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Feto-Maternal Outcomes in Intrahepatic Cholestasis of Pregnancy

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ABSTRACT

Intrahepatic cholestasis of pregnancy is most common pregnancy related liver disorder and unique to pregnancy. It is characterised by pruritus with onset in the 2nd or 3rd trimester of pregnancy without skin rash, elevated serum amino transferases and bile acid levels and spontaneous relief of signs and symptoms within 2-3 weeks after delivery. To find out the adverse effects of intrahepatic cholestasis of pregnancy on feto-maternal outcomes. The present study was a prospective observational study. This Study was conducted from 1 ½ years (March 2018 to July 2019) at department of obstetrics and gynaecology in Chittaranjan Seva Sadan College of Obstetrics and Gynecology and Child Health. In 59.0% of the cases mode of delivery was Caesarean section which was significantly higher than that of VD (41.0%) (Z=2.54.,p=0.0107). Intrahepatic cholestasis of pregnancy is associated with elevated risks of preterm delivery, increased cesarean section rates and adverse neonatal outcomes. Effective management and timely delivery are crucial in minimizing these risks. Ongoing monitoring and interdisciplinary care are recommended to optimize both maternal and fetal health. Future research should explore strategies for better management and long-term outcomes of women with ICP.

INTRODUCTION

Intrahepatic cholestasis of pregnancy is most common pregnancy related liver disorder and unique to pregnancy. It is characterised by pruritus with onset in the 2nd or 3rd trimester of pregnancy without skin rash, elevated serum amino transferases and bile acid levels and spontaneous relief of signs and symptoms within 2-3 weeks after delivery[1]. The symptoms and biochemical abnormalities resolve rapidly after delivery but may recur in subsequent pregnancies and with the use of hormonal contraception.

The incidence of ICP (Intrahepatic cholestasis of pregnancy) varies widely with geographical location and ethnicity. ICP affects 0.7% of pregnancies in whites in the United Kingdom and approximately double this proportion of women of South Asian in origin[2]. In South Asian population, it varies from 0.8-1.4 %.

The etiology of ICP is elusive, although current investigations suggest a combination of hormonal, genetic and inflammatory factors that impair bile secretory function, which increases maternal serum bile acid and elevates the production of liver enzymes. Patients with intra hepatic cholestasis of pregnancy have distressing pruritus worsening at night and affect mainly the abdomen and palms and soles[3-4]. According to several studies, although the maternal course is usually benign, except slight increase in risk of postpartum haemorrhage and there is an increased risk of perinatal morbidity and mortality as in increased risk of spontaneous preterm delivery, non- reassuring feta status, fetal compromise, meconium-stained amniotic fluid and intrauterine fetal demise(IUFD).

The presenting feature of intrahepatic cholestasis of pregnancy is pruritus in the majority of cases. This typically occurs in the third trimester, with up to 80% of women presenting after 30 weeks of gestation. And some patients presenting as early as in the seventh gestational week.

The diagnosis of ICP is essentially one of exclusion and is finally confirmed by resolution of symptoms and biochemical abnormalities postpartum[5]. And other causes of pruritus, hepatic impairment, or both should be investigated. The most sensitive and specific marker for diagnosis is the serum bile acid level[6], which if raised in a woman with typical pruritus is considered to be diagnostic of intrahepatic cholestasis of pregnancy in the absence of evidence for an alternative diagnosis. Complications like spontaneous pre-term delivery, meconium stained liquor and fetal asphyxia occur more commonly in pregnancies in which the bile acid levels are greater than 40micromol/L If serum bile acid measurement is not available, the Royal College of Obstetricians and Gynaecologists guidelines, U.K currently recommend that intrahepatic cholestasis of pregnancy may be diagnosed in a woman with typical pruritus and abnormal liver function tests with resolution of both after delivery. There is rise in serum transaminases (ALT and AST) in majority of cases and the rise in majority of cases is two-three fold. There is also rise in serum bilirubin and GGT.

MATERIALS AND METHODS

Place of Study: The study was conducted at department of obstetrics and gynaecology in Chittaranjan Seva Sadan College of Obstetrics and Gynecology and Child Health.

Study Period: 1 ½ years (March 2018 to July 2019).

Study Design: It was a prospective observational study.

Sample Size: 100 women (112 considered for study, among them 4 developed preeclampsia, 5 cases were lost to follow up and 3 cases refused to be a part of the study).

Inclusion Criteria:

- All Primigravid and Multigravida mothers attending OPD/ admitted in antenatal ward with complaints.
- pruritis (or).
- clinical jaundice (or).
- Combination of complaints with period of gestation between 28-40 weeks.

Exclusion Criteria:

- Any H/O Hepatic Infection.
- Any H/O Hepatotoxic Drugs.
- Past H/O Liver and Gall Bladder Diseases.
- Pruritus Due to Any Skin Disease.
- Pregnant women with Chronic Hypertension, Pre-Eclampsia, Eclampsia.
- Pregnant women with thyroid disorder.
- Pregnant women with Gestational Diabetes Mellitus.
- Common haematological disorders.

RESULTS AND DISCUSSIONS

Table 1: Showing CTG Finding (N=100)

CTG finding	Number	%
Abnormal	16	16.84%
Normal	79	83.16%
Total	95	100%

Table 2: Showing Gestational Age at Delivery (N=100)

Gestational age at delivery(weeks)	Number of patients	%
32-34 weeks	1	1%
34+1-35 weeks	3	3%
35+1- 36 weeks	2	2%
36+1-37 weeks	4	4%
37+1-38 weeks	22	22%
38+1-39 weeks	38	38%
39+1-40 weeks	26	26%
40+1-41 weeks	4	4%

Table 3: Showing Onset of Labour in Patients (N=100)

Onset of Labour	Number of patients	%
Elective LSCS	21	21.00%
Induced	36	36.00%
Spontaneous	43	43.00%
Total	100	100.00%

Table 4: Showing Induction of Labour of the Patients (n=36)

Induction of labour	Number	%
PGE2 gel	21	57.1%
Foleys Induction	10	28.6%
MISO+MIFE	5	14.3%
Total	36	100.0%

Table 5: Showing Indication of Induction of Labour (n=36)

Indication of Induction of labor	Number	%
IUFD	5	13.90%
POSTDATED	1	2.80%
PROM	5	13.90%
TERM	25	69.40%
Total	36	100.00%

Table 6: Showing Mode of Delivery (N=100)

Mode of delivery	Number	%
ELECTIVE CS	21	21.0%
EMLUCS	38	38.0%
IVD	3	3.0%
NVD	38	38.0%
Total	100	100.0%

Table 7: Showing Indication of LUCS and Type of LUCS

Indication of LUCS	ELCS	EMLUCS	TOTAL
BOH	1(4.8%)	0	1(1.7%)
CDMR with OC	1(4.8%)	0	1(1.7%)
CPD	5(23.8%)	0	5(8.5%)
Elderly Primi With Subfertility	1(4.8%)	0	1(1.7%)
FD	0	5(13.2%)	5(8.5%)
IF WITH OC	0	9(23.7%)	9(15.3%)
MSL WITH FD	1(4.8%)	6(15.8%)	7(11.9%)
MSL WITH POOR BISHOPS SCORE	0	5(13.2%)	5(8.5%)
NPOL	0	2(5.3%)	2(3.4%)
Obstructed Labor	0	1(2.6%)	1(1.7%)
Pathological CTG with OC	0	9(23.7%)	9(15.3%)
Persistent less FM	5(23.8%)	1(2.6%)	6(10.2%)
Placenta Previa	2(9.5%)	0	2(3.4%)
Postdated with unfavarable CX	2(9.5%)	0	2(3.4%)
PRIMI BREECH with FPD	3(14.3%)	0	3(5.1%)
TOTAL	21(100%)	38(100%)	59(100%)

In our study, 83.16% of the patients had normal CTG and 16.84%of the patients had abnormal CTG. In our study, 38% of the patients had delivery between 38-39 weeks of gestation. In 43.0% of the cases onset of labor was Spontaneous which was higher but it was not significant (Z=0.42 p=0.66). 36% of patients were induced and 21% of patients delivered by elective caesarean section.

In 57.1% of the cases PGE2 gel was used for induction which was significantly higher (Z=3.99., p<0.0001). In our study, 69.4% of the case were term pregnancy which was significantly higher (Z=7.89., p<0.0001). In 59.0% of the cases mode of delivery was Caesarean section which was significantly highe r than that of VD (41.0%) (Z=2.54., p=0.0107). Chi-square (x^2) test showed that there was significant association between Indication of LUCS and type of LUCS (p<0.0001).

Intra hepatic cholestasis of pregnancy has remained an enigmatic problem till date. It is a relatively common cause of hepatic impairment in pregnancy. It has a complex etiology with genetic, endocrine and environmental components. Intrahepatic cholestasis of pregnancy was originally described by Ahlfeld as recurrent jaundice in pregnancy that resolved following delivery[7]. The pathophysiology remains unclear and there is no such guideline for proper management of the condition. On the other hand the perinatal complications in the form of meconium staining of liquor, pre term delivery and NICU admission remains a matter of concerned.

The present study was a prospective observational study in a tertiary care centre of Eastern India in which 100 cases of ICP were taken.

In our study the young age group is mostly affected, contributing 42% and were between 21-25 years of age with the mean age of 24.91±4.23 years with range 17 -38 years and the median age was 25 years. In a study conducted by Padmaja *et al* (2010), the mean age of the patients was 28.7 years[8]. Another study conducted by Ray *et al* (2005) the mean age was found to be 24.7 years[9]. This is also similar to the results shown by Rasheed S *et al* (28 year+5.19) and Sosa SY *et al* (29.2±6.8 yrs). The mean age in Indian study was similar to our study. Mishra *et al* in their study found that, the maximum number of cases was in the group of 20-30 years (74.3%).

Most of the women in our study were primigravidae accounting for 68% of patients. In the study conducted by Ray[9] 71.8% of the patients were found to be affected by obstetric cholestasis in the first pregnancy. Majority of our patients (87%) belonged to lower middle status. It was found in our study that most of the patients (67%) belonged to BMI range 18.5-24.9 kg/m^2 .In study conducted by Garg Renu *et al* , mean BMI distribution was being 22.40 and 23.17 kg/m^2 in case and control group that supports our study 10. Significance unknown., no references found in comparative literature.

Pruritus mainly encountered in third trimester. In our study, we found that most of the patients (63%) had onset between 32-36 wks and the mean gestational age of onset were 34.08±2.71 weeks and the median was 34.45 week. Padmaja[8] found onset of pruritus mainly in the 3rd trimester (71.1%) and Ray *et al* found onset of pruritus in 84.3% of patients after 30 weeks of gestation. In another study conducted by Rosales *et al* (2010) the median gestational age for the onset of pruritus found to be 34 weeks[11]. These studies had been found comparable to our study. The result is also corroborating to the findings of other authors like Dang A *et al* (mean age 31±4 weeks) and Kenyon AP *et al* (33.7 weeks).

Pruritus was the cardinal symptoms in all the patients. In our study, 48% presented with complaints of pruritus over palm and soles, 30% patients with itching over abdomen and rest 22% presented with complaint of itching all over body. Padmaja[8] found affection of palms and soles in 37.8% cases and Ray[9] found affection in 46.8% of cases. Generalized pruritus mostly affecting palms and soles were the cardinal features without skin rash and clinical jaundice. This has been found similar to our study.

The incidence of recurrence of ICP in our study was 56.3%. Recurrence of ICP in subsequent pregnancies were upto 60-70% (Ray A et al)9. In a study done Medda S *et al*, has shown recurrence of ICP was 64.7%[12].

Most commonly elevated LFTs have been reported as transaminases and total serum bile acid. The peak value of SGOT and SGPT in our study ranged from 151-200 IU/L (34%) and 201-205 IU/L (35%) respectively. According to Reyes et al Levels of liver transaminases in serum are usually 2–10-fold increased. In our study ALP was raised in 90% of the patients, the value of ALP in these women varied from normal to as high as 968 IU/L. The level of ALP beyond 451 IU/L is seen in 59% of patients. Mild hyperbilirubinemia was present in 39% of patients and the highest bilirubin level noted was 2.9 mg/dL. In the study conducted by Padmaja *et al* SGOT and SGPT levels increased in >95% of cases[8]. However Alkaline phosphatase level increased in only 15.8% cases and S. Bilirubin in 18.45% of cases.

13% patients had elevated level of Gamma Glutamyl Transferase (GGT). In a study Brouwers *et al*, bilirubin and all liver enzymes. All other parameters of LFTs were significantly elevated but GGT failed to reach the significance[13].

7% patients in our study had deranged coagulation profile as in raised INR, 32% patient had prolonged PT but only 4% patient had prolonged APTT. Medda S. *et al* found in their study that 19% of the patients had deranged coagulation profile with increased PT or APTT level[12]. Dang A *et al* (29.78%) and Ray A *et al* (25%) reported that as a result of malabsorption of vitamin K, due to steatorrhoea of cholestasis, lead to coagulation problem[9].

Routinely Ursodeoxycholic acid had been given to all the patients of ICP in our study. With UDCA at a dose of 300 mg thrice daily, the relief of symptoms occurred in 79% of patients. Padmaja *et al* found a reduction rate of 94.4% with UDCA52. Ray et al has found a reduction in itching in 75% cases with UDCA[9]. In another study conducted by Chappel *et al* (2011) had found a reduction rate of itching by 95% with UDCA[15]. So Ursodeoxycholic acid found to be very effective in our as well as others studies and is comparable.

In our study, most of the deliveries occurred between 38-39 weeks (38%), Padmaja *et al,* found 62.2% delivery rate at 37 weeks of gestation[8].

In our study induction of labour was done in 36% of cases. It was done either by PGE2 gel or Foley's or combination of Mifepristone and Misoprost (in case of IUFD in unscarred uterus) if the cervix was unripe. It was similar to our study. 43% patients went into spontaneous labour and in 21% cases elective caesarean section was done in our study. Among all the cases of ICP 38 cases (38%) had normal vaginal delivery, 59 patients (59%) underwent caesarean section in our study. These include both elective and emergency cases.

Out of caesarean section performed maximum i.e 64% underwent emergency LSCS, most common indication being fetal distress in 31% of cases followed by induction failure and pathological CTG in 24% of case. 36% were put for elective LSCS, most common indication being persistent less FM in 29% of cases. 3% of patients had instrumental delivery by forceps. Similarly, Medda Set al study showed high incidence of operative delivery (66%), which comprises of Elective CS (32%), Emergency CS (30%) and Forceps delivery (4%). It was significantly higher than that of VD (34%) ($p<0.01$). Caesarean section rate (59%) was high in present study, as like many UK hospitals, our tertiary private hospital also adopts a policy incorporating antenatal surveillance of some form with elective delivery by 37-38 weeks.

Preterm delivery, PPROM, PPH rates are higher in almost all studies conducted on ICP. In our study, preterm delivery rate was 10%, PPH rate was 8% and PPROM rate was 8%. In the study conducted by Padmaja et al preterm delivery rate was (24.4% vs 15.6%)(p value>0.05) and PPROM rate was (8.9% vs 1.1%)(p value<0.05). However there were no PPH in both the groups8. Medda et al found 10% PPH, PROM in 10% of cases and 7% of patients had spontaneous preterm labour in their study[12].

Coming to fetal outcome it is a well-known fact that meconium staining of liquor is seen more commonly in ICP patients. In our study we found that meconium staining of liquor was much higher accounting for 53% of cases. The NICU admission rate was also high in 19% of cases. Abnormal CTG was seen in 16% of cases and Apgar score<7 at 5 min in 9% of cases. 5% cases accounted for intrauterine fetal demise. Padmaja *et al*, in their study found meconium staining of liquor found to be statistically significant as compared to control group.(17.8% vs 1.1%)(p value<0.05) In their study NICU admission rate(15.6% vs 15.6%)(p value >0.05), abnormal CTG (4.4% vs 5.6%)(p value>0.05) and Apgar core <7 at 5 mins (4.4% vs 2.2%)(p value>0.05) were not statistically significant[8]. In the study conducted by Ray et al meconium staining of liquor was seen in 32.2% and NICU admission rate was 40.6%. However in their study Abnormal CTG rate was higher (35%). In a study by Medda S. *et al*, found abnormal CTG in 17% of cases, 41 patients had meconium stained liquor during delivery (41.0%) which was significantly higher ($p<0.01$). Alsulyman OM *et al* also found that risk of meconium passage was higher in the cholestasis group (44.3% cases vs. 7.6%of control[12].

Renu Garg et al in their study found non reassuring intrapartum CTG patterns (26% vs 8%) and meconium stained amniotic fluid (24% vs 6%). Renu Garg *et al,* also found rate of NICU admissions was high in the babies born in the study group (20% vs 4%)[10]. These results are similar to our study. Mishra et al found, NICU admission rate was 10%[18].

The low incidence of preterm deliveries, NICU admission, IUFD, postpartum haemorrhage can be explained by the fact that in our institution, active

intervention, closure follow up and experienced management enabled to ameliorate possible adverse delivery outcomes.

CONCLUSION

Intrahepatic cholestasis of pregnancy is associated with elevated risks of preterm delivery, increased cesarean section rates and adverse neonatal outcomes. Effective management and timely delivery are crucial in minimizing these risks. Ongoing monitoring and interdisciplinary care are recommended to optimize both maternal and fetal health. Future research should explore strategies for better management and long-term outcomes of women with ICP.

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