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Original Research Article

Perinatal outcomes and intrahepatic cholestasis of pregnancy: a prospective study

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ABSTRACT

Background: Women with intrahepatic cholestasis of pregnancy (ICP) have an increased risk for postpartum haemorrhage, dyslipidaemia, preterm labour and operative interference. Fetus in ICP has been associated with an increased incidence of preterm labour, preterm prelabour rupture of membrane, fetal distress, abnormal CTG, meconium staining, spontaneous intrauterine death. The present study was done to evaluate the perinatal outcomes – maternal outcomes and fetal outcomes of ICP.

Methods: This was a prospective observational study carried out in a tertiary care teaching hospital. Total 1100 pregnant women were screened during the study period. Patients with ICP were identified in maternity care units after eliciting history about itching. Pregnancies with pregnancy induced hypertension and other liver diseases in pregnancy were excluded.

Results: 62 pregnant women with prevalence rate of 5.64% have been found to be suffering from ICP. The most frequently affected (22, 35.48%) age-group with ICP were belong to age > 35 years. A majority of pregnant women with intrahepatic cholestasis of pregnancy was of multipara. ICP was highly significantly associated with small for gestational age (SGA, p-value: 0.0003); abnormal cardiotocography (CTG, p-value: 0.0002); and meconium stained liquor (p-value: 0.0001). Caesarean section as mode of delivery found significantly associated (p-value: 0.0033) with ICP. Insomnia (p-value: 0.0045); dyslipidemia (p-value: 0.0011); and postpartum haemorrhage (p-value: 0.0122) were also found significantly with ICP.

Conclusions: ICP can adversely affect fetal as well as maternal pregnancy outcomes. Maternal outcomes have good prognosis, but fetal outcomes can be improved by timely and effective intervention.

Keywords: Adverse perinatal outcomes, Fetal outcomes, Intrahepatic cholestasis of pregnancy, Maternal outcomes

INTRODUCTION

The liver is one of the many organs affected by the physiological and hormonal changes that occur during pregnancy.[1] Hepatic disorders diagnosed before pregnancy may be unaffected or exacerbated by the pregnant state.[2] Liver disorders like intrahepatic cholestasis of pregnancy (ICP), toxaemias, HELLP syndrome may have a profound impact on the morbidity and mortality rates of the mother and fetus.[3] Although an equivocal diagnosis is often difficult to make, it should be attempted in a timely manner so that optimal treatment can be determined.[3] Intrahepatic cholestasis of pregnancy (ICP) is a cholestatic syndrome characterized by:

- Pruritus with onset in the second or third trimester of pregnancy.
- Elevated serum aminotransferases and bile acid levels.
- Spontaneous relief of signs and symptoms within two to three weeks after delivery.[4]

The syndrome of ICP, the most frequent of liver disorders specific to pregnancy, was recognized by Ahlfeld in 1883 as maternal pruritus and jaundice in the last trimester of pregnancy disappearing after delivery.[5] The most comprehensive studies of modern era initially were performed in Scandinavian women in 1950s by Svanborg and Thorling.[6-8]

Reported incidence rates may vary with geographic location and race.[8] Highest incidence rates of 12-20% are in Chile and rest include 9% in Bolivia, 2%-3% in Sweden 0.2%-0.8% in Australia, 0.2% in France, 0.13% in china and 0.1% in Canada.[9-11] The incidence of ICP among Indian women has been reported to be around 1%.[12,13] The exact cause of ICP is not known but genetic, hormonal and exogenous factors do play a role.[14]

Pruritus with or without jaundice, is a hall mark feature and involves palms, soles, extremities and trunk but spares mucous membranes.[8,10,11] Pruritus persists with fluctuating severity till delivery and disappears after parturition.[10,11]

ICP is second only to viral hepatitis as a cause of jaundice during pregnancy and accounts for 20% of cases.[15] Whenever jaundice occurs, it generally follows onset of pruritus by 2-4 weeks and usually resolves by 1-4 weeks post- partum.[16] Typical features of obstructive jaundice, including pale stools and dark urine, accompany jaundice, but the patients feel generally well in contrast to viral hepatitis.[17,18]

ICP is associated with significant maternal morbidities. Women with ICP have an increased risk for postpartum haemorrhage, dyslipidaemia, preterm labour and operative interference.[19,20] Fetus in ICP has been associated with an increased incidence of preterm labour, preterm prelabour rupture of membrane, fetal distress, abnormal CTG, meconium staining, spontaneous intrauterine death.[19-22]

The present study was done to evaluate the perinatal outcomes, maternal outcomes and fetal outcomes, of intrahepatic cholestasis in an Indian population.

METHODS

This was a prospective observational study, carried out to analyse the impact of intrahepatic cholestasis of pregnancy on the maternal and fetal outcome. The study was conducted in Department of Obstetrics and Gynaecology, Sri Maharaja Gulab Singh (SMGS) Hospital, Jammu and Gastroenterology section of Department of Medicine, Govt. Medical College, Jammu between July 2010 to June 2012.

The study was approved by Institutional Ethics Committee. Written informed consent was obtained from patient before enrolling them into the study.

Total 1100 pregnant women were screened during the study period. Patients with ICP were identified in maternity care units after eliciting history about itching. The diagnosis was based on:

- Clinical examinations, generalized pruritus in the absence of any dermatologic condition.
- Laboratory results, cholestatic pattern: serum aspartate and alanine transferase exceeding 40 U/L; that returned to normal after delivery.
- No signs of viral hepatitis, negative results in assays for hepatitis B surface antigen and anti-hepatitis A and C antibodies.
- Normal ultrasonography of the liver and biliary tract.

To eliminate confounding factors for the present study, pregnancies with pregnancy induced hypertension and other liver diseases in pregnancy were excluded.

The pregnant women with ICP, underwent careful weekly outpatient clinical monitoring. During the visit, the patients were advised Nonstress Test (NST), amniotic fluid (AF) volume assessment using the four-quadrant amniotic fluid index (AFI) and liver function tests (LFT). Extreme elevation of LFT results combined with abnormal fetal heart rate (FHR) or decreased AFI necessitated hospitalization for induction of delivery process. Otherwise, labor was induced routinely at 38–40 weeks' gestation.

Patients' demographic data and pregnancy outcome measures were recorded in case record form. For the present study, following maternal outcomes were studied: insomnia due to severe pruritus; dyslipidemia; abnormal coagulation profile (increase PT); mode of delivery; preterm pre-labour rupture of membrane (PROM); and postpartum hemorrhage.

Abnormal cardiotocography (CTG); Birth weight (low birth weight <2.5kg); small for gestational age (SGA: the bottom tenth percentile for weight according to week of gestation and gender); pre-term delivery (birth before 37 weeks of gestation); meconium stained liquor were assigned as fetal outcomes.

The data was entered in the excel sheet. The data was analyzed using descriptive statistics. The test variables were compared using Chi-square test for qualitative variables and Student's test for quantitative variables. The p-value <0.05 was considered statistically significant for difference and association between variables.

RESULTS

Total 1100 pregnant women were screened during the study period. As per the diagnostic criteria defined criteria for intrahepatic cholestasis of pregnancy (ICP) for the present study, 62 pregnant women have been found to be suffering from ICP. This give the overall prevalence of 5.64% of HG for the present study (Figure 1).

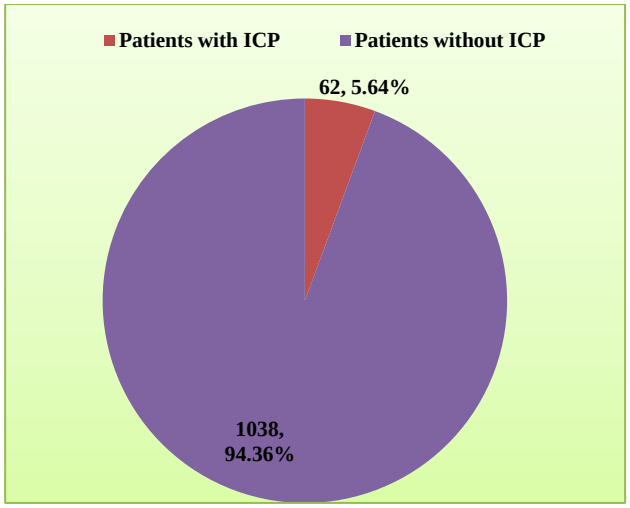

Figure 1: Prevalence of intrahepatic cholestasis of pregnancy (ICP).

According to Table 1, the most frequently affected (22, 35.48%) age-group with ICP were belong to age > 35 years, followed by age groups of 30-34 years (18, 29.03%) and 25-29 years (13, 20.97%). The age group of > 35 years significantly (p-value: 0.0099) associated with development of intrahepatic cholestasis of pregnancy. Around two-third of the pregnant women with ICP were of more than 30 years. A majority of pregnant women with intrahepatic cholestasis of pregnancy was of multipara.

Table 1: Background characteristics of the study participants.

Parameters	Patients with ICP (N=1038)		Patients with ICP (N=62)		p-value
	N	%	N	%	
Maternal age					
< 20 years	12	1.16	1	1.61	0.7464
20-24 years	116	11.18	8	12.90	0.6760
25-29 years	430	41.43	13	20.97	0.0454*
30-34 years	378	36.42	18	29.03	0.2393
> 35 years	102	9.83	22	35.48	0.0099**
Parity					
Primipara	524	50.48	18	29.03	0.0428*
Multipara	576	55.49	44	70.97	
Smoking habit					
Non-smokers	990	95.38	54	87.10	0.0832
Smokers	48	4.62	8	12.90	

ICP: Intrahepatic cholestasis of pregnancy; * p-value < 0.05: significant difference; ** p-value < 0.001: significant difference

The significant association (p-value: 0.0428) has been found between parity and intrahepatic cholestasis of pregnancy. There were no association found between smoking habit with development of intrahepatic cholestasis of pregnancy. Table 2 represent the fetal outcomes of pregnancy. Development of intrahepatic cholestasis of pregnancy was highly significantly associated with small for gestational age (SGA, p-value: 0.0003); abnormal cardiotocography (CTG, p-value: 0.0002); and meconium stained liquor (p-value: 0.0001). There were no association found between pre-term delivery and low birth weight with ICP.

Table 2: Fetal outcomes of pregnancy in study participants.

Fetal outcomes	Patients without ICP (N=1038)		Patients with ICP (N=62)		p-value
	N	%	N	%	
Low birth weight	356	34.30	28	45.16	0.8128
SGA	148	14.26	21	33.87	0.0003*
Pre-term	302	29.09	25	40.32	0.0602
Abnormal CTG	62	5.97	11	17.74	0.0002*
Meconium stained liquor	88	8.48	25	40.32	0.0001*

ICP: Intrahepatic cholestasis of pregnancy; * p-value < 0.001: significant difference

According to Table 3 regarding maternal outcomes of pregnancy, caesarean section as mode of delivery found significantly associated (p-value: 0.0033) with intrahepatic cholestasis of pregnancy. Insomnia (p-value: 0.0045); dyslipidemia (p-value: 0.0011); and postpartum haemorrhage (p-value: 0.0122) were also found significantly with ICP.

Table 3: Maternal outcomes of pregnancy in study participants.

Maternal outcomes	Patients without ICP (N=1038)		Patients with ICP (N=62)		p-value
	N	%	N	%	
MOD					
CS	368	35.45	36	58.06	0.0033**
Vaginal	670	64.55	26	41.94	
Insomnia	248	23.89	38	61.29	0.0045**
Dyslipidemia	48	4.62	20	32.26	0.0011**
ACP	189	18.21	15	24.19	0.2388
PRM	104	10.02	10	16.13	0.1252
PH	98	9.44	12	19.35	0.0122*

ICP: Intrahepatic cholestasis of pregnancy; * p-value < 0.05: significant difference; ** p-value < 0.001: significant difference, MOD: Mode of delivery; CS: Caesarean section; ACP: Abnormal coagulation profile; PRM: Pre-labour rupture of membrane; PH: Postpartum hemorrhage

Though, the incidences of abnormal coagulation profile and pre-labour rupture of membrane were more in the patients with, ICP, the present study failed to found out significant associations of abnormal coagulation profile

and pre-labour rupture of membrane with intrahepatic cholestasis of pregnancy.

DISCUSSION

In the present study, total 1100 pregnant women were screened, and 62 pregnant women have been found to be suffering from ICP with prevalence of 5.64%. The different study reported different incidence rates according to their geographic location and race.[8] The reported incidence of ICP are -Chile: 12-20%; Bolivia: 9%; Sweden: 2%-3%; <1.0% in in Australia, France, China and Canada.[9-11] The Indian studies reported the incidence of ICP among Indian women has been reported to be around 1%, which is quite low in comparison to the present study.[12,13] The present study was carried out at the tertiary care teaching hospital, so, chances of more complicated cases been treated in this set-up. This may be the reason for higher incidence of ICP in the present study. The present study has shown the age group of > 35 years significantly (p-value: 0.0099) associated with development of intrahepatic cholestasis of pregnancy. Around two-third of the pregnant women with ICP were of more than 30 years. In a study done by Heinonen S et al., pregnant women with relatively advanced age (>35 years) were at increasing risk of developing ICP.[23] The average maternal age of pregnant women with ICP has been found more than 30 years in an Australian study.[24] There are many risk factors has been found for ICP which include advanced maternal age (≥35 years); history of hepatitis C; cholelithiasis; cholecystectomy; previous history of ICP; family history of ICP; and multiple gestation pregnancy.[25-27]

In the present study, a majority of pregnant women with intrahepatic cholestasis of pregnancy was of multipara. The significant association (p-value: 0.0428) has been found between parity and intrahepatic cholestasis of pregnancy. There was no significant difference in incidence according to parity (primigravida 9.7% and multigravida 10.0%) in a study done by Medda, et al.[28] There were no association found between smoking habit with development of intrahepatic cholestasis of pregnancy. Development of intrahepatic cholestasis of pregnancy was highly significantly associated with small for gestational age (SGA, p-value: 0.0003); abnormal cardiotocography (CTG, p-value: 0.0002); and meconium stained liquor (p-value: 0.0001) in the present study. A similar study done by Medda, et al., including 100 patients with ICP, had shown following fetal outcomes: fetal distress (23%); abnormal CTG (17.0%), meconium stained liquor (41.0%), preterm birth (22.0%) excluding IUFD; low birth weight babies (32.0%); neonates required admission to NICU (27.0%).[28]

There are other studies in which lower mean birth weight has been noted, although this does not appear to be due to intrauterine growth restriction.[23,29,30] Several studies have shown that there is no increase in the number of small for gestational age infants born to women with ICP.[31,32] Abnormalities in CTG, both ante- and intrapartum, have been reported in association with ICP.[30,33] In normal term pregnancies, the incidence of meconium staining of amniotic fluid (MSAF), a sign of fetal distress, is approximately 15%. In case pregnancies complicated by ICP, the incidence of MSAF has been reported to increase up to 58%.[30,34]

The exact etio-pathogenesis for adverse fetal outcomes in pregnancies with ICP is not known. It may be related to an increased flux of bile acids into the fetal circulation, as indicated by elevated levels in amniotic fluid, cord serum and meconium.[8] This hypothesis further supported by a recent study of fetal outcomes in ICP which has shown that the risk of adverse fetal outcomes increases with increasing levels of maternal serum bile acids.[25]

Caesarean section (CS) as mode of delivery found significantly associated (p-value: 0.0033) with intrahepatic cholestasis of pregnancy. Insomnia (p-value: 0.0045); dyslipidemia (p-value: 0.0011); and postpartum haemorrhage (PPH, p-value: 0.0122) were also found significantly with ICP in this study. In a study done by Medda et al., 62% of pregnancies were delivered by caesarean section [Elective CS (32%) + Emergency CS (30%)] which is comparable with rate (58.06%) of CS in the present study.[28] The same study has reported following maternal outcomes: insomnia (60%); dyslipidemia (30%); abnormal coagulation profile (19%); PPH (10%) and PROM (10%).[28] In term of prognosis, Maternal prognosis is good and and a majority of symptoms resolve rapidly after delivery, accompanied by normalization of LFT.[4]

CONCLUSION

Intrahepatic cholestasis of pregnancy is one of the common causes of hepatic impairment in pregnancy. ICP is associated with adverse fetal outcomes like, low birth weight babies; premature infants; abnormalities in CTG. ICP is also associated with maternal outcomes like, insomnia, dyslipidemia, PPH. Maternal outcomes have good prognosis but fetal outcomes can be improved by timely and effective intervention.

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

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