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AN OBSERVATIONAL STUDY OF PREGNANCY OUTCOMES IN PATIENTS WITH INTRAHEPATIC CHOLESTASIS OF PREGNANCY

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ABSTRACT

Background: Obstetric cholestasis, also known as intrahepatic cholestasis of pregnancy, is a hepatic disease unique to pregnancy which presents with intense generalized pruritus without any skin rash. The pathophysiology of intrahepatic cholestasis is poorly understood, but it is believed to be multifactorial. **Aim and Objectives:** To study the maternal and neonatal outcome in pregnancy complicated by IHCP Materials and **Methods: Study Design:** A prospective observational study. **Study Area:** Department of Obstetrics and Gynaecology, M R Bangur Hospital, Kolkata. **Study period:** Jan 2020 to June 2021(18 months). **Study population:** All pregnant patients ≥ 20 weeks gestation having symptoms suggestive of Intrahepatic cholestasis of pregnancy attending Gynaecology OPD and indoor patients delivering in MR Bangur Hospital. **Sample size:** 137 patients **Results:** Premature rupture of membrane was observed in 11% of women. Preterm labour was observed in 9% of women. Postpartum haemorrhage was observed in 14% of women. Number of IUD, still birth and live birth cases were 5 (4%), 3 (2%) and 129 (94%) respectively. Meconium stain was present in 31% newborns, fetal distress in 29% and low birth weight in 14%. NICU admission was required in 33% newborns. **Conclusion:** Cholestasis in pregnancy is a dreaded yet an unavoidable condition in several women in their pregnancy and majority present with pruritus. It has been related to fetal distress in newborns and adverse pregnancy outcomes. SGPT and SGOT levels decrease significantly after delivery following ursodeoxycholic acid treatment with resolution of pruritus.

KEYWORDS : IHCP – Intra-hepatic Cholestasis of Pregnancy, UDCA-Ursodeoxycholic acid.

INTRODUCTION

Cholestasis refers to impairment in formation or excretion of bile. This can be due to defects in intrahepatic production of bile, defects in the transmembrane transport of bile, or mechanical obstruction to bile flow. Intrahepatic cholestasis of pregnancy (IHCP) is the most common cholestatic liver disease during pregnancy[1].

Clinical features of cholestasis reflect the retention of components of bile (bilirubin, bile acids, cholesterol) in the body[2]. Cholestatic jaundice can thus be classified into intrahepatic or extrahepatic cholestasis, depending upon the level of obstruction to bile flow. Intrahepatic cholestasis or functional cholestasis can be due to a disease involving the liver parenchymal cells and/or the intrahepatic bile ducts. Extrahepatic cholestasis or obstructive cholestasis is due to excretory block outside of the liver, along with the extrahepatic bile ducts[3].

Bile acids are physiological detergents that generate bile flow and facilitate intestinal absorption and transport of lipids, nutrients, and vitamins. The enterohepatic circulation of bile acids exerts important physiological functions not only in feedback inhibition of bile acid synthesis but also in control of whole-body lipid homeostasis[4].

Intrahepatic cholestasis of pregnancy affects 0.1–2% of pregnant women[5]. It is characterized by maternal pruritus, and elevated serum transaminases and bile acids. Intrahepatic cholestasis of pregnancy (IHCP) is a disorder of liver function, commonly occurring in the third trimester but sometimes also as soon as the end of the second trimester of pregnancy[6].

The etiology of obstetric cholestasis is undoubtedly multifactorial, with genetic, environmental, and hormonal factors having important roles[7]. The increase in estrogen levels occurring during twin pregnancies (TP) is associated with a greater risk of developing intrahepatic cholestasis of pregnancy (IHCP)[8]. Assisted reproductive technique (ART) treatment increases the risk of adverse maternal complications of IHCP[9]. IHCP is more common in women with pre pregnancy hepatitis C, chronic hepatitis and gallstone disease[10]. Some drugs may be associated with this condition e.g. – Clavulanic acid, Erythromycin, Fluconazole or herbal medicines[11]. Environmental and seasonal factors have also correlated with IHCP. IHCP is noted to be more prevalent in women with a low level of selenium and vitamin D. It is also common in some countries in winters when selenium and vitamin D may be low[1].

The most common presenting symptom of IHCP is pruritus that usually presents in the third trimester. This becomes progressively more severe as the pregnancy advances and typically resolves within 48 hours of delivery. Many women report that their pruritus worsens at night and may become so extreme that it causes insomnia. Approximately 80% of affected women present after 30 weeks of gestation, but IHCP has been reported as early as 8 weeks[11]. There have been some reports of the co-existence of IHCP with other pregnancy-related disorders including pre-eclampsia, acute fatty liver of pregnancy, and gestational diabetes.

IHCP is associated with adverse fetal outcomes. The risk of meconium-stained liquor, fetal asphyxia and spontaneous preterm delivery is greater in these patients. The condition is also associated with IUD.

The most effective pharmacological therapy for improvement of maternal symptoms and biochemical abnormalities is UDCA, and this has also been shown to reduce placental

abnormalities and to improve placental bile acid transport in in vitro studies[12]. Managing these patients is of paramount importance to reduce the feto- maternal morbidity and mortality. They should be delivered either by Induction or by Caesarean Section between 37 and 38 weeks as per current recommendation[13].

The present study has been conducted to study the incidence of intrahepatic cholestasis of pregnancy, biochemical changes in these patients and the maternal and neonatal outcome.

AIM

To study pregnancy outcome in patient with intrahepatic cholestasis of pregnancy.

OBJECTIVES

Primary Objective:

To study the maternal and neonatal outcome in pregnancy complicated by IHCP

Secondary Objective:

1) To study incidence of intrahepatic cholestasis in pregnancy.
2) To study the biochemical changes in patients with IHCP.

MATERIALS & METHODS

Study Design: A prospective observational study. Study Area: Department of Obstetrics and Gynaecology, M R Bangur Hospital, Kolkata.

Study period: Jan 2020 to June 2021 (18 months).

Study population: All pregnant patients ≥ 20 weeks gestation having symptoms suggestive of Intrahepatic cholestasis of pregnancy attending Gynaecology OPD and indoor patients delivering in MR Bangur Hospital.

Sample size: 137 patients

Inclusion criteria:

Pregnant ladies with pruritus due to IHCP (not due to other causes) developing after 20 weeks of gestation.

Exclusion criteria:

1) Pregnant ladies <20 weeks period of gestation.
2) Pregnant ladies with skin disease with itching.
3) Pregnancy with acute or chronic liver disease (Infective hepatitis).
4) Other dermatological causes of pruritus.
5) Those who didn't come for regular follow-up.
6) Those who didn't give consent for the study.

Diagnostic criteria:

The diagnosis of IHCP is based on-

(i) pruritus without skin lesion.
(ii) elevated serum transaminases (SGPT 40 U/L or SGOT 35 U/L).
(iii) spontaneous relief of signs and symptoms (e.g. pruritus and jaundice) within two to three weeks after delivery.
(iv) absence of other dermatological or medical causes of pruritus.

Laboratory investigations:

As serum bile acid concentration could not be performed because of the non- availability of the test in this hospital, diagnosis of IHCP was done by exclusion by symptoms and by performing-

1) Liver function test (SGOT, SGPT and Alkaline phosphatase)
2) Viral markers (HBsAg, HCV, HAV, HEV)

Outcome and parameters studied:

Maternal outcome:

1) Presentation of pruritus.
2) Response of symptom- with medication.
3) SGPT & SGOT before and after treatment.
4) Mode and type of delivery.
5) Pre-term labour.
6) Premature rupture of membrane.
7) Post-partum haemorrhage.

Fetal outcome:

1) Meconium-stained liquor.
2) Fetal distress.
3) Live born / still born / IUD.
4) Low birth weight.
5) APGAR score at 5 minutes.
6) NICU admission.

Methodology:

Scientific and Ethical committee approval was obtained prior to this study. The purpose of study and the procedures were explained to the patients. Written consent was obtained by signature or thumb print. Detailed general physical and systemic examination were done. Investigations were carried out are liver function tests (Total bilirubin, SGPT, SGOT) and serology for Hepatitis B surface antigen (HBsAg), Anti-hepatitis-C viral antibodies, and anti-hepatitis-A viral(HAV) antibodies and anti-hepatitis-E viral(HEV) antibodies. The patients were treated in OPD (outpatient department) with tab Ursodeoxycholic acid(10–20 mg/kg/day) if needed during antenatal period. Patients having signs of IUGR, oligohydramnios or with adverse USG findings were admitted in this hospital, followed up and treated accordingly. Uncomplicated cases of IHCP were terminated at 37 completed weeks either by cervical ripening with Cerviprime or by Oxytocin induction as per Bishop's score. Patients with Bishop's score <6 was primed with cerviprime before induction with pitocin. All the patients were monitored during intrapartum for feto-maternal outcome and post- partum period till 6 weeks after delivery to confirm resolution of clinical and laboratory parameters. Maternal and fetal data were recorded and tabulated thereby for each case.

Statistical Analysis:

1) For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5.
2) Chi-square test was used to test the association of different study variables.
3) Z-test (Standard Normal Deviate) was used to test the significant difference between two proportions.
4) Numerical data was expressed as mean ± standard deviation, and categorical data was expressed as relative frequency and percentage.
5) A p-value ≤ 0.05 was considered statistically significant.

RESULTS AND ANALYSIS

During the study period, total 7640 pregnant women with pruritus were screened for intrahepatic cholestatic jaundice, out of which 191(2.5%) was diagnosed as IHCP based on the diagnosis criteria. Among the 191 cases of IHCP, first 137 women were included in the study based on inclusion and exclusion criteria.

Mean age of study population was 26.00±4.21 years (minimum 19 years, maximum 36 years).

Parity 1 patients were most common (n=97, 71%), followed by parity 2 (n=40, 29%).

Mean gestational age at the time of diagnosis of IHCP was 34.39 ±2.14 weeks. 36th week was the most common (19.71%) gestational age.

History of OCP intake was present in 37(27%) of cases.
Sole was the most common (n=69, 50%) site of itching. Other sites were palm(n=30, 22%), abdomen (n=24, 18%), both palm and sole(n=13, 9%) and whole body(n=1, 1%).

32nd week was the most common (21.17%) gestational age at

which itching started.

Mean total serum bilirubin level in the study population was 0.764 ± 0.237 mg/dl.

Mean SGOT level at the time of diagnosis was 235.9±55.9 while mean SGOT after treatment was 142.6±98.2. Mean SGOT level has significantly decreased after delivery following UDCA treatment (p-value <0.001).

Mean SGPT level at the time of diagnosis was 288.8±57.3 while mean SGPT after treatment was 137.0±93.2. Mean SGPT level has significantly decreased after delivery following treatment (p-value <0.001).

With treatment improvement of pruritus was seen in 111(81%) women, while there was no improvement in 26(19%).

Vaginal delivery was done in 103(75%) and LSCS was done in 34(25%) cases.

Spontaneous labour was seen in 69(50.36%) cases, induction of labour was needed in 41(29.93%), LUCS was done in 27(19.71%) cases.

Preterm labour was observed in 12(9%) women. Premature rupture of membrane was observed in 14(11%) women. Postpartum haemorrhage was observed in 19(14%) women.

Number of IUD, still birth and live birth cases were 5(4%), 3(2%) and 129(94%) respectively.

Meconium stain was present in 42(31%) newborns.

APGAR score was 0 in still birth (n=3). For 5 IUD cases APGAR score was not applicable. For 129 live birth cases mean APGAR score (5 min) was 8.41±1.83. Low APGAR score (<7) was founded in 30(23.26%) newborns.

Fetal distress was present in 37(29%) newborns.
18(14%) newborns had low birth weight.
NICU admission was required in 42(33%) newborns.

DISCUSSION

During the study period, total 7640 pregnant women with pruritus were screened for intrahepatic cholestatic jaundice, out of which 191 (2.5%) was diagnosed as IHCP.

In our study, mean age of study population was 26.00 years. In Hak et al[14] and Alakananda et al[15] study, the mean age of study population was 25.79 and 25.98 years respectively.

In our study, 71% patients were primiparous and 29% patients were multiparous. This is similar to Hak et al[14] study(62.67% primiparous and 37.33% multiparous) and Alakananda et al[15] study(62% primiparous and 38% multiparous), with primiparous being more common.

In our study population, mean gestational age at the time of diagnosis of IHCP was 34.39 weeks. Similarly, Alakananda et al[15] observed mean gestational age of 33.32 weeks.

In our study, history of OCP intake was present in 27% of cases. Pegu et al[16] observed that 32.16% of IHCP women had history of OCP intake.

In our study, sole was the most common (50%) site of itching. Similarly, Alakananda et al[15] observed that most common (47%) site of itching was palms and soles.

In our study, mean total serum bilirubin level in the study population was 0.764 ± 0.237 mg/dl. In Alakananda et al[15] and Pegu et al[16] study, the mean total serum bilirubin level was 0.632 and 0.82 respectively.

In our study, with treatment improvement of pruritus was seen in 81% of women. Similarly, Alakananda et al[15] observed improvement of symptoms in 89.02% of women after treatment with UDCA.

In our study significant reduction in SGOT level was seen in patients before(235.9) and after (142.9) treatment within UDCA. Similarly, Arora et al[17] found significant reduction in SGOT level in week 1(176.01) and week 3(111.2) of initiating UDCA treatment.

In our study significant reduction in SGPT level was seen in patients before(228.8) and after (137.0). Similarly Arora et al[17] found significant reduction in SGPT level in week 1(208.3) and week 3(138.3) of initiating treatment.

In our study, vaginal delivery was done in 75% and LSCS was done in 25% cases. In Hak et al[14] study, vaginal delivery was done in 57.33% and LSCS was done in 42.67% cases.

In our study, spontaneous labour was seen in 50.36%, induction of labour was needed in 29.93% cases, LUCS was done in 19.71%. In Hak et al[14] study, spontaneous labour was seen in 50.67%, induction of labour was needed in 39.33% cases and LUCS was done in 38.67%.

In our study, preterm labour was observed in 9% of women, premature rupture of membrane was observed in 11% of women and postpartum haemorrhage was observed in 14% of women. In Hak et al[14] study, preterm labour was observed in 10% of women, premature rupture of membrane was observed in 2% of women and postpartum haemorrhage was observed in 7.33% of women.

In our study, percentage of IUD, still birth and live birth cases were 4%, 2% and 94% respectively. Hak et al[14] observed IUD, still birth and live birth cases in 2.67%, 0.67%, and 96.66% of cases.

In our study, meconium stain was present in 31% of newborns. Alakananda et al[15] observed meconium stain in 29% newborns.

In our study, fetal distress was present in 29% of newborns. Hak et al[14] observed fetal distress in 6% of newborns.

In our study, low birth weight was present in 14% of newborns. Hak et al[14] observed low birth weight in 10% of newborns.

In our study, NICU admission was required in 33% of newborns. Alakananda et al[15] observed NICU admission in 21% of newborns respectively.

CONCLUSION

Obstetric cholestasis, also known as intrahepatic cholestasis of pregnancy, is a hepatic disease unique to pregnancy which presents with intense generalized pruritus without any skin rash. It is a temporary condition caused by maternal liver dysfunction during pregnancy and blood tests reveal increased levels of the liver enzymes. The pathophysiology of intrahepatic cholestasis is poorly understood, but it is believed to be multifactorial with genetic, environmental or hormonal factors being involved. They have an increased risk for postpartum haemorrhage, dyslipidaemia, preterm labour and operative interference. Adverse fetal outcomes associated with the conditions include preterm labour, preterm prelabour rupture of membrane, fetal distress, abnormal CTG, meconium staining, spontaneous intrauterine death. SGPT and SGOT levels decrease significantly after delivery following ursodeoxycholic acid treatment with resolution of the pruritus.

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