Original Article

Prevalence of Liver disease in pregnancy and its Outcome with emphasis on Obstetric Cholestasis : An Indian Scenario

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Abstract

Objective: To determine the prevalence of liver disease in pregnant Indian women and the risk of adverse pregnancy outcomes resulting from intrahepatic cholestasis. **Methods:** We analyzed 5947 pregnant women, A total of 79(1.32%) patients had abnormal liver tests. 47 (0.79%) women who gave birth at Sant Parmanand Hospital from January 1997 to August 2008 had pregnancy complicated by cholestasis. Fisher's exact 2-Tail p-value analysis was used to compare pregnancy characteristics of this group with those of the general obstetric population (n = 5300). **Results:** Obstetric cholestasis started at a mean $\pm$ SD of 31 $\pm$ 4 weeks' gestation, with pruritus as the leading symptom.. Affected pregnant women had meconium stained liquor significantly more often (40.4%) than the general obstetric population (18.86%). Intrahepatic cholestasis increased the low basic risk of preterm delivery ,thereby increasing the need for neonatal care in the general population. Increased incidence of postpartum hemorrhage was also significant(29.78%) $p < 0.0004$. **Conclusion:** Intrahepatic cholestasis of pregnancy has an adverse effect on maternal and fetal prognosis, and affected pregnancies merit closer surveillance.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a clinical syndrome of unknown pathophysiology, characterized by generalized pruritus and biochemical cholestasis, occurring during the second half of pregnancy and persisting until delivery. The incidence of ICP varies from 0.1% to 1.5% of pregnancies in Europe, North America, and Australia and from 9.2% to 15.6% in South Amer-

ican countries such as Bolivia and Chile. Intrahepatic cholestasis of pregnancy is common in Chile (14-24% of live births) and in Scandinavia (2% of live births). The prevalence in North America is 1-2 per 10,000 pregnancies.⁽¹⁾

It carries a substantial recurrence risk and has a tendency toward familial clustering. Its pathogenesis is likely to involve a genetic hypersensitivity to estrogen, and autosomal transmission has been suggested. Intrahepatic cholestasis of pregnancy (ICP) is a benign disorder that occurs in the second or third trimester and resolves spontaneously after delivery. Seasonal variation has been reported in Chile, with the highest rates observed in November. The condition occurs in all ages and in both primiparous and multiparous women. It can recur in subsequent pregnancies and is more common in the presence of multiple gestations. This study was done to evaluate the maternal and fetal consequences of intra-

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hepatic cholestasis in an Indian population receiving modern obstetric care.

Intrahepatic cholestasis of pregnancy may be associated with significant fetal risks, including premature births in 19% to 60% of deliveries, intrapartum fetal distress in 22% to 33% of affected pregnancies, and stillbirths in 1% to 2%.⁽²⁾

Materials and Methods

We reviewed the total population at Sant Parmanand Hospital who gave birth between January 1997 and August 2008. Data were collected prospectively and analyzed retrospectively from 5947 pregnant women over a period of 11 years. Incidence of liver diseases complicating pregnancy was calculated including viral hepatitis and pregnancy specific conditions like preeclampsia and associated conditions and HELLP. None of the patient had acute fatty liver of pregnancy. In this study, 47(0.79%) women had obstetric cholestasis and 5300(99.12%) were unaffected controls. Pregnancies with pregnancy induced hypertension and other liver diseases in pregnancy were excluded to eliminate confounding factors.

Patients with intrahepatic cholestasis were identified in maternity care units after questioning about itching. The diagnosis was based on clinical examinations (generalized pruritus in the absence of any dermatologic condition), laboratory results showing a cholestatic pattern (serum aspartate and alanine transferase exceeding 40 U/L) that returned to normal after delivery with no signs of viral hepatitis (negative results in assays for

hepatitis B surface antigen and antihepatitis A and C antibodies), and normal ultrasonography of the liver and biliary tract. None of our subjects had liver biopsies; however, in our area, liver function tests were done to evaluate the causes of stillbirth to exclude the ascertainment bias that would occur if an affected case had gone undiagnosed and resulted in fetal death.

Subjects in this study, underwent careful weekly outpatient clinical monitoring. The testing scheme included an NST, amniotic fluid (AF) volume assessment using the four-quadrant amniotic fluid index (AFI) and liver function tests. Testing was considered nonreassuring when the NST was nonreactive, the AFI was less than 5 cm, or liver function indices were at levels greater than ten times normal. Extreme elevation of liver function test results combined with abnormal fetal heart rate (FHR) or decreased AFI necessitated hospitalization for induction, if immediate operative delivery was not elected. In affected pregnancies, labor was induced routinely at 38–40 weeks' gestation unless nonreassuring antepartum testing was recorded earlier. Demographic data and pregnancy outcome measures were collected by the delivery team.

The following definitions were used to record pregnancy outcomes: preterm birth, delivery before 37 weeks' gestation; preeclampsia, repeated blood pressure measurements exceeding 149/90 mmHg with proteinuria exceeding 0.5 g/day; and low birth weight (LBW), birth weight less than 2500 g. Infants were considered small for gestational age (SGA) when the sex- and age-adjusted birth weight was below the tenth percentile according to the normal tables for our popula-

Fig 1
Study Protocol

Table 1. Maternal Risk Factors

Risk factor	Cases (n = 47)	Controls (n = 5300)	P
Age (y)			
<18	1(2.12%)	21(0.39%)	0.497461929
>35	1 (2.12%)	219 (4.13%)	0.682667271
PARITY			
PRIMIPARITY	34 (72.3%)	3063 (57.79%)	0.036419565
MULTIPARITY	13(27.65%)	2237(42.2%)	0.036419565
RISK FACTORS			
BOH	3(6.38%)	667(12.58%)	0.215644136
ANEMIA	3(6.38%)	130(2.45%)	0.278940291
IUGR	3(6.38%)	358(6.75%)	1
BREECH	1(2.12%)	176(3.32%)	1
PREVIOUS LSCS	10(21.2%)	430(8.1%)	0.014776449
GDM	3(6.38%)	111(2.094%)	0.278940291
INFERTILITY	2(4.25%)	196(3.69%)	1
OLIGOHYDRAMNIOS	2(4.25%)	335(6.32%)	0.747462959
RSA	2(4.25%)	1109(20.9%)	0.000763234
APH	2(4.25%)	80(1.5%)	0.368606013
TWINS	2(4.25%)	72(1.35%)	0.368606013

tion. If a subject had two abnormalities, such as LBW and preterm delivery, each was considered an independent outcome and the subject was included in both categories.

Statistical differences between subjects and controls were evaluated using Fisher exact test. $P < .05$ was considered statistically significant. Continuous variables were analyzed using a two-tailed, pooled t test.

Results

Figure 1. shows liver disease complicating pregnancy

was found in 79 (1.32%) pregnant women. Incidence of Hepatitis A 3(0.05%), B 15(0.28%), C 1(0.01%), E 3(0.05%). Pregnancy specific conditions like preeclampsia and associated conditions had an incidence of 568(9.55%), HELLP 10 (0.18%). None of the patient had acute fatty liver of pregnancy. 47(0.79%) women had obstetric cholestasis and 5300(99.12%) were unaffected controls.

Intrahepatic cholestasis complicated forty seven of 5947 pregnancies (0.79%). The mean ($\pm$ standard deviation) ages in the study and control groups were 26.5 ± 4 and 26.7 ± 5.2 years, respectively. : Intrahepatic

Table 2. Pregnancy and Delivery Characteristics

CHARACTERISTIC	CASES (N = 47)	CONTROLS (N = 5300)	P
MODE OF DELIVERY			
NORMAL DELIVERY	23(48.93%)	3260(61.5%)	0.086196406
INSTRUMENTAL	7(14.89%)	1106(20.86%)	0.000763234
LSCS	17(36.17%)	1934(36.49%)	1
DELIVERY CHARACTERSTICS			
FETAL DISTRESS	2(4.25%)	631(11.9%)	0.104454053
MECONIUM	19(40.4%)	1000(18.86%)	0.000949865
POSTDATISM	2(4.25%)	102(1.92%)	0.368606013
PRETERM	9(19.14%)	398(7.5%)	0.019258493
TERM	36(76.59%)	4800(90.5%)	0.011220887
FETAL CHARACTERSTICS			
AGA	33(71.21%)	4296(81%)	0.135715018
IUGR	9(19.14%)	604(11.39%)	0.164553388
LGA	5(10.63%)	400(7.54%)	0.613140093
POST DELIVERY COMPLICATION			
PPH	14(29.78%)	492(9.28%)	0.000487301

cholestasis of pregnancy started at a mean $\pm$ SD of 31 ± 4 weeks' gestation, with pruritus as the leading symptom. The study and control groups had similar mean gestational ages at delivery and birth weights 2.92 ± 0.4 and 2.73 ± 0.57 respectively. ($p > 0.05$, t test). However, women with pruritus were more likely to have meconium-stained liquor, preterm delivery and postpartum hemorrhage (PPH) ($p < 0.05$, Fisher's exact test). There appears to be a trend towards a higher rate of instrumental delivery ($p < 0.007$) in the study compared to the control group, reaching statistical significance. Table 1. shows the distribution of maternal risk factors. The ratio of primigravidas was similar between groups. When women with intrahepatic cholestasis were compared with the general obstetric population, maternal risk factors were similar with the exception of recurrent spontaneous abortions ($p < 0.00076$) which was statistically significant.

Table 2. summarizes the frequencies of various pregnancy and delivery complications. Pregnancy-induced

hypertension was excluded on the basis of our inclusion criteria. Overall, pregnancy outcomes were similar between the groups with the exception of the meconium stained liquor, preterm delivery which were found to be statistically significant. Incidence of IUGR was also increased though not statistically significant. Women with intrahepatic cholestasis had instrumental vaginal deliveries significantly more often than the general population, whereas no statistically significant difference was found between the groups in the number of cesarean deliveries. Incidence of postpartum hemorrhage was increased and was statistically significant in the study group.

Discussion

In our study, 5947 deliveries occurred during 11 years period. A total of 79 patients had abnormal liver tests, 22 had viral hepatitis, 10 had HELLP syndrome. Incidence of Hepatitis A 3(0.05%), B 15(0.28%), C 1(0.01%), E 3(0.05%). Reported incidence in literature

of Hepatitis A is 1 per 1000 pregnancies, B is 5-15 per 1000 pregnancies. Hepatitis C virus infection does not affect the course of pregnancy unless cirrhosis is present. The risk of vertical transmission is low (<10%). Vertical transmission is more likely to occur in patients who are co-infected with human immunodeficiency virus (HIV) and in those with high maternal viral titers (>1 million copies/mL). Hepatitis D virus infection occurs in conjunction with hepatitis B virus infection. Vertical transmission is rare. Control of hepatitis B virus can help prevent spread. Hepatitis E virus infection is rare in the United States and Europe. It mainly occurs in developing countries and is usually mild and self-limiting. However, hepatitis E can cause fulminant hepatic failure. This infection is more severe in the third trimester, with a mortality rate of 20%. The risk of spontaneous abortion and intrauterine death is 12%. Vertical transmission can occur. Breastfeeding is permissible.(3) 568 (9.6%) had preeclampsia and associated conditions and were not included in our study to minimize bias. We found no significant maternal or fetal morbidity and mortality though risk of instrumental deliveries, preterm labour and post partum hemorrhage was significantly increased.

C L Ch'ng et al. in their prospective study of liver dysfunction in pregnancy in Southwest Wales followed up 4377 deliveries during the 15 month study. A total of 142 patients had abnormal liver tests. There were 206 contributing diagnoses, the great majority being pregnancy specific. Among the most important were preeclampsia (68), HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome (30), obstetric cholestasis (23), hyperemesis gravidarum (11), acute fatty liver of pregnancy (five), and hepatic infarct (one). Sepsis, postoperative factors, and placental pathology (51) were not uncommonly responsible but incidental or pre-existing hepatobiliary disease was infrequent (17). Sixty five patients were delivered early by induction or caesarean section because of liver dysfunction. Despite substantial liver related morbidity, there were no maternal deaths. (4)

Thomas Pusch et al. reported, ICP increases the risk of preterm delivery (up to 19–60%), meconium staining of amniotic fluid (up to 27%), fetal bradycardia (up to 14%), fetal distress (up to 22–41%), and fetal loss (up to 0.4–4.1%), particularly when associated with fasting serum bile acid levels > 40 $\mu\text{mol/L}$. Fasting serum bile acid levels and severity of pruritus at diagnosis were independent predictors of preterm delivery in a recent

analysis. Interestingly, most recent data show a marked decrease in fetal complications possibly in part due to greater awareness for the disease, closer follow-up and experienced management in specialized centers. In a prospective study of ICP in patients with bile acid levels > 40 $\mu\text{mol/L}$ the frequency of meconium passage was 44% compared to 22% in a group with only mild ICP.(5)

Recently, Rioseco et al. found that intrahepatic cholestasis was associated with a two-fold increase in the incidence of AF meconium and a three-fold increase in the incidence of preterm delivery. In their study, active intervention enabled them to ameliorate possible adverse perinatal outcomes by lowering the incidence of stillbirth and abnormal intrapartum FHR.(6)

We found that the women who developed intrahepatic cholestasis of pregnancy had history of frequent miscarriages compared with the controls. Using Fisher's exact 2-Tail p-value analysis, we found that affected women had a significantly higher frequency of passage of meconium, instrumental deliveries and preterm delivery, which in turn led to an increased need for intensive neonatal care. Otherwise, pregnancy outcomes were comparable with those in the general obstetric population. Using the general population for comparison of outcomes is less than ideal, although it can put the overall results into perspective. There was no perinatal mortality or morbidity found in our study. This improvement in perinatal mortality and morbidity was perhaps brought about by increased fetal surveillance combined with liver function tests and careful timing of delivery to avoid fetal compromise and death.

Conclusion

Obstetric cholestasis can be a progressive process, and an upward trend in liver function test results may indicate that the fetus is at risk of death and requires immediate delivery. Acceptable upper limits of liver function test results are a dilemma for obstetricians. If expectant management lasts too long and an infant is asphyxiated, the obstetrician is criticized for inaction. If the obstetrician decides to forestall asphyxia by immediate induction and cesarean delivery, the criticism may be unnecessary interference. Further, a genetic, metabolic predisposition may play a role in pathogenesis, thereby affecting severity of the disease and the overall outcome. A hereditary pattern has been described in women with cholestasis of pregnancy, and autosomal

dominant transmission has been suggested. The mutation responsible for the illness may vary according to the population studied, thus explaining the less severe phenotypes found in Scandinavia than in Chile.

The consequences of intrahepatic cholestasis primarily affect the mother, with discomfort from pruritus, occasional mild jaundice, and nausea. Although there is no long-term hepatic injury to the mother, it is advisable that patients with intrahepatic cholestasis be monitored for fetal effects. Careful timing of delivery is usually the only active therapy required in singleton pregnancies to achieve a normal outcome. Future genetic studies may provide a better understanding of the pathogenetic mechanisms of cholestasis and new options for treatment.

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