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ORIGINAL RESEARCH

Bile acid blood levels in detecting severity of IHCP and its role in deciding the time of delivery for better perinatal outcome

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ABSTRACT

Introduction: Obstetric cholestasis typically occurs during the later stages of pregnancy and is characterized by severe itching, increased liver enzymes, and has multiple causes. Fetal monitoring in intrahepatic cholestasis of pregnancy (IHCP) is difficult as the conventional antepartum surveillance methods are not reliable in predicting the fetal outcome in these patients. This is because of the fact that sudden intrauterine death is seen in IHCP patients with elevated liver enzymes. The present study was done to evaluate the perinatal outcome using serum bile acids in obstetric cholestasis patients. **Material and methods**: The present observational study was conducted at department of obstetrics and gynaecology of SMGS Hospital among 100 pregnant women with symptoms of pruritis during the study period of one year. Maternal and fetal outcomes were noted and results were analysed using SPSS 25.0. **Results:** The mean age of patients was 29.34 years. The average serum bile acid was 35.71 umol/L. 60 patients had mild cholestasis and 40 had severe/moderate cholestasis. 85 patients delivered vaginally while 5 through instrumental delivery and 10 delivered by caesarean. The majority of births occurred at or after 37 weeks of gestation. In terms of neonatal outcomes, namely birth weight and Apgar scores at 1 and 5 minutes, they were all favorable. None of the infants had an Apgar score below 7 at 5 minutes. One stillbirth was noticed in the severe cholestasis group. There were no instances of neonatal mortality observed. **Conclusion**: Further research is required to assess the impact of serum bile acid levels on maternal and fetal outcomes in obstetrics cholestasis, as the current study yielded mostly favorable results. Early delivery at 34 to 36 weeks is recommended if serum bile acids are greater than 100 mmol/l.

Keywords: Bile acid, Cholestasis, Obstetric, Perinatal Outcome, Pregnancy

INTRODUCTION

Obstetrics cholestasis is the prevailing hepatic disease that occurs frequently during pregnancy [1]. This condition is reversible and is characterized by severe itching that affects the entire body, including the palms and soles of the feet, resulting in sleep loss[2].It typically occurs during the second or third trimester of pregnancy, accompanied with abnormally elevated serum aminotransferases and/or increased bile acid levels. The increase in total bilirubin levels is commonly linked to cholestasis. Clinical jaundice is rare but may present in 14-25% patients after 1-4 weeks of pruritus [3]. However, symptoms usually improve within 48 hours after giving birth but may reoccur in future pregnancies. [4,5] The precise etiology of this specific illness remains mostly unknown. [6,7] The diagnosis of IHCP is made through the process of elimination, when there is no evidence of liver or gallbladder illness. To diagnose the condition, it is necessary to measure the serum levels of liver enzymes, bile acid, bilirubin, and perform viral marker assays for hepatitis B and C. Additionally, an upper abdomen sonography may be required. The presence of mild upper abdomen pain, nausea, vomiting, anorexia, dark colored urine, and steatorrhea is frequently accompanied by malabsorption of fat-soluble vitamins. This can result in a deficiency of Vitamin K-dependent clotting factors, hence increasing the likelihood of postpartum hemorrhage (PPH). [2]

Prior research on the impact of obstetric cholestasis has indicated a correlation with an increased incidence of negative outcomes in newborns, such as premature birth, neonatal respiratory distress syndrome (RDS), meconium-stained amniotic fluid, admission to the neonatal intensive care unit, and stillbirth.[8,9] The estimated prevalence of mortality during pregnancy and shortly after birth is 0.5%. Severe cholestasis

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accompanied by elevated bile acid levels is correlated with an increased likelihood of neonatal problems [9,10]. The exact pathways connecting cholestasis to stillbirth are not yet fully understood. However, it has been shown that in utero deaths caused by cholestasis often occur in pregnancies that also have other underlying medical conditions [11]. Multiple animal investigations have demonstrated that elevated levels of BA have a detrimental impact on cardiomyocytes [12]. Therefore, it has been theorized that IHCP could cause abnormal heart rhythm in the fetus, potentially resulting in fetal demise. Perez et al. found that an acute high dose of cholic acid given to a pregnant sheep did not cause any harmful consequences. This shows that harm may only occur with prolonged exposure to the substance [13].

Currently, there is still uncertainty regarding both the management of prenatal care and the most favorable timing for delivery. There is currently no fetal monitoring method that has been proven to predict or decrease the risk of unfavorable perinatal outcomes. Hence the present study was done to evaluate the perinatal outcome using serum bile acids in obstetric cholestasis patients.

MATERIAL AND METHODS

The present observational study was conducted at department of obstetrics and gynaecology at SMGS, GMC Jammu among pregnant women during the study period of one year. Ethical clearance was taken from institutional ethics committee before commencement of study. Patients were asked to sign an informed consent form after explaining them the complete procedure of the study.

Through convenience sampling method, 100 pregnant patients in their second or third trimester were selected on the basis of inclusion and exclusion criteria.

Inclusion criteria

1. Patients with age above 18 years.
2. Patients with singleton pregnancy with symptoms of pruritus
3. Patients with diagnosis of intrahepatic cholestasis of pregnancy with elevated liver enzymes.
4. Patients with serum bile acid levels ≥10 μmol/L.

Exclusion criteria

1. Patients with multiple pregnancy.
2. Patients with HELLP syndrome
3. Patients with Acute Fatty Liver of pregnancy.
4. Patients with one or more medical diseases such as cardiac, hematologic, acute or chronic renal disease.
5. Patients with other hepatobiliary disorders like hepatitis A, B, C, D and E, biliary stones, cholangitis.

The severity of IHCP was classified according to fasting serum bile acid levels (bile acid levels of ≥10–39 μmol/L and ≥40 μmol/L regarded as mild and severe/moderate ICP, respectively(40 to 100 mmol as moderate and >100 mmol/l as severe).A comprehensive record of the patient's medical history and examination results was documented. The women were closely watched using various methods including daily fetal movement count, cardiotocography, biophysical profile, and fetal ultrasonography at regular intervals to ensure proper fetal surveillance. According to worldwide guidelines, patients were administered a standardized treatment program. They were put on ursodeoxycholic acid andor cholestyramine with dosage as per severity of symptoms. Information was collected on maternal events of preterm premature rupture of membranes (PPROM) and method of birth, as well as perinatal outcomes such as fetal distress, Apgar score at 5 minutes, presence of meconium-stained amniotic fluid (MSAF), and admission to the neonatal intensive care unit (NICU). The RCOG recommendations were adhered to in order to diagnose non-reassuring fetal heart rate patterns and document fetal distress. Our study examined poor perinatal outcomes, including fetal distress, a low Apgar score (defined as less than 7 at 5 minutes), preterm birth, admission to the neonatal intensive care unit (NICU), and stillbirth in the severe cholestasis group. The study considered these unfavorable perinatal outcomes as unanticipated results.

The results were reported as the mean value plus or minus the standard error of the mean (SEM), or as a number or median, depending on the situation. Comparisons between the two groups were conducted using Fischer's test or Chi-square test, depending on the suitable circumstances. A significance level of $P < 0.05$ was used to determine statistical significance.

RESULTS

The mean age of patients was 29.34 years, average weight was 71.6 kgs and height was 162.8 cm with BMI of 27.8 kg/cm^2. The average serum bile acid was 35.71 umol/L as shown in table 1.Out of 100 patients 60 had mild cholestasis and 40 had severe /moderate cholestasis as shown in figure 1.

Table 1 Demographic data of patients

Variable	Mean±SD
Age (years)	29.34±0.63
Weight (kg)	71.6±2.4
Height (cm)	162.8±1.3
BMI (kg/cm^2)	27.8±0.2
Serum bile acid (umol/L)	35.71±4.02

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Figure 1 Distribution of patients according to severity of cholestasis

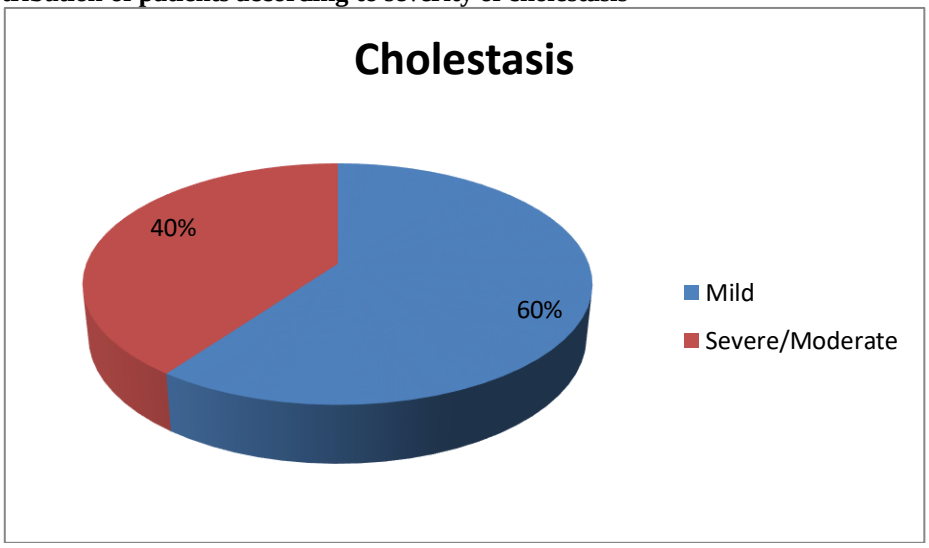

Table 2 displays the fasting serum bile acid levels, liver enzymes, and bilirubin levels. With the exception of the SGPT values, there were no notable disparities in these parameters between the two groups.

Table 2 Fasting serum bile acid levels, bilirubin levels and liver enzymes of patients

Enzyme level	Mild	Severe	P value
Serum bilirubin	0.87±0.05	0.89±0.06	0.056
SGOT	109.2±11.2	115.8±16.2	0.102
SGPT	107.9±8.7	119.2±16.3	0.003
S.ALP	197.02±15.4	205.3±21.6	0.067
PT	11.2±0.4	11.7±0.1	0.071

Table 3 displays the maternal outcome of patients who have been diagnosed with cholestatsis. 85 patients delivered vaginally while 5 though instrumental and 10 delivered caesarean. The primary reasons for emergency lower segment cesarean section (LSCS) and instrumental deliveries were fetal distress, followed by labor dystocia. The gestation age, neonatal demographics, and poor outcomes were recorded. The majority of births occurred at or after 37 weeks of gestation. Majority of the iatrogenic pre term births occurred in the severe cholestasis group which was statistically significant.

Table 3 Maternal outcome according to severity of cholestasis

Maternal outcome	Mild (60)	Severe (40)	P value
Vaginal delivery	50	35	0.213
Instrumental delivery	3	2	0.127
Caesarean delivery	7	3	0.198
Iatrogenic preterm birth	2	5	0.001
Spontaneous preterm labour	4	2	0.278
Mean Gestational age	39.23±0.107	38.90±0.102	0.002

The perinatal results are displayed in Table 4. In terms of neonatal outcomes, namely birth weight and Apgar scores at 1 and 5 minutes, they were all favorable. None of the infants had an Apgar score below 7 at 5 minutes. There were no instances of early neonatal mortality observed. One stillbirth was observed in the severe/moderate cholestasis group.

Table 4 Perinatal outcome according to severity of cholestasis

Perinatal outcome	Mild (60)	Severe (40)	P value
Meconium stained liquor	2	3	0.103
Abnormal intrapartum FHS pattern	3	1	0.131
Mean birth weight	2897.8±90.87	2690.7±102.7	0.189
1- minute Apgar	7	7	0.203
5- minute Apgar	9	9	0.341
Still birth	0	1	0.438

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DISCUSSION

Cholestatis is frequently seen in the field of obstetrics during pregnancy. The development of cholestasis is believed to be caused by multiple factors, mostly influenced by genetic makeup, geographic location, environmental fluctuations, and ethnicity. We studied 100 pregnant women with symptoms of pruritus who visited to department of obstetrics and gynecology of SMGS Hospital during the study period of one year.

The study group had a mean age of 29.34±0.63 years for women. In a comparable study, Renu et al [6] and Celik et al [14] reported that the average age of their study participants was 26.42 ± 5.79 years and 27.7 ± 5.3 years, respectively. Their findings were in line with the results obtained in the current investigation. The mean gestational age in the study group with was 39.23± 0.10 weeks. Pegu et al [15] and Arthuis et al [16] both reported a mean age of 37 and 38 weeks in their respective studies.

In our study, the maternal outcomes were predominantly favorable, as evidenced by numerous prior publications [17-20]. The majority of patients, specifically 85%, had vaginal deliveries, while the other patients underwent cesarean and instrumental deliveries. In line with the research conducted by Brouwers et al., we observed a much greater proportion of vaginal deliveries (76.7%) in comparison to caesarian deliveries [21].The current findings were in direct opposition to the study conducted by DeLeon et al., which reported a cesarean section rate of 65%[22.]

Pregnancy outcomes may be impacted by the severity of cholestasis of pregnancy, particularly when bile acid levels surpass 40 μmol/L [23,24]. According to these studies, we classified cases with a bile acid level of ≥10-39 μmol/L as mild, and cases with a bile acid level of ≥40 μmol/L as severe/moderate. Previous studies also classified cases into three categories: mild, moderate, and severe, with bile acid levels of 10-39, 40-99, and >/100 μmol/L respectively. The current study found that the prevalence of mild and severe/moderate was 60% and 40% correspondingly.

The only discernible distinction between the mild and severe instances, when examining maternal characteristics, was that the severe group had a tendency to deliver at an earlier gestational age, specifically due to an increase in iatrogenic premature deliveries. This finding aligns with the Brower's study, which involved a sample size of 215 women. The study revealed that the group of women with severe cholestasis of pregnancy had significantly shorter gestational age at diagnosis and gestational age at delivery compared to the mild group (P <0.001)[20].

The birth weights, Apgar ratings, and rates of fetal distress and meconium stained fluid were similar across mild and severe cases of cholestasis of pregnancy. In contrast to the study conducted by Garcia FJ et al., patients with severe cholestasis (with bile acid levels over 40 μmol/l) exhibited a greater incidence of meconium-stained amniotic fluid, admission to the neonatal intensive care unit (NICU), and overall neonatal morbidity [25]. The current findings contradict the conclusions of Glantz A et al's meta-analysis, which shows a substantial association between raised levels of bile acids in pregnant women and an increased risk of several negative outcomes during childbirth, including overall unfavorable perinatal outcomes, preterm birth, meconium-stained amniotic fluid, and suffocation or respiratory distress syndrome[26]. The decrease in gestational age at birth, namely due to an increase in the incidence of medically induced preterm deliveries, can be attributed to the proactive management of patients diagnosed with cholestatsis during pregnancy.

ESTIMATING TIME OF DELIVERY

Early delivery is recommended to reduce risk of sudden IUD's in patients with cholestasis of pregnancy. The timing of delivery should depend on balancing risk of fetal demise against the risk associated with preterm delivery. ACOG guidelines suggest to deliver baby at 34 to 36 weeks if serum bile acids are greater than 100 micromol/l and at 36 to 39 weeks if levels of seum bile acids are less than 100 micromol/l [27].

CONCLUSION

Women who have high levels of bile acid are more susceptible to experiencing negative outcomes during childbirth. Close monitoring of the fetus and regular testing of liver enzymes and bile acid levels are necessary to determine the best time for delivery in order to prevent negative outcomes for the fetus in pregnancies complicated by cholestasis.

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