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ORIGINAL ARTICLE

Evaluating the Utility of Liver Transaminases as Predictors of Feto-Maternal Outcome in Lieu of Serum Bile Acids in Intrahepatic Cholestasis of Pregnancy: A Prospective Observational Study

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Abstract

Introduction Intrahepatic Cholestasis of Pregnancy (ICP) is a disorder of the second half of pregnancy causing pruritus and abnormal liver function tests (LFT). Incidence in India is 1.2–1.5%. ICP leads to adverse feto-maternal outcomes with early delivery indicated before serum bile acids (SBA) (gold standard) and hepatic transaminases are critically high. With paucity of evidence these levels are not well defined.

Objectives To determine the association of liver transaminases with pregnancy outcomes in ICP and evaluate critical levels for prediction of adverse outcomes.

Material and Methods A prospective observational study was conducted comprising 88 pregnant women with pruritus not associated with rash. After history and examination, LFT and SBA levels were done, treatment given and followed till pregnancy termination to determine the feto-maternal outcome.

Results The mean age of participants was 26.43 ± 3.35 years. The mean SBA, ALT and AST levels were 18.97 ± 10.320 µmol/L, 206.06 ± 45.71units/litre and 175.37 ± 101.088 units/litre respectively. 39.7% of participants were symptomatic for ICP while 38.6% responded to treatment. 34.1% underwent LSCS majorly (43.3%) formeconiumand 23.3% had foetal distress. 33% had preterm delivery. 5.68% of the neonates needed NICU admission and 6.8% had respiratory distress syndrome.

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The cut off for ALT on ROC curve analysis was 151.5 units/litre with AUC as 0.905, sensitivity and specificity of 89.7 and 70% respectively.

Conclusion ICP leads to adverse pregnancy outcomes. ALT is a promising predictor of adverse outcome and termination of pregnancy can be planned accordingly.

Keywords Intrahepatic cholestasis of pregnancy · Pruritus in pregnancy · Liver transaminases · Serum bile acids

Introduction

Abnormal liver function tests or elevated liver enzymes in pregnancy essentially needs a thorough interpretation to avoid being misled or pitfalls in diagnosis. There is a significant effect of these liver diseases in pregnancy on outcomes of pregnancy especially foetal outcome [1]. The liver disorders specific to pregnancy include hyperemesis gravidarum, pre-eclampsia, hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, acute fatty liver of pregnancy and intra hepatic cholestasis of pregnancy (ICP). These are mostly trimester specific [2].

Intrahepatic cholestasis of pregnancy is currently the most common hepatic disease/condition associated with pregnancy. The classical presentation includes nocturnal pruritus affecting the palms and soles in the absence of a rash, usually presenting in the second or the third trimester whereas diagnosed is confirmed by hypercholanemia (an elevated fasting levels of serum bile acid (SBA) level ≥ 10 mol/L) or elevated transaminases (alanine transaminase ALT, aspartate transaminase AST) [3]. Although measurement of SBA levels remains the gold standard for diagnosis, the availability of this test is still limited especially in remote areas. Also, the cost of the test may be burdensome for the underprivileged sections of the society. The worldwide incidence of ICP reported ranges between 0.2 and 2% [4, 5]. It varies broadly with ethnicity and change in geographic location and is most common in South America and northern part of Europe reportedly [4]. The incidence reported in India is 1.2–1.5% [6].

ICP has been found to be associated with many adverse feto-maternal outcomes, which includes heightened risk of preterm birth (both spontaneous and iatrogenic), meconium-stained liquor, neonatal depression, intrauterine demise, stillbirth, respiratory distress syndrome in the neonates and increased caesarean delivery rates [4, 5, 7–10]. Although ICP mostly presents in the second or third trimester of pregnancy, it can rarely present as early as the first trimester [4, 7].

The focus of treating ICP is to alleviate symptoms and avert foetal morbidity and mortality. Ursodeoxycholic acid (UDCA) is the drug of choice widely used for this purpose [4]. To avoid these adverse complications, early delivery is indicated before SBA and liver transaminases (alternative marker) reach a critical level but still their cut off levels are not determined and there is paucity of evidence regarding the same. In this study, we investigated the associations between adverse perinatal outcomes and serum transaminase levels at the time of diagnosis of ICP.

Objectives

To determine the utility of serum alanine transaminase levels compared with serum bile acids to predict the feto-maternal outcome of ICP and evaluate its critical levels.

Methodology

Study design Prospective Observational Study
Study Setting Department of Obstetrics and Gynecology, Dr. RMLIMS, Lucknow
Study duration 12 months
Study Participants Pregnant women of second or third trimester with symptoms of IHCP
Inclusion criteria

- All pregnant women attending the antenatal OPD with complaints of pruritus not associated with rash.
- Cooperative

Sample size For sample size estimation, study by Ahuja et al. (2021) was used [11].

$X = Z_{\alpha/2}{}^2 * \sigma^2/d^2$, Z$\alpha$/2-critical value of the normal distribution at α/2(for a confidence level of 95%, $\alpha = 0.05$ and the critical value is 1.96), σ–Standard of mean ALT levels among pregnant women with IHCP (value is 45.55), d–Margin of error for appropriate level of precision (value is 0.01) At 95% confidence interval, the minimum sample size was 80 pregnant women. With 10% loss to follow up, the total sample size was 88 pregnant women.

Data Collection Procedure

Patients fulfilling the inclusion and exclusion criteria were enrolled in the study after informed written consent. A detailed clinical assessment was done in the antenatal OPD.

Table 1 Baseline Characteristics of the Participants

Baseline characteristics		Mean ± SD	`N = 88	%
Age		26.43 ± 3.35	–	–
Religion	Hindu	–	78	88.6
	Muslim	–	10	11.4
Residence	Rural	–	38	43.2
	Urban	–	50	56.8
Parity	Nullipara	–	47	53.4
	Multipara	–	41	46.5
Diet	Veg	–	81	92.0
	Non-Veg	–	7	8.0
BMI (kg/m^2)		24.48 ± 1.94	–	–
HB (gm/dl)		11.04 ± 1.37	–	–
S. Bilirubin (µmol/L)		0.90 ± 0.639	–	–
S. SGPT/ALT (units/litre)		206.06 ± 45.71	–	–
S. SGOT/AST (units/litre)		175.37 ± 101.088	–	–
S.ALP (IU/L)		342.28 ± 157.965	–	–
T. Bile acids (µmol/L)		18.97 ± 10.32	–	–

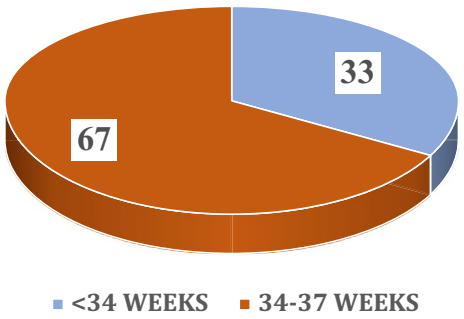

Fig. 1 Period of Gestation at the time of diagnosis of IHCP

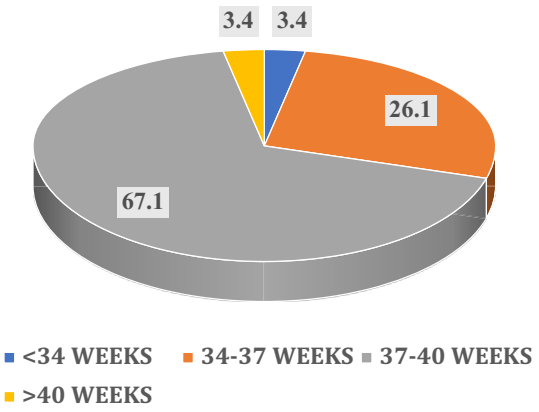

Fig. 2 Period of gestation at the time of termination of pregnancy

Antenatal obstetric history, history regarding onset and progression of symptoms, general physical examination, and obstetric examination; to rule out any pregnancy dermatoses presenting with pruritus. All pregnant women presenting with pruritus were advised liver function tests and total bile acids at the time of presentation along with routine antenatal investigations. 2 ml of blood sample was collected in a heparinized vial and sent to biochemistry laboratory for assessing the AST, ALT and bile acids level.

Data Analysis

Data were entered in Microsoft excel sheet. The data were analysed using SPSS version 24.0. Descriptive summary using frequencies, percentages, graphs, mean, and standard deviation were used to present study results. Probability (p) was calculated to test statistical significance at the 5% level of significance. Continuous variables were compared between two groups using the independent t test. Categorical variables were analysed using chi square test.

Receiver operator curve has been constructed for Serum ALT and AST levels with Serum bile acids (gold standard) to assess the area under the curve (AUC), sensitivity, specificity, NPV, PPV and diagnostic accuracy.

Results

The mean age of the study participants was 26.43 ± 3.35 years. 43.2% of the study participants were residing in the rural areas. More than half of the females (53.4%) were nulliparous. The mean serum bile acid levels were 18.97 ± 10.32 µmol/L. The mean ALT and AST levels were 206.06 ± 45.71 and 175.37 ± 101.088 units/Litre respectively (Table 1).

Out of the 88 study participants, **35** (39.7%) were symptomatic for ICP and total 34 (38.6%) responded to the treatment. 33% of the pregnant females were diagnosed with ICP before 34 weeks of gestation while 67% were diagnosed between 34 and 37 weeks of gestation (Fig. 1). More than two-third of the females (67.1%) had pregnancy terminated between 37 and 40 weeks of gestation either spontaneously or by labour induction or caesarean section (CS) (Fig. 2).

The mean serum ALT levels among the study participants who developed concomitant medical disorders in pregnancy namely gestational diabetes and pre-eclampsia was 112.67 ± 24.12 and 157.83 ± 67.98 units/L respectively and AST for the same was 107.45 ± 34.86 and 138.09 ± 28.91 units/L respectively and this difference was statistically significant. Out of the 88 study participants, 65.9% of the females with ICP underwent normal vaginal delivery and among them, 48.3% had induced labour due to high levels of transaminases. There was a significant difference in the mean serum ALT and AST levels of spontaneous and induced normal vaginal delivery ($p = 0.023$). The mean serum ALT and AST levels among those females who had CS due to

Table 2 Maternal Outcome of ICP and its association with Bile acids and Liver transaminases

Maternal outcome		*N* = 88	%	S.ALT (units/litre)	S. BILE ACIDS (μmol/L)	S. AST (units/litre)
Co-morbidities	Gestational Diabetes Mellitus	6	5.68	112.67 ± 24.12	8.69 ± 4.88	107.45 ± 34.86
	Pre-eclampsia	9	4.55	157.83 ± 67.98	10.13 ± 4.12	138.09 ± 28.91
p value		–	–	0.065	0.136	0.058
Normal Vaginal Delivery		58	65.9	98.12 ± 29.54	13.38 ± 1.72	92.93 ± 11.89
Spontaneous		30	51.7	143.45 ± 10.56	12.56 ± 6.42	135.12 ± 11.91
Induced		28	48.3	184.32 ± 12.83	18.41 ± 7.19	176.13 ± 23.3
***p* value**		–	–	**0.023**	0.281	**0.031**
LSCS		30	34.1	107.26 ± 21.76	16.43 ± 4.21	97.51 ± 31.11
Acute foetal distress		7	23.3	120.41 ± 15.38	10.05 ± 6.92	112.67 ± 14.12
Meconium stained liquor		13	43.3	157.92 ± 16.32	18.97 ± 6.4	144.82 ± 19.32
Associated surgery condition (APH, Contracted Pelvis)		3	10.0	123.42 ± 54.09	8.32 ± 2.11	118.43 ± 15.45
Elective		3	10.0	115.83 ± 18.34	7.98 ± 1.87	104.83 ± 23.3
Failed induction		4	13.3	121.97 ± 12.65	12.86 ± 6.19	119.32 ± 18.31
p value		–	–	0.257	0.145	0.832
Gestational Age at the time of delivery	Preterm	29	32.95	204.34 ± 56.76	17.62 ± 3.17	196.77 ± 38.14
	Term	54	61.36	92.34 ± 12.88	8.91 ± 2.01	88.02 ± 18.88
	Post-dated	5	5.68	156.45 ± 63.42	13.76 ± 3.89	145.92 ± 56.34
***p* value**		–	–	**0.004**	**0.023**	**0.762**

Bold values significant the *p* value < 0.05

Table 3 Foetal Outcome of ICP and its association with Bile acids and Liver transaminases

Foetal outcome		*N* = 88	%	Maternal		
				S. ALT (units/litre)	S. BILE ACIDS (μmol/L)	S.AST (units/litre)
Birth weight (Kgs)	< 2.5	12	11.4	109.56 ± 18.43	13.56 ± 5.9	98.34 ± 21.1
	≥ 2.5	78	88.6	110.05 ± 21.89	10.11 ± 2.3	109.66 ± 12.28
NICU admission		5	5.68	214.39 ± 9.18	18.88 ± 3.4	208.32 ± 13.48
Prematurity		29	32.95	108.45 ± 19.01	14.73 ± 2.8	103.17 ± 26.70
Apgar < 7 at 5 min		17	11.36	152.65 ± 16.57	16.43 ± 2.57	147.23 ± 28.12
RDS		6	6.81	135.13 ± 17.91	17.42 ± 5.2	126.92 ± 15.72

Table 4 ROC between S. ALT and bile acids

Parameters	Values
Area Under the Curve (AUC)	0.905
Std. Error	0.035
95% confidence Interval	0.837–0.973
p value	0.0001
Cut off	151.5
Sensitivity	89.7%
Specificity	70%
Positive Predictive Value (PPV)	50.0%
Negative Predictive Value (NPV)	96.15%
Diagnostic Accuracy	92.86%

Table 5 ROC between S. AST and bile acids

Parameters	Values
Area Under the Curve (AUC)	0.919
Std. Error	0.032
95% confidence Interval	0.856–0.983
p value	0.0001
Cut off	153.5
Sensitivity	85.9%
Specificity	80%
Positive Predictive Value (PPV)	40.0%
Negative Predictive Value (NPV)	97.44%
Diagnostic Accuracy	90.91%

meconium-stained liquor (MSL) (157.92 ± 16.32 units/L) was higher than those who had CS due to acute foetal distress (120.41 ± 15.38 units/L). 32.95% of the females with ICP had preterm delivery. Those females who had preterm delivery had very high serum ALT levels (204.34 ± 56.76 units/L) and AST levels (196.77 ± 38.14 units/L) when compared to term and post-dated delivery and it was statistically significant ($p = 0.004$). The SBA levels were significantly different among females with preterm, term and post-dated pregnancy (Table 2).

11.4% of the pregnant females with ICP gave birth to baby with birth weight less than 2.5 kg. 5.68% of the neonates born to the ICP mothers had NICU admission. 11.36% of the neonates had Apgar score < 7 at 5 min. 6.81% of the new born had respiratory distress syndrome. The females with ICP whose neonate were admitted NICU had higher serum ALT levels (254.39 ± 9.18 units/L) and AST levels (208.32 ± 13.48 units/L), followed by those whose neonate had Apgar score < 7 at 5 min (Table 3).

A receiver operator curve was constructed between Serum ALT and serum bile acids (considering it as gold standard for IHCP) and area under the curve (AUC) was 0.905. The cut off was 151.5 with sensitivity of 89.7%and specificity of 70% (Table 4). Similarly, for S.AST, the AUC was 0.919. The cut off was 153.5 with sensitivity of 85.9%and specificity of 89% (Table 5).

Discussion

Intrahepatic cholestasis of pregnancy is crucial condition which can result in fatal maternal and foetal outcomes. ICP leads to raised serum bile acid, pruritus as well as raised other liver enzymes like S.ALT and S. AST which can cross the placental barrier and cause sudden foetal death due to foetal arrhythmias caused by vasospasm of placental chorionic vessels. Hence ICP needs urgent management and for this purpose, there is necessity of potential markers for its early diagnosis and treatment. The following study was planned with the aim to determine the cut off of S.ALT levels to decide the termination of pregnancy before any adverse foetal outcome occurs.

The mean age of the study participants in our study was 26.43 ± 3.35 years. Similar mean age was also observed in study by Ahuja et al. (2021) as well as by Sumangali PK et al. (2017) who reported that majority cases of ICP occurs in the age group 21–30 years [2, 11]. More than half of the females (53.4%) were nulliparous. This finding agreed with Mitra B et al. (2020), who also observed that majority cases were nulligravida [12]. Majority of the pregnant females in our study were diagnosed with ICP between 34 and 37 weeks of gestation and other researchers have also made similar observations in their studies [12, 13].

In our study, out of the 88 study participants, 65.9% of the females with ICP underwent normal vaginal delivery (NVD) and among them, 48.3% had induced labour, while 34.1% had CS. Our findings are in concordance with study by Jhirwal et al. (2022) who also observed in their study that 31.58% ICP females underwent CS and 68.4 had NVD and majority of NVD had induced labour [13]. This is attributed to the fact that bile acids increase myometrial oxytocin receptors, due to which patients respond well to induction of labour. Moreover, due to risk of unfavourable foetal outcomes, timely decision of termination of pregnancy must be taken if the liver enzymes including bile acids levels are very high [11].

In our study, approximately one-third (33%) females had preterm delivery. A much higher proportions of preterm delivery have been reported in other studies by Sumangali et al. (2017), Desai A et al. (2020) and Jhirwal M et al. (2022) [2, 13, 14]. This can be attributed to iatrogenic prematurity due to risk of sudden unpredictable IUD and, also in cases where response to treatment is poor or there is clinical exacerbation of symptoms. However, the potential risk of prematurity needs to be carefully weighed against the risk of foetal demise when evaluating the cases individually [15]. There is paucity of specific guidelines for management of ICP worldwide. The guidelines published in 2011 by the Royal College of Obstetricians and Gynaecologists have created much need for discussion with women regarding management owing to scarce evidence in support of early term delivery to minimise stillbirth risk [16].

In the following study, the mean serum ALT levels among those females who had CS due to meconium-stained liquor (MSL) (157.92 ± 16.32 units/L) was significantly higher than those who had LSCS due to acute foetal distress (120.41 ± 15.38 units/L). Similar finding was also reported by Ahuja et al. [11] in their study and it was also statistically significant. In the study by Ahuja et al. [11], a correlation between MSL, foetal distress and NICU admission and levels of serum ALT was established. The results suggested cut off value for ALT at 133 units/L for predicting MSL and thus recommended induction of labour be planned above the cut off value to avoid adverse events. Likewise, in the present study, cut off of S.ALT for predicting adverse outcomes of ICP was found to be 153.5 units/L with sensitivity and specificity of 89.7 and 70% respectively. [11]. However, our cut off was slightly higher than their study. This can be due to variation in the methodologies of both the studies. Mahajan et al. [17] also predicted the cut off for S.ALT which was 64 IU/L with sensitivity and specificity of 88 and 90% and for S.AST which was 66 IU/L with sensitivity and specificity of 90

and 88% for feto-maternal complications in pre-eclamptic females with raised liver enzymes. Our study has showed that diagnostic accuracy of S. ALT levels is higher than that of S.AST in predicting need for early termination of pregnancy in ICP. Also, S.ALT is more sensitive for adverse foetal outcomes when compared with S.AST. Since, SBA are not easily available and are expensive, so serum ALT levels can be a promising and cost-effective marker for predicting prognosis of IHCP especially in low-resource settings [11].

The following study has few limitations. Firstly, the study has been conducted at a single tertiary care centre hence this limits the generalizability of the results. Secondly, serum ALT levels were not assessed at the time of termination of pregnancy in-order to understand its role in the immediate foetal outcome and estimate the amount of reduction in S.ALT, S.AST and bile acid levels following the treatment for ICP.

Conclusion

The ICP leads to adverse feto-maternal outcomes. Alanine Transaminase, being a cost-effective and easily available marker can be predictive of adverse outcomes; and therefore, termination of pregnancy can be planned above the critical cut off levels. However there is still need of more evidence based systematic reviews and meta-analysis to determine the most accurate cut off of S.ALT for predicting outcome and prognosis of ICP.

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Declarations:

Conflict of interest The authors declare that they have no conflict of interest.

Consent to Participate Informed consent was obtained from all individual participants included in the study.

Ethical Approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was obtained and granted by the Institutional Ethics Committee of Dr. Ram Manohar Lohia Institute of Medical Sciences. (IEC 49/20). As per Institutional Ethical Policy.

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