

Original Research Article

Fetomaternal Outcome in Intrahepatic Cholestasis of PregnancyGarg Renu¹, Mirza Nooren², Gupta Abhilasha³, Tanwar Neetu⁴, Gupta Vinita⁵, Iqbal Rabinder⁶¹Senior Resident (Obst. & Gynae), ²Assistant Professor (Obst & Gynae), ³Senior Resident (Obst & Gynae), ⁴Senior Resident (Obst & Gynae), ⁵Medical officer (Obst & Gynae), ⁶Resident (Obst & Gynae)

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Abstract: Intrahepatic cholestasis of pregnancy (ICP) is a condition in which serum bile acids are raised and it is associated with adverse fetal outcome. This is associated with severe pruritus with or without jaundice that resolves completely within 48 hrs following delivery and has a high recurrence rate in subsequent pregnancies. The prevalence of the condition varies worldwide from 0.2% in France to 2% in Scandinavia. The cause of obstetrical cholestasis is unknown. The study was undertaken to evaluate the correlation between maternal serum bile acid & fetomaternal outcome in intrahepatic cholestasis of pregnancy in Indian population. This was a prospective study done in tertiary care hospital over one year. Detailed history, investigations, fetomaternal outcomes were recorded and analysed. To conclude women with intra hepatic cholestasis of pregnancy is associated with increase adverse fetomaternal outcomes.

Keywords: respiratory distress syndrome, meconium stained amniotic fluid, meconium aspiration syndrome, transient tachypnoea of the newborn, abnormal cardiotocography

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP), which is also known as obstetric cholestasis, is a condition in which serum bile acids are raised and it is associated with adverse fetal outcome. First described in 1883 by Ahlfeld as recurrent jaundice of pregnancy [1] that is associated with severe pruritus with or without jaundice that resolves completely within 48 hrs following delivery and has a high recurrence rate in subsequent pregnancies [2]. The prevalence of the condition varies worldwide from 0.2% in France to 2% in Scandinavia. The cause of obstetrical cholestasis is unknown. The hepatic transport system which is normally utilized for excretion of bile acids is saturated due to formation of large amounts of sulfated progesterone metabolites, in some genetically predisposed women [3, 4]. Constitutional symptoms of cholestasis are pruritis, anorexia, malaise and abdominal pain. Pale stools and dark urine have been reported and steatorrhea may occur [5]. Steatorrhea is associated with an increased risk of post-partum haemorrhage as a result of malabsorption of vitamin K [6]. Intrahepatic cholestasis of pregnancy poses a significant risk for the fetus [7, 8]. The adverse effects

of intrahepatic cholestasis of pregnancy on the fetus include increased risks of meconium stained amniotic fluid, preterm delivery, fetal distress and fetal death. No ideal method of fetal surveillance (Cardiotocography, biophysical profile, Doppler flow velocimetry) [9] has been determined till date and fetal antenatal testing has had limited predictability in this disorder. Because the data accrued over the past two decades are ambiguous concerning maternal serum bile acid in predicting adverse fetomaternal outcome, the present study will try to evaluate the correlation between maternal serum bile acid & fetomaternal outcome in intrahepatic cholestasis of pregnancy in Indian population.

AIMS AND OBJECTIVES

The study was undertaken to compare maternal & fetal outcomes in women with or without obstetric cholestasis and to evaluate the association between maternal serum bile acid & adverse fetomaternal outcome in intrahepatic cholestasis of pregnancy.

MATERIAL & METHOD

This was a prospective study conducted in the Department of Obstetrics & Gynecology, SDM Hospital, Jaipur from 01.06.14 to 31.10.15. Institutional Review Board clearance and ethical committee approval was taken prior to the study. The data were presented as mean \pm SD or percentages. Z test was used to compare mean values while the χ^2 tests were used to compare the dichotomous variables in both groups. P value $<$ 0.05 was considered to be statistically significant. Study participants were divided in two groups with each group having 50 patients. Study group consisted of women who presented with pruritis in their second & third trimester of pregnancy with associated abnormal liver function in the absence of other liver and skin disease. Control group consisted of 50 cross-matched women with uncomplicated pregnancy and no history of pruritus & with normal liver function test.

Pregnant women aged $>$ 18 years, any parity with singleton pregnancy, non-hypertensive, non-diabetic, non-smoker, non-alcoholic were included in the study. Pregnant women with preeclampsia, dermatological disorder, Gestational Diabetes, hepatitis positive status, gall bladder or liver disease (on USG), hemolytic disease or any other hematologic disorder, women on hepatotoxic drugs, Crigler-Najjar syndrome, multiple pregnancy, and thyroid disorder were excluded from the study. A fasting blood sample was withdrawn for measurement of fasting serum total bile acids, alanine transaminase (ALT), aspartate transaminase (AST) and serum bilirubin. These tests were repeated as per need of the patients and in cases where more than one laboratory test was performed, the maximum value was used for data analysis.

Patients with mild itching received local soothing agents, like Calamine lotion for symptomatic relief. In moderate to severe cases, Ursodeoxycholic acid (UDCA) was administered in dose of 600– 900 mg/day for 3 weeks as it has antipruritic effect and lowers the risk of adverse fetal outcome. Water soluble vitamin K supplementation (10mg orally daily) was commenced by 34 weeks or at the time of diagnosis. Antenatal care protocol with respect to interval between clinical examination, Ultrasonography, Cardiotocography and induction of labour was decided on the merit of obstetric indication. Pregnancy was terminated at 38 weeks or earlier in case of fetal compromise or deteriorating LFTs in patients with intrahepatic cholestasis. The data collected included maternal age at the time of delivery, weight (kg), height (cm), gravidity, parity, spontaneous vs. induced labor, mode of delivery, postpartum haemorrhage and

maternal serum biochemical assays. BMI was calculated based on pre-pregnancy weight and height. The perinatal outcomes studied were the birth weight, preterm labour (spontaneous / iatrogenic), fetal viability, intrapartum cardio topographic abnormalities, meconium stained amniotic fluid, neonatal ICU admission. The definitions of normal and non-reassuring fetal heart rate (FHR) patterns were according to RCOG clinical guidelines.

OBSERVATIONS AND DISCUSSION

Table 1 shows the sociodemographic profile of both the groups. The mean age of subjects in the study and control group was 26.42 and 26.52 years respectively. BMI distribution was also comparable, with the mean BMI being 22.40 and 23.17 kg/m², in cases and controls respectively. Primipara constituted maximum number of subjects in both the groups (48% control and 44% study group). Table 2 shows the mean \pm SD of maternal serum biochemical analytes. The serum levels of total bile acids (28.54 vs 6.12) and alanine transaminase (158.08 vs 44.10) were significantly higher in the study group, while total bilirubin and aspartate transaminase were only slightly higher in women with cholestasis. The authors found that 64% of women in study group delivered vaginally and 36% had caesarean section (Table 3). Heinonen S *et al.*; [10] found that pregnant women affected by cholestasis delivered more often by caesarean than general obstetric population. Similarly, E Wikstorm Shemer *et al.*; [11] found that women with intrahepatic cholestasis had a higher risk of undergoing caesarean. In the present study, the most common indication of caesarean in both the groups was previous caesarean section. No significant difference was seen in the occurrence of PPH (Table 3) between the study and control group (6% vs 4%). Theoretically, there is an increased risk of PPH as a result of malabsorption of Vitamin K secondary to steatorrhea seen in cholestasis. These findings may be due to vitamin K supplementation given to the study subjects. Kenyon AP *et al.*; [12] also found higher incidence of PPH in women with cholestasis, not taking vitamin K. There was no significant difference in the mean gestational age at delivery in both the groups, despite more number of preterm deliveries (Table 3). This may be due to the small sample size.

Table 4 depicts the fetal outcome in both the groups. Preterm deliveries were more common in the study group as compared to controls (16% vs 6%), and most of them were iatrogenic. During labour, the cholestasis group had significantly higher non-

reassuring intrapartum CTG patterns (26% vs 8%) and meconium stained amniotic fluid (24% vs 6%). It is postulated that placental perfusion may decrease along the course of disease due to accumulation of bile acids in the placental vasculature. Victoria genes *et al.*; [13]

found a significant increase in the number of spontaneous and iatrogenic preterm deliveries in their study. A study done by Richard H Lee *et al.*; [14] revealed that the risk of meconium passage increased linearly with increase in serum bile acids concentration.

Table-1: Sociodemographic Profile of Study Subjects

Sociodemographic Variables	Cases (n=50)	Controls (n=50)
Age		
18-24	18 (36%)	20 (40%)
25-29	16 (32%)	17 (34%)
30-35	10 (20%)	9 (18%)
>35	6 (12%)	4 (8%)
Mean age ± sd	26.42 ± 5.79	26.52 ± 4.69
BMI		
<18.5	10 (20%)	11 (22%)
18.5-24.99	28 (56%)	26 (52%)
25-29.99	8 (16%)	9 (18%)
>30	4 (8%)	4 (8%)
Mean BMI ± sd	22.40 ± 4.00	23.17 ± 4.08
Education status		
Primary	6 (12%)	8 (16%)
Secondary	16 (32%)	16 (32%)
Graduate	28 (56%)	26 (52%)
Level of significance	$\chi^2 = 0.360$ d.f. = 2 p>0.05 (Not Significant)	
Parity		
Nullipara	16 (32%)	14 (28%)
Primipara	22 (44%)	24 (48%)
Multipara	12 (24%)	12 (24%)
Level of significance	$\chi^2 = 0.220$ d.f. = 2 p>0.05 (Not Significant)	

Table 2: Liver Function Tests in the study subjects

Biochemical markers	Mean±SD		p-value	Significance
	Cases (n=50)	Controls (n=50)		
AST(IU/L)	48.98±17.89	44.44±18.61	>0.05	Not significant
ALT(IU/L)	158.08±44.83	44.10±21.78	<0.001	Highly significant
Bilirubin (mg/dl)	1.21±1.10	0.93±0.38	>0.05	Not significant
Bile Acids (µmol/L)	28.54±11.55	6.12±2.02	<0.001	Highly significant

Table 3: Maternal Outcome of Study Subjects

Outcome measures Studied	Cases (n=50)	Controls (n=50)	Level of significance
Mode of delivery			
LSCS	18 (36%)	9 (18%)	$\chi^2 = 3.929$ d.f.=1 p<0.05 significant
Vaginal delivery	32 (64%)	41 (82%)	
Occurrence of PPH			
Present	3 (6%)	2 (4%)	$\chi^2 = 0.000$ d.f.=1 p>0.05 not significant
Absent	47 (94%)	48 (96%)	
Gestational age at delivery (mean ± sd)	37.42±0.73	38.00±0.85	p>0.05 not significant

Table 4: Fetal outcome in study subjects

Fetal outcome	Cases (n=50)	Controls (n=50)	χ^2	d.f.	p-value	Significance
Abnormal CTG	13 (26%)	4 (8%)	2.076	1	<0.05	Significant
Meconium stained amniotic fluid	12 (24%)	3 (6%)	3.646	1	<0.05	Significant
Iatrogenic preterm birth	5 (10%)	1 (2%)	1.596	1	>0.05	Not significant
Spontaneous preterm birth	3 (6%)	2 (4%)	0.000	1	>0.05	Not significant
IUFD	1 (2%)	0 (0.0%)				
NICU admission	10 (20%)	2 (40%)	4.640	1	<0.05	Significant

Table 5: Association of adverse fetal outcome with serum bile acids

Adverse fetal Outcome	Mean±SD		p-value	Significance
	cases	Controls		
Yes	35.35 ± 10.52 (n=26)	6.45 ± 1.82 (n=11)	< 0.001	Highly significant
No	21.17 ± 7.32 (n=24)	6.02 ± 2.06 (n=39)	<0.001	Highly significant

Intrahepatic cholestasis has been reported to be associated with an increased risk of intrauterine fetal demise. The mechanism underlying has been poorly understood but it is said that bile acids and meconium have the ability to penetrate the placenta and umbilical cord leading to spasm of umbilical vessels and acute fetal anoxia. In the present study, there was only one intrauterine fetal death in the study group while none in the controls (Table 4). These findings are inconsistent with those of Victoria genes *et al.*; [13]. The low incidence seen in the present study may be due to increased attention paid to women and early intervention once they were found to have cholestasis. However the small size of the present study is insufficient to draw any inference.

The authors found a higher rate of NICU admissions in the babies born in the study group (20% vs 4%). Indications being respiratory distress syndrome (5 neonates), meconium aspiration syndrome (4 neonates) and transient tachypnoea of the newborn (1 neonate). Zecca E *et al.*; [15] also reported that the incidence of respiratory distress is twice in mothers with cholestasis. It has been hypothesized that bile acids deplete the surfactant in the alveoli. Table 5 shows the association between total bile acid concentration and adverse fetal outcome. Mean bile acid level was significantly higher in women with signs of adverse

fetal outcome in the study group. Similar findings were reported by Richard H Lee *et al.*; [14] and Glantz A [16], who have reported higher incidence of adverse fetal outcome with increasing bile acids.

CONCLUSION

Intrahepatic cholestasis of pregnancy is associated with increase adverse fetomaternal outcome, though in view of small number of cases enrolled further studies with a larger data are required to confirm the above facts and to draw any conclusions.

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