Perinatal Outcome of Intrahepatic Cholestasis of Pregnancy

Hira Shafqat, Abeera Ch, Munawar Jannat, Almas Yasmeen, Zainab Abbas, Yusra Almas

Pak Emirates Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

Objective: To determine the perinatal outcome of intrahepatic cholestasis of pregnancy and its association with obstetric and biochemical parameters.

Study Design: cross-sectional study.

Place and Duration of Study: Pak Emirates Military Hospital, Rawalpindi, from Feb to Aug 2020.

Methodology: Among 3201 obstetric patients, 50 patients of obstetric cholestasis were included in the study. Data was collected on a well-designed proforma. Patients' characteristics such as age, parity, gestational age at diagnosis and delivery, mode of delivery and co-morbidities were taken along with biochemical markers. Two groups were made based on perinatal outcome, and associations with all variables were checked.

Results: Obstetric cholestasis was found to be 1.6%. The mean age of subjects was 27.36. The itching was the most common presenting complaint. (74%) subjects were primigravida. The majority, 29 (58%), were diagnosed between 34-35 weeks. The mean gestational age at delivery was 37.54 ± 1.96 weeks, with 70% caesarean section. Among perinatal outcomes, 24 (48%) had fetal distress, 2 (4%) had intrauterine growth restriction, 20(40%) had meconium-stained liquor, 2 (4%) had intrauterine fetal demise, 7(14%) had low birth weight babies,16.7% had poor APGAR score and 14 needed intensive care admission. The mean alanine aminotransferase (ALT) was higher among those with the adverse perinatal outcome, with a cut-off value of alanine aminotransferase (ALT) of 93.5 by ROC analysis.

Conclusion: Obstetric cholestasis leads to adverse outcomes. Although no definite marker can rule out the risk of intrauterine demise, increased fetomaternal surveillance with active management induction of labour protocols may reduce the incidence of adverse maternal and fetal outcomes.

Keywords: Adverse perinatal outcome, Alanine aminotransferase (ALT), Obstetric cholestasis.

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INTRODUCTION

Obstetric cholestasis, also known as intrahepatic cholestasis of pregnancy, is the most commonly diagnosed liver associated illness in pregnancy.[1] Obstetric cholestasis is characterized by pruritus all around the body, particularly palms and soles, worsening at night with the elevation of liver enzymes with or without raised serum bile acids. It occurs in the late second or third trimester of pregnancy and settles with the delivery of the baby with an excellent maternal prognosis.[2] Its prevalence is reported to be 0.3 to 5.6 per cent, and it varies across the globe.[3]

All differential diagnosis must be ruled out, as it is usually a diagnosis of exclusion. Exact pathogenesis and aetiology remain unclear but could be multifactorial such as geographical difference, genetic influence, steroid exposure in pregnant women, and hormonal factors.[4] Obstetric cholestasis have been related to adverse pregnancy outcomes and fetal complications. Previous studies have suggested an increase in spontaneous or iatrogenic premature delivery, intra-partum fetal distress, meconium-stained liquor, abrupt intrauterine fetal demise, caesarean section rates, neonatal intensive care unit admissions, meconium aspiration, respiratory distress syndrome and postpartum haemorrhage.[5,6] The cause of fetal demise is suggested to be sudden anoxia and cardiac arrhythmias probably due to high serum bile acids.[7] Oral Ursodeoxycholic acid 500 mg has widely been used as symptomatic relief, and it also lowers maternal liver function tests.[8] The aim of this study was to explore the adverse perinatal outcome in obstetric cholestasis and its association with biochemical parameters.

Correspondence: Dr Hira Shafqat, Department of Obs/Gynae, Pak Emirates Military Hospital, Rawalpindi-Pakistan

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METHODOLOGY

This cross-sectional study was carried out at Pak Emirates Military Hospital, Rawalpindi, from February to August 2020. Ethical approval (EC 190) was taken from the Ethical committee of Pak Emirates Military Hospital. The sample size was calculated using a WHO calculator with a 95% confidence interval using a descriptive study done in Shalamar medical and

dental college Lahore, from Oct 2014 to Oct 2015, as the reference article.[9] The diagnosis of intrahepatic cholestasis was made according to RCOG guidelines. Data was collected on a well-designed pro-forma after taking informed consent.

Inclusion Criteria: Patients presenting in the late second or third trimester of pregnancy with pruritus and abnormal liver function tests were included in the study.

Exclusion Criteria: Patients with cholelithiasis, acute or chronic viral hepatitis, primary biliary cirrhosis, pre-eclampsia, multiple pregnancies, allergic skin diseases and acute fatty liver of pregnancy were excluded from the study.

In addition, all differential diagnosis were excluded using liver ultrasound, serology for hepatitis A, E, B and C and liver autoantibodies. After diagnosis, all patients were prescribed ursodeoxycholic acid. Feto-maternal monitoring was done every week with maternal serum liver function tests and a modified biophysical profile. In addition, mothers were asked to maintain fetal kick count charts, and where necessary, a cardiotocograph and umbilical artery Doppler were also done. Pregnancy was prolonged till 38 weeks if all tests were reassuring except for a few patients who failed to follow up on time and presented at later gestations.

Patients' characteristics such as age, parity, previous mode of delivery, gestational age at diagnosis, gestational age at delivery, the current mode of delivery, history of obstetric cholestasis and co-morbidities were jotted down on a predesigned proforma. The biochemical parameters evaluated at the time of diagnosis were Alanine aminotransferase (ALT), total serum bilirubin, alkaline phosphatase (ALP), haemoglobin, platelet count, total leukocyte count and coagulation profile. In addition, neonatal APGAR score at one min, gender, weight and well-being was taken at delivery time.

We defined adverse perinatal outcomes as the occurrence of intrauterine fetal demise, fetal growth restriction, preterm delivery, pathological CTG or absent or reversed end-diastolic flows on umbilical artery Doppler indices, meconium-stained liquor, low birth weight, neonatal ICU admission, meconium aspiration and respiratory distress syndrome and early neonatal death. In addition, maternal postpartum haemorrhage was also evaluated.

Statistical Package for Social Sciences (SPSS) version 23.0 was used for the data analysis. Quantitative variables were summarized as Mean ± SD. All patients were later divided into two groups based on at least one adverse perinatal outcome. Normality of distribution was assessed via Kolmogorov-Smirnov test. Pearson chi-square and fisher exact were used for categorical data and independent sample t-test for normally distributed continuous variables. Mann-Whitney U test was operated for non-normally distributed data. The *p*-values were calculated and values ≤0.05 were assumed as significant. ROC curve was used to estimate the cut off value of serum alanine aminotransferase to envisage adverse outcomes.

RESULTS

Between February and August 2020, 52 patients with obstetric cholestasis were diagnosed out of 3201 obstetric patients who came for antenatal check-ups and delivery. Out of these, two patients lost to follow-up and were excluded from the study. The incidence was found to be 1.6%. The mean age of patients was 27.36 ± 2.99 years. The itching was the most common presenting complaint. Thirty-seven (74%) subjects were primigravida, and the rest were multigravida. Out of multigravida mothers, 3 (23.1%) had a recurrence of ICP. Six (12%) patients were diagnosed at the gestational age of 30-31 weeks, 8 (16%) between 32-33 weeks, 29 (58%) between 34-35 weeks and between 37 and 38 weeks were seven patients (14%). Co-morbidities included gestational hypertension in 5 (10%) subjects, gestational diabetes in 7 (14%) and ITP in one patient. 2 (4 %) patients were delivered between 31 and 32 weeks, eight between 33 and 36 weeks. The rest were delivered at or after a term, with the mean gestational age of delivery being 37 ± 2.13. The mode of delivery was vaginal in 15 (30%) and LSCS in 35 (70%) subjects.

Among perinatal outcomes, 24 (48%) had fetal distress, 2 (4%) had intrauterine growth restriction, 18 (36%) had meconium-stained liquor, grades 1-2, and 2(4%) had passed grade 3 meconium, 2 (4%) intrauterine fetal demise, 1 (2%) baby was Microprimie and required ventilatory support and expired in the early neonatal period, 6 (12%) were very low birth weight babies and rest 43 (86%) had normal birth weights (Figure-1). We had 37 (74%) male babies, and 13 (26%) were baby girls. 16.7% had poor APGAR score at one minute. Fourteen (29%) needed intensive care admission, out of which 3 had MAS and eight had RDS/TTN, as seen in Figure-2.

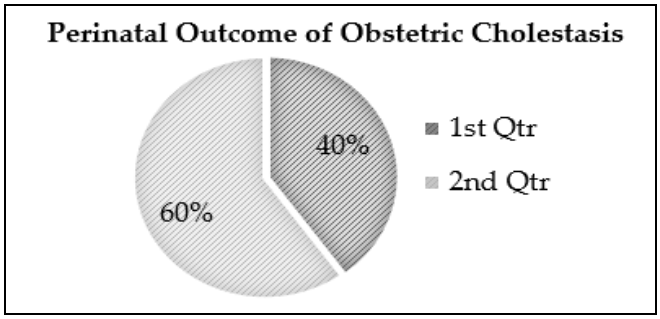

Figure-1: perinatal outcome of obstetric cholestasis: 40% Normal outcome 60% adverse perinatal outcome.

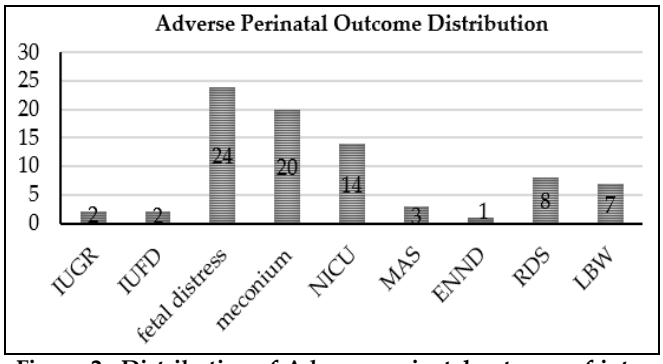

Figure-2: Distribution of Adverse perinatal outcome of intrahepatic cholestasis.

Among maternal outcomes, only 4(8%) had primary PPH. The mean of all characteristics and biochemical parameters are shown in the Table-I.

Table-I characteristics and biochemical parameters of obstetric cholestasis.

Characteristics	Mean	SD
Age (Year)	27.14	2.87
Gestational Age at Delivery (weeks)	37.54	1.96
Gestational Age at Diagnosis (weeks)	34.40	2.19
Alanine Aminotransferase (IU/L)	116.96	72.02
Bilirubin (mmol/l)	15.92	17.45
Alkaline Phosphatase (IU/L)	266.64	80.47
Hemoglobin (g/dl)	11.60	1.31
Platelet Count (×10³/mm³)	194.50	65.93
Total Leukocyte Count (×10³/mm³)	9.22	1.970

All parameters were compared by making two groups based on adverse perinatal outcomes. The mean values of ALT and total bilirubin at the time of diagnosis were higher among the group with the adverse outcome with a significant *p*-value. Those with poor outcomes had lower gestational age when their diagnosis was made compared to those with healthy babies. The previous history of obstetric cholestasis had no significant influence on perinatal outcome. There was no difference between co-morbidities between the two groups (Table-II).

Table-II: Association of obstetric and biochemical characteristics with adverse outcome.

Parameters	Adverse Outcome	Normal Outcome	*p*-value
Age (Years)	27.51 ± 3.14	26.75 ± 2.4	0.667
Gestational Age at Diagnosis (weeks)	33.65 ± 2.33	35.35 ± 1.49	0.027*
Gestational Age at Delivery (weeks)	36.96 ± 2.27	38.30 ± 0.97	0.065
Parity	1.32 ± 0.47	1.15 ± 0.36	0.197
Previous History of Obstetric Cholestasis	3 (26%)	-	0.27
White Cell Count (×10³/mm³)	9.22 ± 1.66	9.23 ± 2.40	0.57
Hemoglobin (g/dl)	11.49 ± 1.24	200.15 ± 64.38	0.44
Platelet Count (×10³/mm)	190.73 ± 67.7	200.15 ± 64.38	0.362
Alanine Aminotransf (IU/L)	141.6 ± 76.1	80.0 ± 46.8	0.001*
Bilirubin (mmol/L)	14.96 ± 7.5	17.35 ± 26.35	0.049*
Alkaline Phosphatase (IU/L)	273.96 ± 74.9	256.40 ± 88.58	0.46

ROC analysis was used to determine the cut off value of ALT, which was statistically significant. Values above 93.5 could be used to foresee adverse outcomes with 66.7 % sensitivity and 75% specificity, as shown in Figure-3.

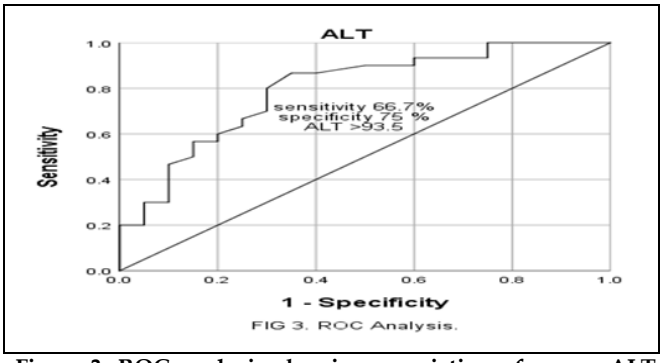

Figure-3: ROC analysis showing association of serum ALT levels with adverse perinatal outcome.

DISCUSSION

Intrahepatic cholestasis of pregnancy is characterized by itching without the appearance of the rash and increased serum ALT with or without raised serum bile acids. It is a liver associated illness specifically occurring in pregnancy. It resolves immediately postpartum.[10] In our study, all patients of obstetric cholestasis presented with generalized pruritis, particularly around the palms and soles. Our study revealed this disease among our population to be 1.6%.[11] San Francisco General Hospital conducted a study on 101 pregnant women with obstetric cholestasis between

January 2005 to March 2009 and found the prevalence to be 1.9%.[12]

Its aetiology and pathogenesis remain controversial but are supposed to be multifactorial. Some studies have suggested that genes encoding hepatobiliary transport proteins are mutated, which results in ICP.[13] It tends to recur in subsequent pregnancies. The mean age of patients was 27.36 ± 2.87, according to a previous study on 320 patients between 1988 to 1990 at Pontificia university Catolica de Chile. In our study, the rate of recurrence was 23%. In a study carried out in China on 1241 pregnant ladies in 2007, the recurrence rate was 30.2%.[14] More than 70% of our patients were primigravidas. Gestational age at the appearance of symptoms was 33-34 weeks in most of our patients. Our study revealed that earlier disease onset had a positive association with adverse perinatal outcomes. Earlier onset is deciphered as presenting at or before 33 weeks of pregnancy which corresponds to a retrospective study done at International Peace Maternity and Child Health Hospital Shanghai from January 2014 to December 2016, which showed a cut off gestational age below 34 weeks as a marker of adverse perinatal outcome.[15]

The mean gestational age at delivery was 37.5 weeks. There is evidence that early delivery may reduce perinatal mortality and poor outcomes.[13] As per RCOG guidelines, labour induction should be offered after 37 weeks of gestation. Seventy percent of subjects in our study delivered via caesarean section, which is comparable to a study done by Medda *et al*. which showed the caesarean section rate to be 63 percent.[16] Eight percent of mothers went into primary PPH. This is in contrast to previous studies, where an increased rate of PPH was observed.[1] The present study showed that the disease is linked with the adverse perinatal outcome and demographic, biochemical and obstetric parameters have associations with it. Three large hospitals in Netherland conducted a study on 215 women with obstetric cholestasis from January 2005 to August 2012.[17] Main outcomes included preterm birth, meconium-stained liquor, asphyxia and perinatal death. Results revealed that ICP is associated with a higher incidence of adverse perinatal outcomes.

In the present study, preterm deliveries did happen, but all were Indicated preterm births either due to abnormal CTG or absent Doppler indices. In accordance with the literature, the current study had only 2(4%) intrauterine fetal deaths. Both patients had no additional risk factors.[18,19] Studies on women with OC showed an increased rate of preterm delivery and meconium in liquor.[20] Many studies have reported the risk of intrauterine fetal death significantly higher in women with this disease.[1,5,21] Our study also showed increased meconium-stained amniotic fluid, growth restriction, low-birth weight babies and more intensive care admissions. In conformity with previous studies, 16% of neonates had RDS. According to some authors, bile acids could be responsible for respiratory distress by interfering with surfactant activity.[22]

Based on perinatal consequences, we divided all patients into two groups. The association between all outcomes and characteristics was assessed. It was found that the higher the serum ALT, the worse the baby's outcome. Among biochemical markers considered in this study, there was a positive correlation between serum ALT and bilirubin with poor perinatal outcomes. In 1.5 years retrospective study on ICP patients at Kanuni Sultan Saleyman Training and Research Institute, the association between mother/baby complications and OC was extensively studied. It showed a clear association between raised serum ALT, AST and bilirubin with adverse baby outcomes.

In contrast, the same study has mentioned a positive correlation between older age and adverse perinatal outcomes. There was no statistically significant difference between the two groups' ages in our study. There was only one fetal demise in their study and that too in mothers with multiple risk factors, so they concluded that the aetiology of fetal demise could be multifactorial.[6] RCOG guidelines suggest delivery after 37 completed weeks of gestation with maternal and fetal monitoring at weekly intervals after the diagnosis may reduce the incidence of intrauterine fetal demise.

The fundamental mechanism related to adverse outcomes is unknown, but it has been postulated that higher serum bile acids and their metabolites might be associated with it.[23,24] Nonetheless, our study had limitations. We could not check serum bile acids in our subjects as it required much funding. The relationship of comorbidities with ICP could not be clearly defined. Larger extensive studies are necessary to estimate the severity of this disease and adequate management.

CONCLUSION

Cholestasis of pregnancy leads to adverse perinatal outcomes. Although no definite marker can rule out the risk of intrauterine fetal demise, increased feto maternal surveillance with active management induction of labour protocols

may reduce the incidence of adverse perinatal maternal and fetal outcomes.

Conflict of Interest: None.

Authors' Contribution

HS: Data collection, data analysis, article writing, AC: Drafting of article, MJ: Data analysis, AY: Proof Reading and data collection and analysis, ZA: Data acquisition and analysis, YA: Data interpretation.

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