Estimation of serum bile acid level for diagnosis of intrahepatic cholestasis of pregnancy, and its correlation with maternal and fetal outcome

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ABSTRACT

Introduction: Intrahepatic cholestasis of pregnancy is a disease characterized by pruritis over limbs associated with increased level of liver enzymes seen in the second and/or third trimester after ruling out other causes. Incidence of intrahepatic cholestasis of pregnancy varies widely, ranging from <1 to 27.6%. It causes adverse effects on the maternal outcome, fetal, and/or neonatal outcome.

Material and Methods: A prospective observational study was conducted on 51 pregnant patients in the third trimester (29-40 weeks) with elevated liver enzymes (Serum glutamic pyruvic aminotransferase >41 U/L, Serum glutamic oxaloacetic transaminase >40 U/L, serum alkaline phosphatase >300 IU/L) and/or generalized pruritis with or without skin changes starting in the second half of pregnancy, presenting to the department of Obstetrics and Gynaecology, Shri Ram Murti Smarak Institute of Medical Sciences (SRMS IMS) over a period of one and a half year (November 2019 – April 2021). Pregnant females with pre-eclampsia, Hemolysis elevated liver low platelets, viral hepatitis and other abnormalities of liver and of biliary tract; diseases of skin with itching and rash; acute and chronic kidney disease, bone disease, alcohol and drug addictions were excluded.

Results: Total 51 pregnant females, majority were from lower socioeconomic class (55%) and had an unbooked pregnancy (61%). The mean BMI of the study population was 27.02 ± 4.8 kg/m2. With respect to Body mass index 49% patients were overweight. On studying different liver function test parameters, SGOT and SGPT were elevated in 65% patients. Evaluating and comparing on basis of liver function test parameters 2 groups were divided on basis of serum bile acids- Group A (serum bile acid <10 μmol/L) and Group B ( serum bile acid ≥10 μmol/L). Increased chances of caesarean delivery were seen in group B (p=0.038). The most common indication being abnormal cardiotocography. Regarding neonatal outcome Appearance Pulse Grimace (reflex) Activity Respiration at 5 mins (0.005), respiratory distress at birth (0.022) and Neonatal Intensive care unit admission (p=0.025) had a significant association with raised serum bile acids (Group B).

Conclusion: Patients with intrahepatic cholestasis of pregnancy constitute a high risk group with respect to fetal, neonatal and maternal outcomes. Diagnosis of intrahepatic cholestasis of pregnancy should be supported by serum bile acids even in women with normal liver enzymes. This should be done to decrease the cost of investigations obviously after excluding other etiologies of itching. Early delivery after 37 completed weeks can be considered in women with serum bile acids >10 μmol/L, especially in non-compliant patients.

Keywords: Fetal, Intrahepatic cholestasis, Maternal, Pregnancy, Serum bile acids.


Source of support: Nil

Conflict of interest: None

INTRODUCTION

Liver diseases complicating pregnancy are placed into various categories, including those specifically related to pregnancy that resolve the following delivery. e.g., Intra-hepatic cholestasis of pregnancy. The second category involves acute hepatic disorders which are coincidental to pregnancy such as acute viral hepatitis. The third category includes chronic liver diseases that predate pregnancy such as chronic hepatitis, cirrhosis or esophageal varices.1

Liver injuries that are uniquely related to pregnancy typically resolve with or following delivery.

Intrahepatic cholestasis of pregnancy is a disease characterized with severe pruritis especially over palms and soles, increased level of liver enzymes and increased level of serum bile acids seen in the second and/or third trimester. The incidence of intrahepatic cholestasis of pregnancy varies widely, ranging from <1 to 27.6%.

Though there is an increased level of liver enzymes but the diagnosis should be confirmed on an elevated level of serum bile acid. Raised serum bile acid levels have an adverse effect on fetuses such as prematurity, meconium-stained amniotic fluid, fetal distress, respiratory distress, low Apgar scores, stillbirth and intra fetal uterine demise (IUFD); and increased neonatal intensive care unit (NICU) admissions.2 Also, there is an increased rate of cesarean section, most common indication being fetal distress. It can also cause postpartum hemorrhage and coagulopathy in pregnant women with increased intracranial pressure. The aim
of this study is to diagnose intrahepatic cholestasis of pregnancy by estimation of serum bile acid level in patients with abnormal liver function tests and to study its correlation with maternal and fetal outcomes.

MATERIAL AND METHODS

A prospective observational study was conducted on 51 pregnant patients recruited from the department of Obstetrics And Gynaecology, Shri Ram Murti Smarak Institute of Medical Sciences, who satisfied the inclusion exclusion criteria over the period of one and a half years (November 2019 – April 2021).

Inclusion criteria

Pregnant females in the third trimester (29-40 weeks) with:
- Elevated liver enzymes
- SGPT>41 U/L
- SGOT>40 U/L
- Serum alkaline phosphatase >300 IU/L
- And/or generalized pruritus with or without skin changes starting in the second half of pregnancy.

Exclusion criteria

Pregnant females with:
- Pre-eclampsia, HELLP
- Viral hepatitis
- Other abnormalities of liver and of biliary tract
- Diseases of skin with itching and rash
- Acute and chronic kidney disease
- Bone disease
- Alcohol and drug addictions

RESULTS

A total of 51 patients were included in this study. Regarding age-wise distribution, most patients were in the age group of 21-25 years (41%). The mean age of the study population was 26.92 ± 5.06 years. Most of the study population was from low socioeconomic status and a majority had unbooked pregnancies (61%).

On the distribution of the study population on the basis of their clinical presentation, it was found that approximately 26%, i.e., 13 patients were asymptomatic but had increased levels of liver enzymes (SGPT). Out of the symptomatic 38 patients, majority i.e., 92% were having generalized itching or itching especially over palms and soles (69% overall) followed by 55% with decreased fetal movements (41% overall) and 18% skin manifestation of itch marks (14% overall). Only 1 (3%) patient had clay-colored stools.

On studying individual liver function test parameters of the study population, it was found that SGOT was elevated in 86% patients and SGPT was elevated in 78% of patients. In 65% patients serum bile acid level was elevated. Direct bilirubin was found to be elevated in 39% patients.

Based on serum bile acid level, we divided the study population in two groups – Group A with normal serum bile acid level (< 10 µmol/L) (18 patients) and Group B with elevated serum bile acid level (≥ 10 µmol/L) (33 patients) and further analytical studies performed.

In Group A with normal serum bile acid level, 67% (12) were delivered vaginally and 33% (6) underwent cesarean section. Of 33 patients in Group B with elevated serum bile acid level, 64% (21) patients underwent cesarean section and 36% (12) were vaginally delivered. The association of mode of delivery with serum bile acid level showed that if the serum bile acid level was increased, the chances of cesarean delivery also increased significantly (p=0.038). It was found that the occurrence of postpartum hemorrhage and need of blood transfusion was more in Group B, but not statistically significant.

On studying the association of serum bile acid level with different parameters of neonatal outcome, significant association of APGAR at 5 minutes (p= 0.005), respiratory distress at birth (p= 0.022) and NICU admission (p= 0.025) with raised serum bile acid level was observed.

With respect to respiratory distress in newborn it was found that respiratory distress was significantly higher
when bile acid level was above 10 µmol/L (p=0.025). Further, it showed a significant association with raised total and direct bilirubin (mg/dL) (p=0.004 and 0.002, respectively). NICU admissions were significantly higher when bile acid was above 10µmol/L (p=0.025) and direct bilirubin (mg/dL) was elevated (p=0.004). SGOT, SGPT, ALP and total bilirubin have shown an insignificant association (p > 0.05) with NICU admission. APGAR at 5 min was significantly less (≤ 7) when bile acid was above 10 µmol/L (p=0.006). Also it was significantly less (≤ 7) when total and direct bilirubin (mg/dL) were raised, (p=0.028 and p=0.001), respectively. Rest other LFT parameters i.e. SGOT, SGPT, ALP and total bilirubin had no significant association (p > 0.05) with NICU admission.

APGAR at 5 min was significantly less (≤ 7) when bile acid was above 10 µmol/L (p=0.025). Further, it showed a significant association with raised total and direct bilirubin (mg/dL) (p=0.004 and 0.002, respectively). NICU admissions were significantly higher when bile acid was above 10µmol/L (p=0.025) and direct bilirubin (mg/dL) was elevated (p=0.004). SGOT, SGPT, ALP and total bilirubin have shown an insignificant association (p > 0.05) with NICU admission. APGAR at 5 min was significantly less (≤ 7) when bile acid was above 10 µmol/L (p=0.006). Also it was significantly less (≤ 7) when total and direct bilirubin (mg/dL) were raised, (p=0.028 and p=0.001), respectively. Rest other LFT parameters i.e. SGOT, SGPT, ALP and total bilirubin had no significant association (p > 0.05) with APGAR at 5 min.

DISCUSSION

Intrahepatic cholestasis of pregnancy (ICP) is a liver disease that is unique to pregnancy and is characterized by pruritus, associated with elevated serum bile acid level and/or amino-transferase levels; and improves spontaneously after delivery. Incidence of disease varies widely across the world, ranging from 1 to 27.6%. The highest incidence is amongst Araucanos Indians in Chile, that is 27.6%. The reported incidence in India is 1.2-1.5%. In our study, the mean age of the study group was 26.92 ± 5.06 years (mean ± S.D.) and the most common age group was 21-25 years. This was in accordance to a study conducted by Çelik et al. (2019) and Naga et al. (2019), where the mean age was 27.7 ± 3.7 years respectively.

The clinical presentation of the study population showed that 25% cases were asymptomatic but with elevated liver enzymes. Out of the 38 symptomatic patients (75%) from the study population majority complained of itching (92%) followed by persistent decreased fetal movements (55%) and skin manifestation (18%). Our findings were in agreement with a study performed by Arora et al. (2021) who reported that 96.0% women presented with itching, especially over palms and soles.

Considering the affiliation of mode of delivery with elevated serum bile acid level, it was found that with increasing levels of serum bile acids, the chances of cesarean delivery also increase significantly (p=0.038). Our findings were similar to study conducted by Hassan N et al (2020). This was in contrast to the study conducted by Sharma et al (2018) where no significant difference was observed between liver function test parameters and serum bile acid with the mode of delivery.

Shemer et al (2013) conducted a population-based cohort study, in which he concluded that patients with intrhepatic cholestasis of pregnancy were more likely to have a neonate with < 7 APGAR score at 5 min. Thus, we can surmise that in patients with Intra-hepatic Cholestasis (IHCP), low Appearance, Pulse, Grimace, Activity and Respiration score (APGAR) is common.

In the study conducted by Kurt et al (2011) respiratory distress at birth was reported in 28.6% infants from cholestatic pregnancy. In our study respiratory distress was found in 24% of infants of mothers with IHCP and it was statistically significant (p=0.022).

Contemplating the association of deranged LFT parameters with NICU admission, it was found that NICU admissions were significantly higher when bile acid was above 10µMol/L (p = 0.025). Same was observed with direct bilirubin (> 0.3 mg/dL) too. Rest of the parameters have shown insignificant association (p > 0.05). Garcia-Flores et al. (2015) conducted a prospective observational study in 145 pregnant patients with persistent pruritus and concluded that IHCP patients had higher rate of NICU admission and overall neonatal morbidity. According to Hassan et al. (2020) a high occurrence of NICU admissions (49.6% versus 15.4%) was observed in abnormal serum bile acid than the controls (p < 0.05).

CONCLUSION

Intrahepatic cholestasis of pregnancy (IHCP) is the most common cholestatic liver disease encountered during pregnancy. It is characterized by itching over whole body (especially over palms and soles) with onset in the...
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Diagnosis of IHCP should be confirmed by elevated serum bile acids in women with normal liver enzymes to decrease the cost of investigations after excluding other etiologies of itching. Early termination of pregnancy, after 37 completed weeks can be considered in women with bile acids > 10 μmol/L, especially in a noncompliant patient. Maternal morbidity is increased in terms of increased LSCS rates and discomfort due to pruritus. Maternal cholestasis is transient. It resolves postnatally. IHCP is associated with the adverse perinatal outcome as serum bile acid increases drastically. There is increased risk of meconium staining of amniotic fluid, fetal distress, spontaneous preterm delivery and sudden intrauterine fetal demise at term as evidenced in this study.

REFERENCES


Table 6: LFT parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SBA</th>
<th>SGOT</th>
<th>SGPT</th>
<th>ALP</th>
<th>Total Bilirubin</th>
<th>Direct Bilirubin</th>
<th>Indirect Bilirubin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Distress YES (n=8)</td>
<td>8 (100%)</td>
<td>7 (87.5%)</td>
<td>7 (87.5%)</td>
<td>6 (75.0%)</td>
<td>3 (37.5%)</td>
<td>7 (87.5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>NO (n=43)</td>
<td>25 (58.1%)</td>
<td>37 (86%)</td>
<td>32 (74.4%)</td>
<td>27 (62.8%)</td>
<td>2 (4.7%)</td>
<td>13 (30.2%)</td>
<td>2 (4.7%)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.023</td>
<td>0.913</td>
<td>0.423</td>
<td>0.507</td>
<td>0.004</td>
<td>0.002</td>
<td>0.533</td>
</tr>
<tr>
<td>NICU Admission YES (n=12)</td>
<td>11 (91.7%)</td>
<td>11 (91.7%)</td>
<td>9 (75.0%)</td>
<td>8 (66.7%)</td>
<td>2 (16.7%)</td>
<td>9 (75.0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>NO (n=39)</td>
<td>22 (56.4%)</td>
<td>33 (84.6%)</td>
<td>30 (76.9%)</td>
<td>25 (64.1%)</td>
<td>3 (7.7%)</td>
<td>11 (28.2%)</td>
<td>39 (100%)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.025</td>
<td>0.534</td>
<td>0.890</td>
<td>0.872</td>
<td>0.80</td>
<td>0.004</td>
<td>0.000</td>
</tr>
<tr>
<td>APGAR at 5 mins ≤7 (n=11)</td>
<td>11 (34%)</td>
<td>11 (100%)</td>
<td>10 (91%)</td>
<td>9 (82%)</td>
<td>3 (27%)</td>
<td>9 (82%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>&gt;7 (n=40)</td>
<td>22 (55%)</td>
<td>33 (83%)</td>
<td>29 (73%)</td>
<td>24 (60%)</td>
<td>2 (5%)</td>
<td>11 (28%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.006</td>
<td>0.135</td>
<td>0.202</td>
<td>0.179</td>
<td>0.028</td>
<td>0.001</td>
<td>0.449</td>
</tr>
</tbody>
</table>

Table 6: LFT parameters for second trimester or third trimester of pregnancy along with elevated serum aminotransferases and serum bile acid levels. It has considerable clinical implications in the course of pregnancy and on the perinatal and maternal outcome, timely diagnosis is important to improve both maternal and fetal prognosis.

SRMS Journal of Medical Sciences, July-December 2022; 7(2) 67