Original Article

Diagnostic Accuracy of Alanine Aminotransferase in Intrahepatic Cholestasis of Pregnancy and its Association with Maternal & Fetal/Neonatal Complications

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ABSTRACT

Objective: To estimate the accuracy of alanine aminotransferase (ALT), using bile acid levels as the gold standard in the diagnosis of intrahepatic cholestasis of pregnancy (ICP) and to assess the maternal & fetal/neonatal complications between ICP cases and healthy pregnant females as well as cases with high and very high ALT levels.

Methodology: After approval from the ethical committee, this cross-sectional study was carried out at the Department of Obstetrics and Gynecology, Mohi-ud-Din Islamic Medical College, Mirpur during six months from September 2024 to February 2025. Using non-probability convenience sampling, 2500 pregnant women were included after taking their informed consent. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of ALT were evaluated using bile acid levels as a gold standard. The frequencies of maternal and fetal/neonatal complications were compared between cases of ICP and healthy pregnant females and cases with high ALT (41-100 IU/L) and very high ALT levels (>100 IU/L). Data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 26.

Results: The frequency of ICP was 2.4%. Serum ALT has a sensitivity of 83.3%, specificity of 99%, and diagnostic accuracy of 98.6%. A receiver operating characteristic (ROC) curve showed an area under the curve of 0.911 indicating excellent diagnostic accuracy. Preterm delivery, induction of labor, low birth weight, and respiratory distress were more significant in patients with ALT levels >100 IU/L.

Conclusion: Serum ALT is a reliable marker for the diagnosis of ICP with high sensitivity, specificity, and diagnostic accuracy. The maternal and fetal/neonatal complications were significantly higher in patients with ICP particularly those with very high ALT levels.

Keywords: *Alanine aminotransferase. Bile acids. Intrahepatic cholestasis.*

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) frequently occurs in pregnancy with an incidence ranging from 0.1% to 15.6%. The frequency of ICP varies in various ethnic groups and geographical regions with genetic, hormonal, and environmental factors playing their role in the disease causation.[1,2] The disease is prevalent in South Asia.[3] It mostly manifests in the second and third trimester of pregnancy with itching in palms and soles. In 14-25% of pregnant women, jaundice is also present.[1] The disease is more common in increased maternal age, multiple gestations, twin pregnancies, positive hepatitis C serology, gall stones, and positive family history.[2] It is characterized by a compromised flow of bile. Hormones released during pregnancy impair the transport of bile acids into the bile ducts. Normally, bile acids from the fetus are transported into the mother. In ICP, the reciprocal process occurs with bile acids being transported into the fetus.[4] High bile acid levels lead to the secretion of cytokines in the liver with resultant inflammation and liver damage. In addition, it also causes liver damage by inducing oxidative stress and mitochondrial damage. High levels of bile acids are also toxic to the fetus and cause leukocyte migration and inflammation of the placenta.[5]

The diagnosis is made based on clinical manifestations, liver function tests and exclusion of other causes of itching and liver disease in pregnancy.[5] The bile acids are elevated in serum in >90% of the cases with the greatest sensitivity.[6] Serum alanine aminotransferase (ALT) has the greatest sensitivity among the liver enzymes for diagnosis of ICP with 2-10 times higher levels.[7]

The disease is associated with both maternal and fetal complications. The maternal complications include higher chances of developing gestational hypertension, diabetes mellitus, premature rupture of membranes (PROM) and postpartum hemorrhage (PPH). The fetal/neonatal complications include preterm delivery, stillbirth, fetal distress, neonatal asphyxia, and meconium staining of amniotic fluid.[8]

Intrahepatic cholestasis of pregnancy has profound effects on maternal and child health. This study was designed to estimate the diagnostic accuracy of ALT in the diagnosis of ICP keeping bile acid levels as gold standard. In the literature, the data on the diagnostic accuracy of ALT in ICP is limited. Serum bile acids are highly sensitive and specific marker of ICP but they are expensive and not routinely performed. On the other hand, ALT is inexpensive and is routinely done investigation. The results of

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the study would help in using serum ALT as a diagnostic marker in ICP if its sensitivity and specificity are found to be high. The study also determined the maternal and fetal/neonatal complications in these patients compared to normal healthy pregnant females and with respect to the rise in levels of ALT. Knowing the frequency and complications of the disease in our setup will guide us in early diagnosis and management of the condition to combat adverse outcomes.

METHODOLOGY

After approval from the ethical committee (Letter No. 1-2/24-MIMC/ERB/0024, 20-09-2024), this cross-sectional study was carried out at the Department of Obstetrics & Gynecology, Mohi-ud-Din Islamic Medical College, Mirpur during six months from September 2024 to February 2025. A sample size of 2500 pregnant females was calculated using 95% confidence interval, 10% margin of error, 89.7% sensitivity of ALT, and prevalence of ICP among pregnant females at 1.5%.[9] The pregnant women who presented in the Outpatient Department (OPD) for routine antenatal checkups or any complaints of pruritus during the second or third trimester of pregnancy were included after taking their informed consent using non-probability convenience sampling technique. The exclusion criteria were other causes of liver disease such as any type of hepatitis, acute fatty liver of pregnancy, eclampsia), and skin diseases that cause pruritus such as scabies. Pregnant women with pruritus, deranged liver function tests [with alanine aminotransferase (ALT) >40 IU/L, aspartate aminotransferase (AST) >40 IU/L and raised bile acids (>10 µmol/L)] presenting in the second or third trimester of pregnancy with the exclusion of other causes of liver disease were labeled as having ICP.[2] The demographic variables and co-morbidities of the participants were noted. The diagnostic accuracy parameters of ALT were determined by taking bile acids as the gold standard for ICP. True positive (TP) were the patients who are positive on both ALT and bile acid testing while true negative (TN) refers to those negative on both diagnostic modalities. Patients positive on ALT but negative on bile acids are labeled as false positive (FP) & false negative (FN) indicates patients positive on bile acids but negative on ALT. The ALT levels 41-100 IU/L were labeled as high and >100 IU/L were categorized as very high levels. All the participants were followed up and the maternal & neonatal complications were compared between ICP cases and healthy pregnant females & cases with high and very high ALT levels. The maternal complications included preterm delivery, induction of labor, postpartum hemorrhage, placental abruption, and cesarean section. The fetal/neonatal complications were low birth weight, respiratory distress, meconium aspiration, Apgar score (appearance, pulse, grimace, activity and respiration) & intrauterine death (IUD)/stillbirth.

STATISTICAL ANALYSIS

Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) version 26. Descriptive statistics (mean and standard deviation) and frequency (percentage) were used for numeric and categorical variables, respectively. The numeric and categorical variables were compared using an independent t-test and a Chi-square test, respectively. A p-value of ≤ 0.05 was statistically significant. A 2x2 table was made by taking bile acids as a gold standard. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-), and diagnostic accuracy of ALT were calculated. A ROC curve was made to determine the area under the curve (AUC) and the diagnostic accuracy of ALT. An AUC equal to or greater than 0.6 is considered meaningful. Values between ≥ 0.6 and <0.7 indicate poor diagnostic accuracy, ≥ 0.7 to <0.8 suggest fair accuracy, ≥ 0.8 to <0.9 reflect good accuracy while values above 0.9 represent excellent diagnostic accuracy.[10]

RESULTS

In our study, ICP was present in 60(2.4%) out of 2500 patients. The ICP cases and healthy pregnant females did not differ significantly in their demographic variables and co-morbidities (Table 1).

Sixty (2.4%) patients had ICP with high levels of bile acids. Out of these 60, 50(83.3%) patients had ALT levels above the normal range while 10(16.7%) patients had ALT within the normal range. Out of 2440 patients without disease, 25(1.03%) patients had high ALT showing false positive results. The relation of ALT with ICP taking bile acids as the gold standard was statistically significant (Table 2).

Serum ALT has a sensitivity of 83.3%, specificity of 99%, PPV of 66.7%, NPV of 99.5%, LR+ of 83.3, LR- of 0.17, and diagnostic accuracy of 98.6%. A ROC curve showed an area under the curve of 0.911 which indicates the ALT has excellent diagnostic accuracy in the ICP (Figure 1).

Preterm delivery, induction of labor and rate of cesarean section were more common in patients with

ICP as compared to healthy pregnant females with statistical significance (p-values=0.0007, 0.02, and 0.019, respectively). However, the frequency of postpartum hemorrhage and placental abruption were not statistically different. The neonatal complications were significantly more frequent in ICP versus healthy pregnant females except for IUD/stillbirth (Table 3).

Preterm delivery (p-value=0.02) and induction of labor (p-value=0.007) were significantly more common in patients with very high ALT levels. Among fetal/neonatal complications, low birth weight and respiratory distress occurred more frequently in patients with very high ALT levels. These results were statistically significant (Table 4).

Table 1: Demographic Variables and Co-morbidities of the Study Participants

Variables			ICP Cases (n=60)	Healthy Pregnant Females (n=2440)	p-value
Age (Years)		**Mean±SD**	29.1±4.5	28.5±3.8	0.22
BMI (kg/m²)			31.5±5.6	30.4±5.1	0.09
Parity	**Primigravida**	**Frequency (Percentage)**	17(28.3%)	830(34%)	0.35
	Multigravida		43(71.7%)	1610(66%)	
Gestational Diabetes			16(26.7%)	438(18%)	0.08
Gestational Hypertension			7(11.7%)	147(6%)	0.72

Table 2: Relation of ALT with Serum Bile Acids

Serum ALT levels	Gold Standard Test (Serum Bile Acid Levels)		Total	p-value
	ICP Cases (High)	Healthy Pregnant Females (Normal)		
High	50(83.3%) (TP)	25(1.03%) (FP)	75(3%)	0.00001*
Normal	10(16.7%) (FN)	2415(98.97%) (TN)	2425(97%)	
Total	60(2.4%)	2440(97.6%)	2500(100%)	

**Significant p-value*

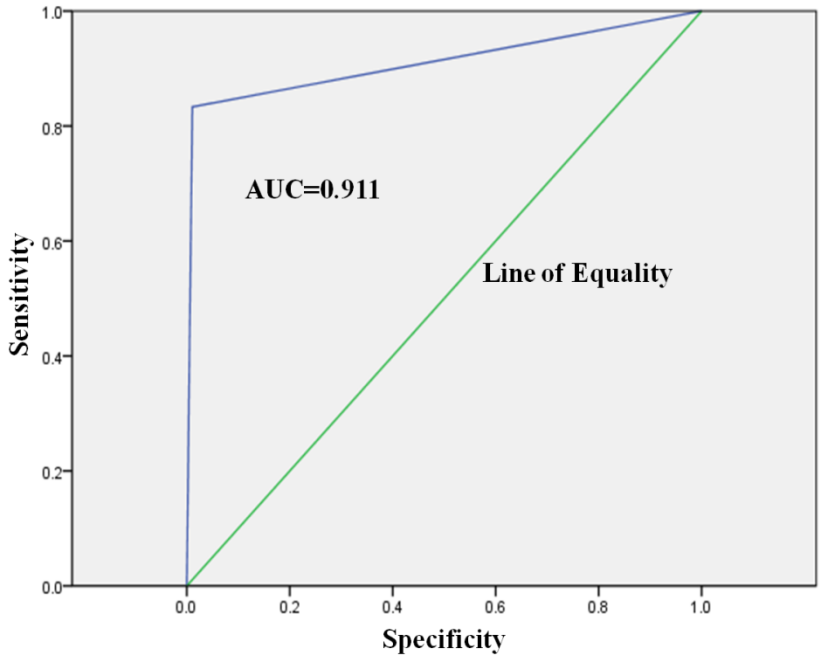

Figure 1: ROC Curve Showing the Diagnostic Accuracy of Serum ALT in ICP

Table 3: Maternal and Fetal/Neonatal Complications in ICP Cases versus Healthy Pregnant Females

Complications		ICP Cases (n=60)	Healthy Pregnant Females (n=2440)	p-value
Maternal	Preterm Delivery	14(23.3%)	244(10%)	0.0007*
	Induction of Labor	26(43.3%)	730(30%)	0.02*
	Cesarean Section	23(38.3%)	611(25%)	0.019*
	PPH	5(8.3%)	172(7.05%)	0.70
	Placental Abruption	4(6.7%)	73(3%)	0.10
Fetal/Neonatal	Low Birth Weight	12(20%)	195(8%)	0.008*
	Respiratory Distress	10(16.7%)	171(7%)	0.004*
	Meconium Aspiration	11(18.3%)	122(5%)	<0.0001*
	Apgar Score <7	10(16.7%)	171(7%)	0.004*
	IUD/Stillbirth	7(11.7%)	171(7%)	0.16

**Significant p-value*

Table 4: Maternal and Fetal/Neonatal Complications in Cases with High and Very High ALT Levels

Complications		ICP Cases with High ALT Levels (n=50)		p-value
		High ALT Levels (41-100 IU/L) (n = 30)	Very High ALT Levels (>100 IU/L) (n=20)	
Maternal	Preterm Delivery	5(16.7%)	9(45%)	0.02*
	Induction of Labor	11(36.7%)	15(75%)	0.007*
	Cesarean Section	11(36.7%)	12(60%)	0.10
	PPH	2(6.7%)	3(15%)	0.33
	Placental Abruption	2(6.7%)	2(10%)	0.67
Fetal/Neonatal	Low Birth Weight	4(13.3%)	8(40%)	0.03*
	Respiratory Distress	3(10%)	7(35%)	0.03*
	Meconium Aspiration	4(13.3%)	7(35%)	0.07
	Apgar Score <7	4(13.3%)	6(30%)	0.14
	IUD/Stillbirth	3(10%)	4(20%)	0.31

**Significant p-value*

DISCUSSION

Intrahepatic cholestasis of pregnancy causes liver dysfunction in pregnancy and its incidence varies from one geographical region to another. Only a few markers have been evaluated for its workup. Most of the studies have evaluated bile acids for the diagnosis of ICP and its relation with maternal and fetal/neonatal complications.[11]

The frequency of ICP was 2.4% in our study. The prevalence of the disease was 1% in the UAE and 3.73% in India.[12,13] The studies conducted in China showed the disease prevalence of 1.73% and 3.81%.[14,15] This indicates that the prevalence of ICP can vary within the same country and from one country to another as well. Our study found no significant difference in age, gestational age, body mass index (BMI), diabetes, and hypertension between cases and healthy pregnant females. Another study also reported no difference in age and gestational age between these two groups. [16]

In our study, serum ALT had a sensitivity of 83.3% and specificity of 99% at the cut-off value of 40 IU/L. The ROC curve showed an AUC of 0.911 indicating excellent diagnostic accuracy. Tasin et al. reported that serum bile acids and ALT were significantly higher in ICP as compared to non-ICP pregnant females. The sensitivity and specificity of ALT were 88% and 87% at 62 IU/L cut-off value and AUC of 0.89 showing good diagnostic accuracy.[16]

Our study results revealed a significantly higher frequency of complications in ICP patients with very high ALT levels. A study conducted in UAE compared complication rate between patients with bile acids <40 μmol/L and >40 μmol/L. The frequency of complications was statistically high in patients with bile acid levels >40 μmol/L such as premature birth, respiratory distress, low birth weight, poor Apgar score, and admission in neonatal intensive care unit (NICU).[12] A meta-analysis conducted by Zhou et al. also showed that severe ICP diagnosed by high bile acid levels was significantly related to poor maternal and neonatal outcomes such as premature rupture of membranes, preterm birth, admission to NICU and meconium-stained liquor.[17] A study conducted in Pakistan

revealed that ICP was responsible for PPH (10%), premature rupture of membranes (73%) and instrumental deliveries (75.5%). The disease caused meconium aspiration in 23.75%, preterm birth in 25%, low birth weight in 18.75%, fetal distress in 20%, NICU admission in 18.75% and stillbirth in 2.5% of the patients.[18] But the study did not compare the frequency of complications in non-ICP pregnant females.

A study conducted by Feng et al. reported that preterm birth, low birth weight, meconium aspiration, low Apgar score, and NICU admission were more common in ICP patients with higher levels of bile acids.[19] Another study reported significant differences in the frequencies of preterm delivery (18.60% in ICP versus 4.87% in non-ICP) and cesarean sections (51.31% in ICP versus 31.60% in non-ICP). Placental abruption and PPH were almost the same between the two groups. The birth weight was significantly less in ICP patients (9.30% versus 3.35%). However, fetal distress and stillbirth were not different between the groups.[14] A study from India revealed higher frequencies of induced labor (64.6% versus 18.8%) and cesarean sections (34% versus 24%) in ICP patients as compared to non-ICP participants. All other maternal and fetal complications were not significantly different between the two groups.[13] Wu et al. found a higher incidence of preterm delivery (22.24% vs 9.26%), PROM (6.02% vs 4.02%), cesarean section (56.14% vs 39.92%), low birth weight (4.63% vs 1.10%), and admission in NICU (27.41% vs 15.13%) in ICP patients as compared to non-ICP pregnant females.[15]

CONCLUSION

Serum ALT is a reliable marker for the diagnosis of intrahepatic cholestasis of pregnancy with a high sensitivity (83.3%), specificity (99%), and diagnostic accuracy (98.6%). The maternal and fetal/neonatal complications were significantly higher in patients with ICP as compared to non-ICP pregnant females. These complications were also significantly high in ICP cases with very high ALT levels (>100 IU/L).

LIMITATIONS & RECOMMENDATIONS

It was a single-centered cross-sectional study. The sensitivity and specificity of serum ALT were not estimated at various cut-off values in our study. Multi-centered studies with analytical designs are recommended. The sensitivity and specificity of serum ALT should be estimated at various cut-off values for accurate diagnosis and management. Our study recommends the use of ALT for the diagnosis of disease and monitoring of patients for maternal and fetal/neonatal complications.

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Authors' Contributions:
A.Y: Conceived the study, drafted the manuscript, and coordinated data collection.
N.S: Supervised the research and reviewed the manuscript.
R.K: Managed patient enrollment and clinical data verification.
F.H: Performed statistical analysis and contributed to results interpretation.
A.F: Assisted in literature review and data organization.
H.Z: Proofread the manuscript and ensured reference accuracy.

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