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Association of Deranged Liver Enzymes in Pregnancy with Fetal Outcomes in the Post-COVID Era

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ABSTRACT

Objective: To assess the association of feto-maternal outcomes of patients with deranged Liver Function Tests having a history of COVID-19 infection.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Gynaecology and Obstetrics, Combined Military Hospital, Rawalpindi and Quetta Pakistan, from Aug 22 to April 2023.

Methodology: A sample of one hundred and forty-six pregnant patients fulfilling the inclusion criteria were enrolled using a consecutive sampling technique. Various investigations were performed to confirm pregnancy-associated liver disease and rule out other causes of hepatitis. Patients with known diabetes, liver disease, renal disease and cancer before the current pregnancy were excluded. Patients were followed up until delivery, and their fetal and maternal outcomes were assessed.

Results: Among 2409 pregnant patients presenting during the study time, 146(6.06%) patients presented with deranged Liver Function Tests. Fetal adverse outcome (Meconium staining of liquor or Intrauterine Device was observed in 55/146(37.7%) cases. Of the 146 participants, four deaths occurred, resulting in a death rate of 4/146(2.74%). Significant differences were observed in haemoglobin levels and platelet counts between the surviving and deceased groups. Significant associations were found between survival outcomes and history of COVID-19 infection, COVID-19 in current pregnancy, and hypertension. However, none of the variables emerged as significant predictors of survival in the regression analysis.

Conclusion: Lower haemoglobin levels, lower platelet counts, history of COVID-19 infection, COVID-19 in current pregnancy, and hypertension were associated with poorer outcomes in pregnant patients with deranged Liver Function Tests.

Keywords: COVID-19 infection, Cholestasis of pregnancy, Liver function tests, Pregnancy.

How to Cite This Article: *Bano I, Naz S, Andleeb M, Khanum R, Nisar Z. Association of Deranged Liver Enzymes in Pregnancy with Fetal Outcomes in the Post-COVID Era. Pak Armed Forces Med J 2024; 74(4): 911-915. DOI: https://doi.org/10.51253/pafmj.v74i4.11144*

INTRODUCTION

The COVID-19 pandemic has brought about numerous health complications, especially in pregnant women. Liver function test (LFT) abnormalities have been observed in pregnant women with COVID-19, indicating potential liver injury because of the infection.[1] Several studies have reported LFT abnormalities in COVID-19 patients, including pregnant women.[2]

The abnormal LFTs in pregnant women may also be caused by intrahepatic cholestasis of pregnancy (ICP), a condition characterized by pruritus, impaired bile flow and elevated liver enzymes.[3] This condition typically develops in the third trimester of pregnancy but can also occur earlier. ICP is relatively rare, with an estimated prevalence ranging from 0.5% to 2% in different populations.[4] The exact cause of ICP is not fully understood, but hormonal and genetic factors are believed to play a role. It has been suggested that increased levels of estrogen and progesterone during pregnancy may contribute to the development of cholestasis by impairing the normal flow of bile.[5] Genetic factors, such as variations in genes involved in bile acid transport and metabolism, have also been implicated in the pathogenesis of the condition.[6]

The derangement of LFTs in pregnant women with COVID-19 infection may have significant implications, i.e., it may increase the risk of adverse maternal and fetal outcomes such as preterm birth, fetal distress, meconium staining and stillbirth.[7,8] The exact mechanisms underlying these complications are not fully understood, but it is thought that the accumulation of bile acids may disrupt placental function and compromise fetal well-being.[9] Moreover, liver injury during pregnancy may have long-term consequences for maternal health, such as the development of liver disease later in life. We, as obstetricians, had observed that more and more patients were received in the OPD having abnormal LFTs either of unknown cause or associated with cholestasis of pregnancy, especially post the COVID-19 pandemic. There

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Received: 06 Nov 2023; revision received: 10 Jan 2024; accepted: 16 Jan 2024

fore, we aimed to investigate the sudden increase in the prevalence of this condition. To look deeper into this emerging health issue of young pregnant patients, we also aimed to check for the association of fetal outcomes with deranged LFTs, current and previous COVID-19 infection and some other parameters.

METHODOLOGY

The cross-sectional study was conducted from August 2022 and April 2023 at the Department of Gynecology and Obstetrics of Combined Military Hospital (CMH), Rawalpindi and Quetta Pakistan. Ethical approval of the study was obtained from the Ethical Committee/ Institutional Review Board (ERC No: 448/8/Jan/2022). Sample size was calculated taking the prevalence of deranged LFTs at 2%.[10]

Inclusion criteria: Pregnant patients presenting to the Obstetrics units of CMH Rawalpindi and CMH Quetta with deranged liver function tests (LFTs) were included.

Exclusion criteria: Patients with known diabetes, liver disease, renal pathologies, and cancer diagnosed during or before the current pregnancy, were excluded.

The sample of 146 pregnant patients having deranged LFTs was enrolled using a consecutive sampling technique after obtaining informed consent. To confirm that the patient had pregnancy-associated liver disease as the cause of deranged LFTs, the following investigations were requested to exclude secondary causes. Baseline investigations such as complete blood count (CBC), renal function tests (RFTs), liver function tests (LFTs), bile acids, and serum electrolytes were requested by all patients. Viruses such as hepatitis A, B, C, and E, EBV and CMV can cause hepatitis of infectious aetiology; therefore, serological tests to rule out these infections were performed. Anti-smooth muscle antibodies and anti-mitochondrial antibodies were requested to rule out auto-immune hepatitis. Through a comprehensive medical history and physical examination, a history of high-risk behaviour, alcoholism and pre-existing chronic liver diseases such as chronic hepatitis, etc., were ruled out. Abdominal ultrasound scans were requested from the radiology department of the hospital to rule out the possibilities of cirrhosis and cholelithiasis. The sociodemographic and clinical data of the patients, including age, parity, gestational age, and history of current or past COVID-19 infection, was collected on a self-prepared structured proforma.

Statistical Package for Social Sciences (SPSS) version 24.0 was used for the data analysis. Quantitative variables with normal distribution were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Chi-square test and Independent sample t-test were applied to explore the inferential statistics. The p-value of ≤0.05 was considered statistically significant.

RESULTS

During the study period, 2409 pregnant patients presented to the Obstetrics unit for delivery. Among these patients, 146 had pregnancy-associated deranged LFTs and were therefore included in this study. The frequency and percentage of patients presenting with deranged LFTs were calculated to be 146/2409(6.06%). Among these 146 patients, only four died, while all the rest recovered within six weeks without residual liver disease as their LFTs returned to their normal ranges. The rate of adverse outcomes (maternal deaths) was 4/146 (2.74%) (Table-I).

The participants had an average age of 29.05±4.34 years, ranging from 21.00 to 38.00 years. The mean gestational age was 36.22±3.37 weeks. Haemoglobin level averaged at 11.07±1.27 g/dl. Systolic blood pressure had a mean of 116.64±13.37 mmHg, and diastolic blood pressure averaged 73.94±9.08 mmHg. Liver function tests showed a mean ALT level of 216.98±167.19 U/L, mean ALP level of 303.68±139.97 U/L, mean bilirubin level of 9.13±5.38 µmol/L and mean bile acids level of 37.68±18.87 µmol/L (Table-II).

Table-III compares maternal characteristics between those who had any adverse fetal outcome (IUD, meconium staining, or preterm birth) and those who did not. The characteristics analyzed include maternal age, gestational age, haemoglobin level, platelet count, systolic blood pressure, diastolic blood pressure, ALT (alanine aminotransferase), ALP (alkaline phosphatase), bilirubin, and bile acid levels. Table-IV presents a comparison of participant characteristics between the patients with and without a history of COVID-19 infection and adverse pregnancy outcomes. The adverse outcomes included the presence or absence of preterm birth, intra-uterine death, and meconium staining and rate of complications.

The analysis found no significant associations between patients with and without a history of COVID-19 infection and duration of pregnancy (p=0.070), Intrauterine death (p=0.938), and meconium staining (p=0.309). These findings contribute to our

understanding of the factors that may influence the outcomes of expectant women with deranged liver enzymes who have a history of COVID-19 infection.

Table-I: Characteristics of Study Participants (n=146)

Parameters	n(%)
Parity	
Primiparous	64(43.8%)
P2-P5	80(54.8%)
P>5	2(01.4%)
Pregnancy	
Singleton	143(97.9%)
Multiple	3(02.1%)
Duration of pregnancy	
Full term	119(81.5%)
Preterm	27(18.5%)
Intra-uterine death (IUD)	
No IUD	144(98.6%)
IUD	02(01.4%)
Mode of delivery	
Normal Vaginal Delivery	49(33.6%)
Elective C-section	77(52.7%)
Emergency C-section	20(13.7%)
Meconium Staining	
Positive	29(19.9%)
Negative	117(80.1%)
Pre-pregnancy COVID-19 Infection History	
Not detected	81(55.5%)
Detected	65(44.5%)
COVID-19 in current pregnancy	
Not detected	138(94.5%)
Detected	8(05.5%)
Maternal Adverse Outcomes (Death)	
Demise	4(2.7%)
Successful Recovery	142(97.3%)
Fetal Adverse Outcomes	
No Complication noted	91(62.3%)
Complication noted	55(37.7%)

Table-II: Clinical and Laboratory Parameters of the Patients (n=146)

Parameters	Mean±SD	Range
Age (years)	29.2±3.8	21.0–38.0
Gestational Age (weeks)	36.2±3.4	18.0–40.0
Hemoglobin Level (g/dl)	11.1±1.3	7.6-13.9
Systolic Blood Pressure (mmHg)	116.6±13.4	100.0–165.0
Diastolic Blood Pressure (mmHg)	73.9±9.1	60.0–105.0
ALT (U/L)	217.0±167.2	71.0–1436.0
ALP (U/L)	303.7±140.0	80.0-716.2
Bilirubin (µmol/L)	9.1±5.4	3.0-32.0
Bile Acids (µmol/L)	37.9±18.9	12.0-99.0

DISCUSSION

The prevalence of deranged LFTs during pregnancy has been reported to range from 3% to 5% in the existing literature.[11] However, in our study, we observed a higher prevalence, with 6.06% of the pregnant patients presenting with abnormal liver function. This discrepancy highlights the relevance and significance of our investigation.

Table-III: Comparison of Participant Characteristics between Survived and Deceased Individuals (n=146)

Parameters	Adverse fetal Outcome		*p*-value
	Positive Mean±SD (n=55)	Negative Mean±SD (n=91)	
Maternal Age in years	29.1±3.5	29.3±3.9	0.711
Gestational Age (weeks)	36.6±2.0	37.9±0.9	<0.001
Hemoglobin Level (g/dl)	10.8±1.2	11.3±1.3	0.021
Systolic Blood Pressure (mmHg)	116.6±14.0	116.7±13.0	0.996
Diastolic Blood Pressure (mmHg)	74.0±9.5	73.9±8.8	0.949
Alanine transaminase (U/L)	219.3±139.0	215.6±182.9	0.890
Alkaline phosphatase (U/L)	313.6±143.3	297.7±138.4	0.510
Bilirubin (µmol/L)	9.9±5.9	8.7±5.0	0.203
Bile acids (µmol/L)	37.5±18.4	37.8±19.3	0.929

Table -IV: Comparison of Pregnancy Outcomes between the Categories of History of COVID-19 Infection (n=146)

Parameters	History of COVID-19 Infection		*p*-value
	Positive (n=77)	Negative (n=69)	
Complications			
Noted	28(50.9%)	27(49.1%)	0.492
Not Noted	41(45.1%)	50(54.9%)	
Delivery			
Term	67(97.8%)	52(2.2%)	0.070
Preterm	10(87.5%)	17(12.5%)	
Intrauterine Death			
Negative	76(99.1%)	68(0.9%)	0.938
Positive	01(92.1%)	01(7.9%)	
Meconium Staining			
Not seen	60(98.6%)	57(1.4%)	0.479
Seen	17(50.0%)	12(50.0%)	

Our findings align with certain previous studies that have reported a higher prevalence of deranged LFTs in pregnancy, such as a study conducted in India, which recorded a prevalence of 11.9% for abnormal LFTs in their study sample.[12] Furthermore, a population-based study in China reported an incidence of 6.06% for abnormal LFTs due to cholestasis of pregnancy.[13] The majority of liver diseases occurring during pregnancy in otherwise healthy women are pregnancy-related, encompassing conditions like hyperemesis gravidarum, cholestasis of pregnancy, pregnancy-induced hypertension, pre-eclampsia, eclampsia, HELLP syndrome, and acute fatty liver of pregnancy.[14]

The rate of adverse maternal outcome, specifically maternal death, in our study was 2.74%. Although the number of adverse events in our study was relatively small, this rate is consistent with the findings of other studies. For instance, a study conducted in India reported that 3.74% of pregnant patients died due to liver disease, further substantiating the clinical relevance of our observations.[15] Another study reported a significantly longer duration of hospital stay in the abnormal LFTs Group (8.2±5.8 days) than in the normal LFT Group (6.0±2.8 days, p=0.02).[16] High levels of bile acids were found to be significantly related to adverse fetal outcomes such as preterm birth, meconium staining and the need for emergency cesarean section.[17]

Post the COVID-19 pandemic, an increased frequency of new-onset auto-immune pathologies such as myocarditis, acute transverse myelitis, thrombotic thrombocytopenia syndrome, rhabdomyolysis, etc., has been reported.[18] Although clinical research studies have provided reassuring data on the safety of COVID-19 vaccines, COVID-19 infection and vaccinations are associated with this emerging health concern.[19] In the context of the post-COVID-19 pandemic era, our study sought to explore the association between fetal outcomes in pregnant patients with deranged LFTs and COVID-19 infection. This investigation was prompted by the increased number of young pregnant patients presenting with deranged LFTs following the pandemic.

Our study identified Haemoglobin levels, gestational age, and bile acid levels as significant factors associated with adverse pregnancy outcomes. Patients without adverse outcomes exhibited higher haemoglobin levels and gestational ages and lesser bile acid levels than those with adverse outcomes.

While our study identified a few factors associated with adverse pregnancy outcomes in pregnant patients with deranged LFTs, certain variables such as maternal age, pregnancy type, COVID-19 vaccination status, and parity did not show significant associations. It is essential to acknowledge that the absence of statistical significance does not diminish their clinical importance, and larger-scale studies may offer further insights. Many studies have documented the relationship between deranged LFTs and ICP with adverse neonatal (preterm delivery, low birth weight, neonatal death) and adverse maternal outcomes (Postpartum haemorrhage, sepsis, multi-organ failure, blood transfusion).[15,16]

Our study contributes to the existing knowledge by demonstrating significant associations between adverse pregnancy outcomes and history of COVID-19 infection, COVID-19 in the current pregnancy, and haemoglobin levels in pregnant patients with deranged LFTs. These findings emphasize the importance of comprehensive prenatal care, early detection, and appropriate management of COVID-19 and anaemia in this vulnerable population.

RECOMMENDATION

COVID-19 Immunization must be done to prevent women from the adverse effects of COVID-19 during pregnancy, such as deranged LFTs. Pregnant patients having either current or past COVID-19 infection should be monitored closely for the emergence of complications.

LIMITATION OF STUDY

The data was collected from just two healthcare facilities. This may limit the generalizability of the results.

ACKNOWLEDGEMENT

We are grateful to Dr. Hamza Javed, Resident Radiology- Ayub Teaching Hospital Abbottabad.

CONCLUSION

Our study underscores the critical significance of timely detection and management of deranged LFTs in pregnant patients. Our findings highlight the multifaceted influence of factors such as COVID-19 infection, liver biomarkers, and haemoglobin levels on maternal and fetal outcomes. Comprehensive prenatal care, early detection, and appropriate management of these factors are imperative in optimizing maternal and fetal health. Our results advocate for the necessity of ongoing research to unveil the complex interactions and identify additional factors influencing pregnancy outcomes in pregnant patients with deranged LFTs.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

IB & SN: Data acquisition, critical review, approval of the final version to be published.

MA & RK: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

ZN: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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