outcome can be avoided, according to the Royal College of Obstetricians and Gynaecologists, by having clinicians and women with ICP discuss the pros and risks of inducing labour after 37 weeks of pregnancy [15].

In our study, 31.5% of newborns had low birth weights, which can be explained by iatrogenic labour inducement for IHCP patients and spontaneous preterm labour to avoid unfavourable perinatal outcomes. Studies by Li et al., and Posh et al., revealed a similar outcome where 40% of infants had a birth weight less than 2500 gms [16, 17].

The study conducted by Brouwers et al., supports the observation that the pregnancy complicated by IHCP affects the fetomaternal outcome in terms of the gestational age at the time of pregnancy termination, meconium-stained liquor, foetal distress, low Apgar score, low birth weight, and NICU admission [18].

## CONCLUSION

Hepatic dysfunction in pregnancy is typically caused by intrahepatic cholestasis. In terms of higher incidence of lower segment caesarean sections and discomfort from pruritus, maternal morbidity has increased. Maternal cholestasis is transient and resolves after birth. Adverse perinatal outcomes are linked to intrahepatic cholestasis. According to this study, there is an increased chance of premature delivery and meconium stained liqour. Ursodeoxycholic acid is recommended for pregnant women whose symptoms and liver enzyme/bile acid levels improve, although early induction is recommended in situations of severe itching and persistently elevated levels in order to improve the foetal prognosis.

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