Original Article

Frequency of Altered Liver Function Tests in Hyperemesis Gravidarum During First Trimester

Saba Nadeem[1], Sara Reza[2], Shahnaz Anwar[1], Naila Shabbir[1], Irum Noor[2] and Shahnaz Noor[2]

ABSTRACT

Objective: To determine the frequency of abnormal liver function tests (LFTs) in hyperemesis gravidarum (HG) during first trimester.

Study Design: Descriptive cross sectional study

Place and Duration of Study: This study was conducted at Gynecology and Obstetrics Department of Bahawal Victoria Hospital in collaboration with Pathology Department, Quaid-e-Azam Medical College from March 2020 to September 2021 for a period of six months.

Materials and Methods: Total 106 pregnant women in their first trimester, presenting with hyperemesis gravidarum were enrolled in the study. Liver function tests of all study subjects were evaluated including total serum bilirubin, alanine transaminases (ALT) and aspartate transaminases (AST).

Results: The results of this study showed a mild increase in serum total bilirubin (1.4±0.4) and a mild to four times elevation in level of serum transaminases i.e. ALT (57.2±39.3) and AST (48.4±28.7). An elevated level of ALT was observed in multiple pregnancies.

Conclusion: Hyperemesis gravidarum is associated with alteration in liver function tests. These abnormalities are mild and resolve after the cessation of symptoms. Persistent elevation warrants further investigation to rule out underlying hepatic disease. The severity of symptoms correlates with degree of derangement. Outcome of HG remains unaffected and only conservative management is required. Moreover, the significant increase in serum ALT levels in multiple pregnancies may suggest a relationship with pregnancy hormones.

Key Words: hyperemesis gravidarum, altered liver function test, first trimester, pregnancy, nausea, vomiting

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INTRODUCTION

During first trimester, around 70-80% of pregnant women experience some degree of nausea and vomiting. The symptoms typically start around 4th to 6th week of gestation, peak during week 8 to 12 and settle by 20th week. In some cases vomiting might persist until delivery. This is a spectrum of disease ranging from mild to severe illness and is termed as nausea and vomiting of pregnancy (NVP).

The most severe and persistent form of NVP is known as hyperemesis gravidarum (HG). It alludes to the state of severe intractable nausea and emesis that requires medical intervention[1]. It is stated that hyperemesis gravidarum affects approximately 0.3 to 03% of the pregnant women[2]. It is accompanied with dehydration, fluid and electrolyte/ acid-base imbalance, volume depletion, ketosis, various nutritional deficiencies and >5% weight loss[1]. Although, HG has a good prognosis but untreated disease can have significant impact on maternal and fetal morbidity. Practically, the patient is diagnosed with hyperemesis gravidarum when there is complaint of exaggerated morning sickness and all other possible diagnoses have been ruled out. The possible risk factors may include primigravida, multiparity, obesity, past history of hyperemesis gravidarum and gestational trophoblastic disease [1].

Although the exact pathogenesis of hyperemesis gravidarum is under investigation but it is hypothesized that a causal relationship exists between HG and rapidly increasing level of beta- human chorionic gonadotropin (HCG) [2]. This may be suggestive of a correlation between vomiting and serum HCG. Moreover, the conditions associated with elevated serum HCG such as carrying multiples and gestational trophoblastic diseases may lead to increased chances of hyperemesis gravidarum. The previously presumed connection of HG with estrogen and progesterone has now been

1. Department of Gynae & Obstetrics, Bahawal Victoria Hospital, Bahawalpur.
2. Department of Pathology, Quaid-e-Azam Medical College, Bahawalpur.

Correspondence: Dr. Sara Reza, Assistant Professor of Pathology, Quaid-e-Azam Medical College, Bahawalpur.
Contact No: 03334603388
Email: sara.qmc@gmail.com

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disapproved [3]. A study related vomiting of pregnancy with a higher incidence of Helicobacter Pylori infection but it seems to be a completely distinct condition with no role in the mechanism of HG [4].

Mild morning sickness is managed by advising the patient to avoid triggers like certain foods and food preparations or by oral medications such as pyridoxine, doxylamine succinate, diphendydramine and metoclopramide[5]. In severe cases when oral medication is not tolerated, intravenous forms of diphendhydramine, metoclopramide, or ondansetron may be required. For management of fluid and electrolyte balance, hospital admission is recommended. Refractory cases are managed with short course of glucocorticoids such as methylprednisolone and hydrocortisone [5]. Nutritional support must always be instituted [6].

The common complications of hyperemesis gravidarum are dehydration; altered liver function tests (LFTs), hypokalemia, hypocalcemia, hypomagnesemia, metaboloic alkalosis, pre-renal acute kidney injury (AKI) and transient hypothyroidism [2,7]. Laboratory results that help in the diagnosis of HG include complete blood count, routine blood chemistry such as liver function tests, renal function tests (RFTs), serum electrolytes, amylase, lipase, thyroid function tests (TFTs) and estimation of serum beta-human chorionic gonadotropin (hCG). Frequently observed lab abnormalities in HG are decreased serum electrolytes (mainly potassium, sodium, and chloride). An increased hematocrit can also occur due to volume depletion. Other laboratory results can also show a rise in urinary ketones, specific gravity, and blood urea nitrogen. Additionally, hCG and thyroxine, have been shown to increase with the severity of HG, while thyroid stimulating hormone decreases. Pertaining to liver function tests, ALT can elevate up to 2 - 5 times the upper limit of normal, while bilirubin levels tend to remain unchanged [8,9].

Abnormal LFTs during hyperemesis gravidarum requires proper interpretation for accurate diagnosis and timely management of patients. The present study is focused to determine the frequency of deranged liver function tests in hyperemesis gravidarum during first trimester of pregnant women. The findings of this study will add to the existing data available on this topic and will be used for the welfare of patients.

MATERIALS AND METHODS

Study Design: Descriptive cross sectional study.

Settings: The study was conducted at Gynecology & Obstetrics Department 2 of Bahawal Victoria Hospital and tests were carried out in Pathology department, Quaid-e-Azam Medical College, Bahawalpur.

Duration of study: The study commenced in March 2020 till September 2021.

Sample size: 106 patients were enrolled in the study.

Sampling Technique: Nonprobability purposive sampling.

Sample selection:

Inclusion criteria: The primary targets of this study were pregnant women in their first trimester, presenting to Gynae & Obst. unit 2 with complain of severe nausea and uncontrollable vomiting requiring hospital admission or day care.

Exclusion criteria: Patients with pre-existing or newly diagnosed liver disease and drug induced abnormal liver chemistry were excluded.

Data collection: After approval of the study by the local ethics committee, patients with hyperemesis gravidarum were identified. After explaining the purpose of study a written informed consent was taken and 125 patients were recruited in the study. A predesigned proforma was used to collect patients' information. Demographic data was recorded. Detailed history was obtained regarding menstrual/obstetric details, any known liver disease and drug intake. The laboratory reports of these patients were also assessed. Out of these 125 women, 8 women gave a history of pre-existing liver disease while 11 were taking drugs such as paracetamol, anti-tuberculosis treatment and previous long term use of oral contraceptives so they were excluded.

Lab evaluation included estimation of serum bilirubin (total), alanine transaminases (ALT) and aspartate transaminases (AST). Analysis of all samples was done in Pathology Department by experienced pathologist on Beckman Coulter AU680.

Data Analysis: The data was analyzed with the SPSS software package version 24.0. Quantitative variables were expressed in terms of mean, standard deviation (SD), and percentage. Continuous variables were compared with the Student's t-test and paired sample t-test. A p-value of < 0.05 was considered to be statistically significant.

RESULTS

The demographic characteristics of study population are given in Table 1. There is mild elevation in serum total bilirubin while ALT and AST range from normal to 3-4 times the upper normal limit. The final observations of this study are summarized in Table 2. Overall, 63.2% (67/106) of the study participants showed some degree of derangement in liver function tests. There were 30.2% (32/106) primigravida and 69.8% (74/106) multigravida. There was no statistically significant difference found between the results of serum bilirubin and transaminase of primigravida and multigravida as shown in Table 3. The ALT level was observed to be high in multiple pregnancies. The patients were given intravenous fluids and antiemetics. None of the patient required termination of pregnancy.

Table No.1: Demographic characteristics of study subjects

Variables	Mean ± SD	Range
Age	27.6± 4.2	19-38
Weeks of gestation	14.7±2.5	8-20
Parity	2.7±1.2	1-6

Table No.2: Liver function tests of study subjects

Investigations	Mean ± SD	Range
Total bilirubin (mg/dl)	1.4±0.4	0.3 – 2.8
AST (IU/L)	48.4±28.7	19-87
ALT (IU/L)	57.2±39.3	18-213

*ALT: Alanine transaminase, AST: Aspartate transaminase

Table No.3: Comparison between LFTS of primigravida and multigravida

Investigations	Primigravida	Multigravida	p-value
Total bilirubin (mg/dl)	1.41±0.34	1.44±0.38	<0.05
AST (IU/L)	47.8±31.2	48.1±27.7	<0.05
ALT (IU/L)	57.2±30.4	58.5±37.1	<0.05

*ALT: Alanine transaminase, AST: Aspartate transaminase, p-value is calculated using two-tailed unpaired t-test

DISCUSSION

Three types of liver disease in pregnancy have been described:

- Pre-existing disease
- New onset disease
- Pregnancy-specific disease [10].

As an uneventful pregnancy does not cause a significant modification in liver physiology, the treatment of pregnancy non-specific hepatic disorder is similar to that of non-pregnant population [11]. It is stated that AST and ALT does not rise during a normal pregnancy but an increased alkaline phosphatase (ALP) and decreased albumin concentration was observed. So any abnormality in AST and ALT requires proper evaluation.

Here is a brief discussion of pregnancy related hepatic disorders that can lead to impairment in hepatic transaminase levels.

Acute fatty liver of pregnancy (AFLP) occurs in 0.01% of all pregnancies. ALT and AST can elevate up to ten times the upper normal limit [10,12]. Liver involvement is frequently observed in hypertensive disorders of pregnancy i.e. pre-eclampsia and eclampsia. They cause hepatocellular necrosis resulting in marked rise of the aminotransferases [10]. A 100 times elevation was also seen in some cases[13]. Syndrome of hemolysis, elevated liver enzymes and low platelets (HELLP) is a variant of pre-eclampsia. In this condition ALT, AST and total bilirubin are mildly raised but ALP can increase up to 1000 IU/L [14].

In hyperemesis gravidarum, liver involvement is subclinical and not marked. So, clinicians do not consider HG as a liver disease of pregnancy [10]. Research data reveals derangement in liver function tests in around 50% of the patients suffering from HG. These biochemical changes are reversible and resolves with the settlement of symptoms [15]. The results of our study are consistent with the available data. Commonly a twofold rise in ALT and AST are seen but values more than 200 IU/L are seldom observed [10,16]. These findings contradict with our results, as values >200 IU/L were recorded in our study population.

The mean increase in ALT level was observed to be more than AST, but the exact pathogenesis is unknown[17]. We have observed similar results in our study subjects. There is mild increase in total serum bilirubin level and rarely can it go up to 4 mg/dL [10]. Similarly, we have observed mild elevation in bilirubin level.

The severity of symptoms can correlate with the degree of alteration in liver function tests [11]. We were also able to establish a relationship between deranged LFTs and symptoms. If the derangement persists after cessation of morning sickness, this should alert the clinician for further investigation to rule out any underlying hepatic disease.

The changes in LFTs during hyperemesis gravidarum have no clinical impact on liver function. The physiological functions remain normal, as evident from normal coagulation. The decrease in albumin is decreased most probably due to poor nutrition [11].

A previous study revealed no significant difference between the abnormal LFT values of primigravida and multigravida [18] which is in agreement to the findings of present study.

We also observed a marked elevation of ALT.

Larry et al, repoted an unusual case where a female experienced hyperemesis gravidarum in all her three pregnancies [19]. The maximum recorded level of aminotransferase was 22 times higher than the upper normal limit.

Hyperemesis gravidarum is not accompanied by any radiological changes in liver architecture, If any abnormality is found, then some other underlying cause should be kept in mind [11].

There is no indication for liver biopsy until and unless there is doubt in the diagnosis.

The exact pathogenesis of hyperemesis gravidarum is not completely known. Some literature says that it is associated with malnutrition that can lead to abnormal LFTs but this seems to be unlikely in scenarios where nutrition status is adequate [20].

Kaplan et al. revealed an increased level of tumor necrosis factor alpha (TNF-α) patients with HG [21]. Placenta is a known source of TNF- α. The rise in this inflammatory cytokine can be hypothesized to be

involved in pathogenesis of hyperemesis gravidarum along with derangement in LFTs [22].

Another theory about the pathogenesis of HG is the production of reactive oxygen species (ROS). ROS are produced as a result of impaired metabolism of fatty acids [23]. ROS can lead to production of inflammatory cytokine, ultimately leading to HG and liver dysfunction.

Sometimes there is incidental finding of a subclinical liver disease, diagnosed only on the basis of isolated increase in LFTs. These are confounding variables in our study and can be addressed by conducting further studies at larger scale. The liver chemistry should be estimated before and after development of HG. But we have not come across any such study during literature search. Even if such a study was conducted, the results would not have been impactful. Reason being that all the patients with hyperemesis gravidarum are not completely investigated. Only the ones with severe or complicated disease and cases where the diagnosis is doubtful undergo detailed investigations. To avoid this shortcoming, a prospective study should be planned. To establish an accurate association between liver dysfunction and the degree of liver dysfunction, a well-defined clinical criterion is required. Recently, a scoring system called PUQE (Pregnancy-unique quantification of emesis and nausea) has been introduced that can help in assessment of the severity of symptoms [24]. It is not a widely used scoring system, does not affect the course of disease or its treatment.

CONCLUSION

Hyperemesis gravidarum is associated with alteration in liver function tests. These abnormalities are mild and resolve after the cessation of symptoms. Persistent elevation warrants further investigation to rule out underlying hepatic disease. The severity of symptoms correlates with degree of derangement. Outcome of HG remains unaffected and only conservative management is required. Moreover, the significant increase in serum ALT levels in multiple pregnancies may suggest some relationship with pregnancy hormones.

Author's Contribution:

Concept & Design of Study:	Saba Nadeem
Drafting:	Sara Reza, Shahnaz Anwar
Data Analysis:	Naila Shabbir, Irum Noor, Shahnaz Noor
Revisiting Critically:	Saba Nadeem, Sara Reza,
Final Approval of version:	Saba Nadeem

Conflict of Interest: The study has no conflict of interest to declare by any author.

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