Perinatal complications in intrahepatic cholestasis of pregnancy

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Abstract

Background and Objective: Intrahepatic cholestasis of pregnancy (ICP) is seen usually in 3rd trimester of pregnancy. Overall incidence is 1.2-1.5% of Indian pregnant women. The biochemical abnormalities often include raised liver enzymes, conjugated bilirubin and bile acids. ICP can complicate perinatal outcomes to a significant extent. The present study was conducted to find out the types and incidence of perinatal outcomes in pregnancy complicated with ICP diagnosed by abnormal LFTS (liver function tests), to help the clinician in initiating timely treatment.

Materials and methods: In the present study, 51 pregnant women diagnosed with ICP and 49 number of age and gravida matched normal pregnant women were included as cases and controls respectively. LFT and Total bile acids were estimated by standard biochemical methods. Both cases and controls were followed to evaluate perinatal outcomes after 7 days of post-partum.

Results: Total bilirubin (0.6 ± 0.08 Vs 0.4 ± 0.03)milligrams/decilitre*; Aspartate transaminases (48 ± 18.6 Vs 27 ± 9.5) International Units/ Litre**; Alanine transaminase (42 ± 14.2 Vs 28 ± 6.1) International Units/ Litre**; Alkaline phosphatase (251 ± 63 Vs 159 ± 58) International Units/ Litre**;Gamma glutamyl transferase (41 ± 5.2 Vs 35 ± 3.6) International Units/ Litre**; Total bile acids (12.7 ± 10.2 Vs 33.4 ± 15.6)µ mol/ Litre ; Albumin (3.3 ± 0.5 Vs 3.2 ± 0.4)grams/decilitre; Total Proteins(6.3 ± 1.2 Vs 6.1 ± 1.5)grams/decilitre were obtained in cases Vs controls.

Significantly higher incidence of total complications in cases compared to controls(54.90% Vs 12.24%)*** were found which include respiratory distress(23.52 Vs 4.08)%***, meconium aspiration (9.80 Vs 2.04)%**, pre-term delivery (9.80 Vs 4.08)%*, hyperbilirubinemia (1.96 Vs 0.0)%, fetal bradycardia (7.84 Vs 2.04)%** and fetal loss(1.96 Vs 0.0)%. (*p value<0.05, **p value<0.01, ***p value <0.001)

Conclusion: The present study found an increase in incidence of total morbidity and mortality during perinatal period in babies born to women suffering from ICP. These findings suggests estimation of total bile acids and liver enzymes for early diagnosis of pregnant women at risk, active monitoring, treatment and induction of labor around 36-38 weeks after establishment of lung maturity in pregnancy associated with ICP to prevent perinatal complications.

Keywords: ICP, Total bile acids, LFT, Perinatal complications

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Introduction

Intrahepatic cholestasis of pregnancy (ICP) also known as obstetric cholestasis is the most common pregnancy specific liver disease.

It is defined as a cholestatic disorder characterized by pruritus in the absence of a rash, elevated serum aminotransferases and bile acid levels with onset in the second or third trimester of pregnancy and spontaneous relief of signs and symptoms after delivery.[2,3]

Overall incidence of 10%, with higher rates seen in women with multiple pregnancy and conception following in vitro fertilization[4]. In the UK, the disease is seen more commonly among women of Asian descent with 39-41% of women being of Indian or Pakistani origin[5]. Overall incidence is 1.2-1.5% of Indian pregnant women. More recently, this has fallen to approximately 1.5%-4%[6].

The aetiology of the condition is multi-factorial. Elevated levels of placental sex hormones affect the function of membrane transport protein of hepatocytes leading to decreased biliary lipid excretion. Genetic defects in specific transport proteins like mutations in ABCB 4(MDR 3) has been implicated.ABCB4 encodes the multi-drug resistance protein 3, a phosphatidyl-choline floppase that transports phosphatidylcholine from the inner to the outer leaflet of the canalicular membrane.[7] Several environmental factors like selenium and vitamin D deficiency have been reported to be associated with higher incidence of ICP. ICP has been consistently associated with a higher incidence of adverse pregnancy outcomes like spontaneous & iatrogenic preterm delivery, respiratory distress, meconium staining of amniotic fluid and sudden intra uterine foetal death (IUFD)[1,8,9]

Recurrence rate in subsequent pregnancies is very high (45-70%)[1] with a higher incidence of hepatobiliary disease later in life. Children born to women with

intrahepatic cholestasis are also reported to be at higher risk of raised body mass index and dyslipidemia at the age of 16years.[10]

Aims and Objective

To find out the different biochemical alterations and types & incidences of perinatal outcomes in pregnancies complicated with ICP which shall help initiate early diagnosis and active management of ICP cases by the clinician in order to decrease perinatal morbidity and mortality.

Materials and Methods

Present study was conducted at VSS Medical College, Burla from January 2011 to July 2013.

Cases: 51 pregnant women diagnosed with ICP from the ante natal department and labour room of Obstetrics and Gynaecology were enrolled as cases.

Diagnosis was based on following features:

1. Pruritus of cholestasis without rash, presenting in the third trimester.
2. Elevated fasting serum bile acids > 10µmol/l along with elevated serum transaminases.
3. Spontaneous relief of signs and symptoms within 48 hours of delivery.
4. Absence of other diseases that cause pruritus and jaundice.

Exclusion criteria include chronic liver diseases (Hepatitis B/C, acute fatty liver, autoimmune hepatitis), previous history of cholelithiasis, chronic cholecystitis, HELLP Syndrome (hemolysis, elevated liver enzymes, and low platelets), alcohol intake and multiple pregnancies.

Controls: 49 numbers of age and gravida matched normal pregnant women, regularly attending the ante-natal department of Obstetrics and Gynaecology were enrolled as controls.

Informed consent was taken from both cases and controls & Institutional Ethical Committee approval was obtained for the above study.

Methods

5ml of fasting blood sample were obtained from cases and controls in plain non vacutainer tubes.

Serum was obtained for the following tests: Liver function tests (Bilirubin-Total & Direct by Gendrassik & Groff metod, aspartate aminotransferase(AST), alanine aminotransferase(ALT), alkaline phosphatase (ALP), gamma glutamyl transferase(GGT) by IFCC kinetic method by Roche Hitachi 917 auto analyzer using commercially available kits. Total protein and Serum Albumin estimated by biuret and bromocresol green methods respectively. Total bile acids are estimated by enzymatic cycling method using liquid stable reagent kit.

Results were expressed in Mean± S.D. "Chi-Square test" and "Students't' test" were used for statistical analysis. A 'p' value of < 0.05 was taken as statistically significant.

Table 1: Biophysical Characteristics in Study and Control Group

PARAMETERS IN MEAN ± SD	CASES	CONTROLS	P VALUE
1. Mean age at delivery(in years) Mean ± SD	24.5 ± 6.2	23.9 ± 5.8	> 0.05
2. Body Mass Index(BMI)	26.9 ± 5.4	24.5 ± 6.1	< 0.05*
3. Gravida	1.34 ± 0.32	1.32 ± 0.29	>0.05
4. Mean estimated gestational age in weeks	37 ± 1.3	39 ± 1.2	>0.05

Table 2: Delivery Methods in ICP Cases vs Controls

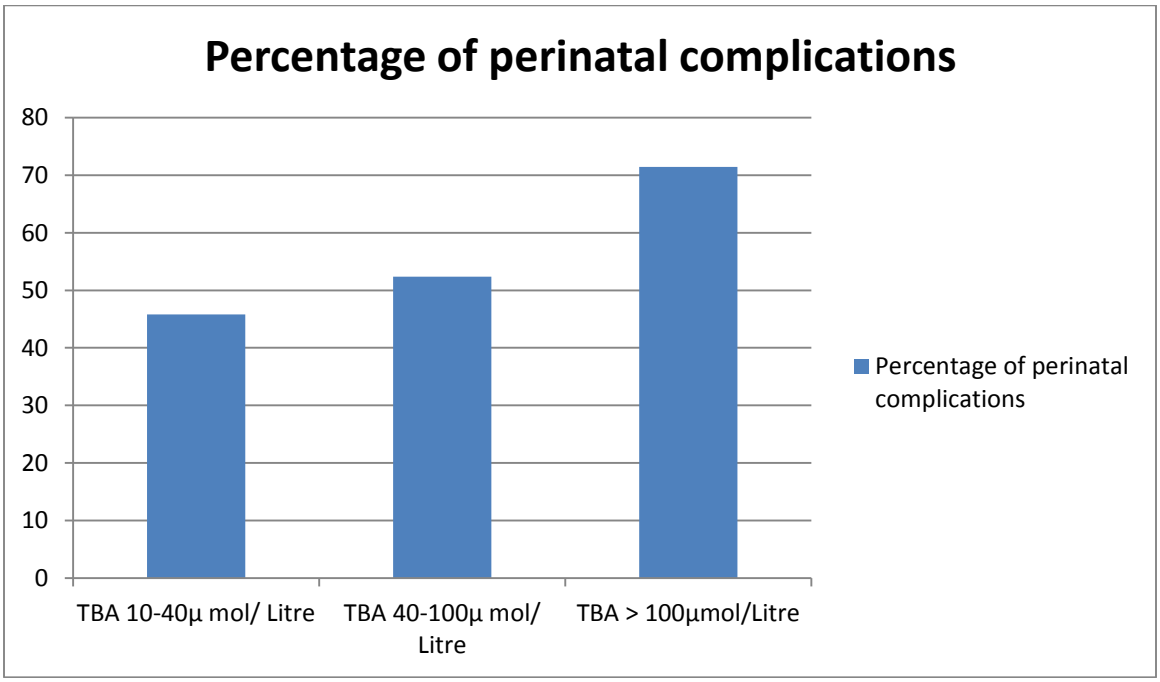
METHODS	CONTROLS	CASES	P VALUE
Normal Vaginal Delivery	81.63%	82.35%	>0.05
Lower section caesarean section	14.28%	15.68%	>0.05
Forceps	2.04%	0.00%	<0.05*
Vacuum assisted	2.04%	1.96%	>0.05

Table 3: Maternal Laboratory Values of Different Biochemical Parameters

PARAMETERS IN MEAN ± SD	CONTROLS	CASES	P VALUE
1.TOTAL BILIRUBIN(mg%)	0.4 ± 0.03	0.7 ± 0.08	<0.05*
2.DIRECT BILIRUBIN(mg%)	0.2 ± 0.05	0.4 ± 0.07	<0.05*
3.AST(IU/L)	27 ± 9.5	48 ± 18.6	<0.05*
4.ALT(IU/L)	28 ± 6.1	42 ± 14.2	<0.05*
5.ALP(IU/L)	159 ± 58	251 ± 63	<0.01**
6.GGT(IU/L)	35 ± 3.6	41 ± 5.2	>0.05
7.TOTAL PROTEIN(gm%)	6.3 ± 1.2	6.1 ± 1.5	>0.05
8.ALBUMIN(gm%)	3.3 ± 0.5	3.2 ± 0.4	>0.05
9.TOTAL BILE ACIDS(µmol/l)	12.7 ± 10.2	33.4 ± 15.6	<0.01**

Table 4: Perinatal Complications in Cases vs Controls

COMPLICATIONS	CONTROLS	CASES	P VALUE
1.Birth weight (in kg)	2.9 ± 0.07	2.7 ± 0.61	>0.05
2.Respiratory distress	4.08%	23.52%	<0.001***
3.Preterm delivery	4.08%	9.80%	<0.05*
4.Meconium aspiration	2.04%	19.60%	<0.05*
5.Hyperbilirubinemia	0.00%	1.96%	<0.05*
6.Fetal bradycardia	2.04%	7.84%	<0.01**
7.Fetal loss	0.00%	1.96%	<0.05*
TOTAL COMPLICATIONS	12.24%	54.90%	<0.001***



Discussion

Our study shows significantly higher ($p<0.05$) levels of Total & Direct bilirubin, AST, ALT and ALP in cases compared to controls which are taken as important markers for diagnosis of ICP. Serum fasting TBA values were very significantly raised (<0.01) in cases as compared to controls. TBA values of >10 µmol/l were found in 72% of ICP cases. In the present study the incidence of perinatal complications were 45.83%, 52.38% and 66.66% in the groups with TBA concentration of 10-40 µmol/L, 40-100 µmol/L and >100 µmol/L respectively. This shows increased TBA values to be one of the important causes for perinatal complications, which advocates its estimation in all cases of pruritus of unknown origin. ICP is known to be relatively benign to the mother with future implications like increased incidence of cholelithiasis and ICP in future pregnancies. But it results in increased risks of perinatal complications like respiratory distress, meconium aspiration, preterm delivery, fetal bradycardia and even unexpected sudden IUFD.

In the present study, 54.90% of ICP cases developed perinatal complications compared to 12.24% ($p <0.001$) in controls which is consistent with the works of other authors[8,9].

The incidence of respiratory distress in the present study is 23.52% in ICP cases which substantiates the results found in other studies[11,12]. The elevation of TBA in foetal circulation reduces the activity of phospholipase A2 and causes the degradation of phosphatidyl choline in the foetal surfactant. There can be also direct toxic effect of bile acids on type II pneumocytes, through an increase in intracellular calcium and pneumonitis[15].

Preterm delivery is estimated to be 11.7- 60% in women with ICP and occur commonly between 32nd to 36th weeks of pregnancy[1,13]. The incidence was found to be slightly lower (9.8%) in the present study than other studies, but is significantly higher than that of controls (4.08%). The incidence of meconium aspiration and meconium stained amniotic fluid is found to be 19.60% in pregnancies complicated with ICP which is consistent with studies by various authors. It may result from foetal distress or from elevated TBA directly increasing contraction of foetal colon[16].

Sudden Intra uterine foetal death (IUFD) occurs in 0.4%-1.5% cases of pregnancy with ICP[1,13]. The majority occurs after 37th weeks of pregnancy. In the current study one case of foetal death (1.96%) was reported in the 38th week. Mechanism of IUFD in ICP seems to be multifactorial. Increased TBA can cause chorangiosis, a higher surface volume of capillaries and terminal villi and increased number of syncytial knots as a result of long lasting placental hypo-perfusion or low grade hypoxia[17]. Bile acid penetrates deep into placental and umbilical cord tissue in less than 3 hours and known to cause vasoconstriction of placental chorionic vessels and umbilical veins which may contribute to the risk of IUFD[18].

Summary and Conclusion

- Most women show no lasting hepatic damage, but ICP recurs in majority of cases with its associated perinatal complications.
- Foetal outcomes can be improved with early diagnosis with the help of estimation of LFTs and various strategies of active management.
- Induction of labour at 37-38 week of gestation with the aim of reducing the risk of sudden IUFD can be done after establishment of lung maturity as the incidence of foetal demise increases after 37th weeks of gestation.
- The results of this study needs to be substantiated with further large scale study.

Abbreviations

ICP – Intra hepatic cholestasis
TBA – Total bile acids
IUFD – Intra - uterine foetal death

Conflict of interest: No conflict of interest exists as the work is done independently by the authors. The study is self-financed and no financial aid has been received for the above work from any individual or organization.

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