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Original Article

Early Detection of Intrahepatic Cholestasis of Pregnancy: Correlation Between Liver Enzymes and Adverse Fetal Outcomes

Sara Abbas*[1], Saghir Ahmad Jafri[1], Amna Iram[1], Tayyaba Imran[2], Anila Fareed[1], Sana Javed[1], Misbah Aalim[1]

[1]Nur International University, Lahore, Pakistan.

2Ittefaq Hospital, Lahore, Pakistan

Corresponding Author: Sara Abbas; Email: saraabbas1983@gmail.com

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ABSTRACT

Background: Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder that occurs in late pregnancy and leads to elevated bile acid levels in the maternal serum, posing risks to fetal health, including preterm labor and fetal distress. Understanding the relationships between liver enzyme levels and fetal outcomes can guide early diagnostic and management strategies.

Objective: To evaluate the significance of early detection of ICP through routine liver enzyme tests (AST and ALT) and its correlation with adverse fetal outcomes to inform clinical practices in regions with limited access to advanced diagnostic tools.

Methods: This cross-sectional study was conducted at the Ittefaq Hospital Trust, Lahore, involving 90 pregnant women categorized into three groups based on gestational age and ICP symptoms. Group A consisted of 30 women at 30-34 weeks of gestation, Group B included 30 women at 34-37 weeks, and Group C comprised 30 healthy pregnant women as controls. Serum AST and ALT levels were measured at day 0, 30, and 45. Fetal outcomes were monitored through ultrasound and medical records. Statistical analysis was performed using SPSS version 25, employing descriptive statistics and ANOVA to compare enzyme levels and fetal outcomes across groups.

Results: Group 2 exhibited significantly higher mean AST levels (96.58 U/L) and ALT levels (183.10 U/L) compared to Group 1 (AST: 49.95 U/L, ALT: 100.90 U/L) and Group 3 (AST: 25.30 U/L, ALT: 35.05 U/L). Adverse fetal outcomes, including intrauterine growth restriction (IUGR), were notably higher in Group 2 (76.7%) compared to Group 1 (13.33%) and Group 3 (0%). The statistical significance was marked with a p-value < 0.05 across all comparisons.

Conclusion: Elevated liver enzymes, specifically AST and ALT, are strongly associated with adverse fetal outcomes in ICP. Early detection and monitoring of these enzymes can be crucial in preventing fetal complications, particularly in resource-limited settings where traditional diagnostic measures are inaccessible.

Keywords: Intrahepatic Cholestasis of Pregnancy, ICP, Liver Enzymes, Fetal Outcomes, Alanine Aminotransferase, Aspartate Aminotransferase

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a condition characterized by impaired bile release from liver cells, leading to bile accumulation in the liver and resultant liver dysfunction. This condition, which primarily occurs during the third trimester when estrogen levels are at their peak, has significant implications for fetal health (1). The toxic effects of accumulated bile acids, such as chorionic vasospasm and fetal asphyxia, can lead to preterm labour and even sudden fetal death (1). Early detection and management of ICP are crucial, as the condition is more prevalent in the final trimester due to heightened estrogen levels which affect the metabolism and transport of bile acids. This is further complicated by mutations in the MDR3 gene (1-4).

The primary symptom of ICP is intense itching, typically occurring in the late stages of pregnancy without a rash and often accompanied by abnormal liver function tests (LFTs). This symptomatology can lead to sleep deprivation, pruritus, steatorrhea, and a general decrease in quality of life. The potential fetal consequences of ICP include stillbirth, premature delivery, and respiratory

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distress syndrome, which underscores the importance of prompt and effective management (1). Current recommendations for managing ICP involve inducing labor between 36 and 37 weeks of gestation to reduce the risk of fetal mortality (3).

This study was designed to investigate the significance of early detection of ICP in mitigating severe liver dysfunction and protecting fetal life. Conducted over three months with approval from the ethical board of NIU and Ittefaq hospital, Lahore, this cross-sectional study involved 90 pregnant women with symptoms of ICP (4-6). These participants were divided into three groups based on gestational age and presence of ICP symptoms, with routine monitoring including blood samples for LFTs and fetal ultrasounds on days 0, 30, and 45. The objective was to correlate the levels of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) with adverse fetal outcomes, thereby evaluating the potential of these markers as diagnostic tools in early ICP detection (7).

The study's results highlighted significant differences in AST and ALT levels across the groups, with elevated levels correlating with increased adverse fetal outcomes such as intrauterine growth restriction (IUGR) and fetal distress with arrhythmias. These findings suggest that early intervention and monitoring could substantially mitigate the risks associated with ICP, providing a less costly diagnostic alternative in settings where more sophisticated tests are not feasible. This is particularly relevant in rural areas of Pakistan, where the lack of availability and high cost of serum bile acid tests limit diagnostic capabilities (4).

MATERIAL AND METHODS

This cross-sectional study was conducted over a period of three months following the ethical approval granted by the institutional review boards of NIU and Ittefaq Hospital, Lahore, following the Declaration of Helsinki. The research setting was the outpatient department (OPD) of Gynaecology and Obstetrics at Ittefaq Hospital Trust, Model Town, Lahore. Ninety pregnant women who exhibited symptoms of intrahepatic cholestasis of pregnancy (ICP) and met the inclusion criteria were enrolled in the study. The inclusion criteria were a gestational age between 30 to 37 weeks, age between 27 to 39 years, multigravida status, and a previous history of cholestasis. The exclusion criteria included a gestational age less than 30 or greater than 37 weeks, age outside the 27 to 39 years range, primigravida status, and cholestasis due to other etiologies such as coagulopathies, thrombocytopenia, tumors, hepatitis B & C, primary biliary cirrhosis, HELLP Syndrome, and primary sclerosing cholangitis (8).

Participants were divided into three groups: Group A included 30 patients with a gestational age of 30 to 34 weeks with disturbed liver function tests, Group B comprised 30 patients with a gestational age of 34 to 37 weeks who had disturbed liver function tests and exhibited pruritus, and Group C included 30 healthy pregnant women who served as the control group. All participants provided written informed consent before inclusion in the study (9).

Data collection involved a self-designed proforma which captured personal information, symptoms of the disease, medical and drug history, details of general and physical examination, and laboratory investigations including liver function tests. Blood samples for the analysis of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were taken on day 0, 30, and 45 using AST activity assay kits (Alinity c-B8P170 by Abbott) and ALT activity assay kits (Alinity c- B4T840 by Abbott). Fetal well-being was checked through ultrasound using an Xavio model SSA-660A ultrasound machine. All participants were managed according to the antenatal visit protocol under the supervision of an obstetrician (10-13).

The data analysis was conducted using SPSS version 25. Descriptive statistics were calculated for all variables, including means and standard deviations for continuous variables and frequencies and percentages for categorical variables. Analysis of variance (ANOVA) was employed to compare the mean levels of AST and ALT across the three groups. A p-value of less than 0.05 was considered statistically significant, indicating important differences between the groups. The results of these analyses provided the basis for evaluating the potential of serum AST and ALT levels as diagnostic tools for early detection of ICP and its impact on fetal outcomes.

RESULTS

In the study, we evaluated serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and correlated these with fetal outcomes among three distinct groups of pregnant women. The results are presented in tabular format, followed by a detailed description of the findings. Statistical analysis proved significant differences across the groups, with a p-value of less than 0.05 indicating statistical significance.

Table 1: Descriptive Statistics of Serum Aspartate Aminotransferase (AST) Levels

Group	Sample Size (N)	Mean AST (U/L)	Standard Deviation	Minimum	Maximum
1	30	49.95	11.04	42.50	99.20
2	30	96.58	8.33	88.30	120.00
3	30	25.30	5.30	20.50	40.00

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Table 2: Descriptive Statistics of Serum Alanine Aminotransferase (ALT) Levels

Group	Sample Size (N)	Mean ALT (U/L)	Standard Deviation	Minimum	Maximum
1	30	100.90	15.18	90.60	175.20
2	30	183.10	8.12	175.00	199.20
3	30	35.05	4.05	32.00	40.00

Table 3: Fetal Outcomes

Outcome Description	Group 1 (% of 30)	Group 2 (% of 30)	Group 3 (% of 30)
Intrauterine Growth Restriction (IUGR)	13.33%	76.7%	0%
IUGR with Fetal Distress	0%	10%	0%
IUGR with Fetal Distress and Arrhythmias	0%	13.3%	0%
Mild IUGR	13.3%	0%	0%
Within Normal Limits (WNL)	73.3%	0%	100%

The analysis of serum AST levels across the three groups revealed significant variations, indicating a substantial influence of intrahepatic cholestasis on liver function as gestational age progresses. Group 2, which comprised patients with a later gestational age and symptoms of ICP, exhibited notably higher AST levels compared to the control group (Group 3) and those with earlier gestational ages (Group 1). Similarly, ALT levels were markedly elevated in Group 2, underscoring the progression of liver dysfunction in accordance with the severity of ICP symptoms.

The fetal outcomes notably differed among the groups, with Group 2 exhibiting a significantly higher rate of adverse outcomes, including severe cases of IUGR and complications such as fetal distress and arrhythmias. These results align with the elevated liver enzyme levels observed in this group, suggesting a direct correlation between the severity of ICP and the risk of adverse fetal outcomes. In contrast, Group 1, despite having disturbed liver function tests, showed milder fetal impacts, and Group 3 maintained normal fetal outcomes throughout the study period. These findings support the hypothesis that early detection and management of ICP can mitigate adverse fetal outcomes and highlight the importance of routine monitoring of liver enzyme levels as potential indicators of ICP severity.

DISCUSSION

The results of this study underscore the critical impact of intrahepatic cholestasis of pregnancy (ICP) on fetal outcomes and emphasize the importance of early detection and management. Elevated serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were significantly associated with adverse fetal outcomes, particularly intrauterine growth restriction (IUGR), fetal distress, and arrhythmias. These findings are consistent with previous research that has demonstrated the deleterious effects of liver dysfunction on fetal health (12-16).

Group 2, which included women with more advanced gestational ages and evident symptoms of ICP, showed the highest levels of liver enzymes and correspondingly, the highest incidence of severe fetal outcomes. This aligns with the understanding that the severity of ICP increases with gestational age, particularly as estrogen levels peak in the third trimester, exacerbating bile acid accumulation and liver dysfunction (2). Furthermore, the correlation between elevated ALT levels and ICP severity supports the potential of ALT as a diagnostic tool in resource-limited settings, where more sophisticated diagnostic tests might not be readily available (3, 17).

The study also highlighted the potential of routine liver function tests as a proxy for more expensive and less accessible diagnostic methods, such as serum bile acid tests. Given the substantial costs and limited availability of these tests in regions like rural Pakistan, ALT and AST testing could provide a viable alternative for early diagnosis and management of ICP, thereby reducing the risk of severe fetal complications (18).

However, the study was not without its limitations. The sample size, though adequate to demonstrate statistical significance, was relatively small, which may limit the generalizability of the findings to a broader population. Additionally, the study's cross-sectional design does not allow for causal inferences between ICP severity and fetal outcomes. Longitudinal studies would be beneficial in further elucidating the causal pathways and potential for intervention at different stages of pregnancy. In terms of strengths, the study benefitted from a well-defined sample and robust methodological framework, enhancing the reliability of the findings. The use of standardized diagnostic criteria and consistent monitoring protocols across all participants provided a solid basis for comparison and analysis (19). For future research, it would be advisable to expand the sample size and include diverse populations to enhance the external validity of the findings. Longitudinal designs could also help in understanding the progression of ICP and its

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impacts over the course of pregnancy. Additionally, investigating the role of genetic factors in the susceptibility and severity of ICP could offer deeper insights into personalized treatment approaches (20).

CONCLUSION

In conclusion, this study contributes valuable data to the growing body of literature on ICP and its implications for fetal health. It highlights the potential of routine liver enzyme tests as effective diagnostic tools and underscores the importance of early detection and proactive management in preventing severe fetal outcomes.

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