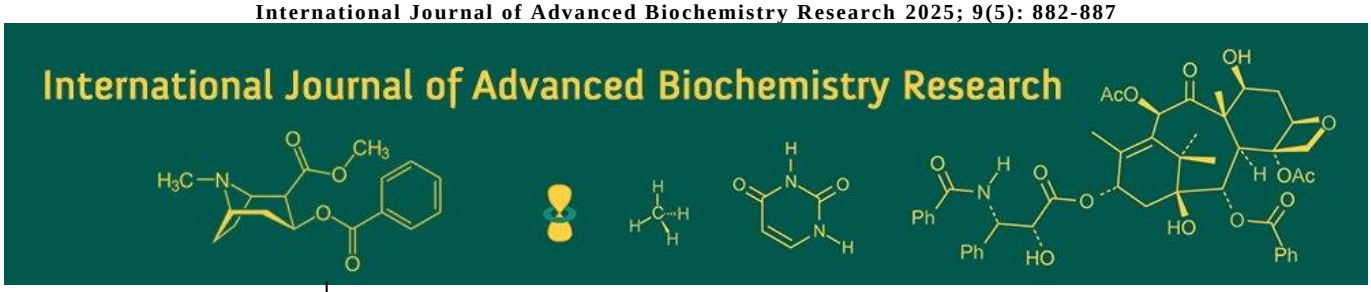

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Liver dysfunction among pregnant women with hyperemesis gravidarum

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Abstract
Background: Hyperemesis gravidarum (HG) is a severe form of nausea and vomiting during pregnancy that can lead to dehydration, electrolyte imbalances, and liver dysfunction. Despite its clinical significance, the impact of HG on liver function is not thoroughly understood.
Objective: This study aims to estimate the prevalence and extent of liver dysfunction among pregnant women diagnosed with HG.
Methods: A retrospective study was conducted at Basrah Maternal and Child Teaching Hospital over a one-year period. It included 100 pregnant women who were admitted for HG. Blood samples were collected to assess liver function through alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase levels, as well as total bilirubin. Hemoglobin levels and white blood cell counts were also measured. Additionally, urine samples were collected to evaluate ketonuria, indicating metabolic status.
Results: The study population had a mean age of 24.2 years, with a mean gestational age of 9.8 weeks. Liver enzyme analysis showed that 21% of the women exhibited at least one abnormal liver function test. Ketonuria was observed in all participants, with 42% exhibited severe ketonuria, 33% with moderate ketonuria, and 25% with mild ketonuria. Hemoglobin levels averaged 10.5 g/dL, indicating mild anemia in several cases.
Conclusions: This study showed that mild increases in liver enzymes and ketonuria are common but not indicative of severe liver dysfunction. Parity does not significantly influence these markers. Future research should involve larger populations and track changes over time to better understand the metabolic effects of HG.

Keywords: Hyperemesis gravidarum, abnormal liver functions, pregnancy, liver enzymes

Introduction

Hyperemesis gravidarum is a term refers to intense and uncontrollable vomiting marks a medical disorder in the early stages of pregnancy. Although nausea and vomiting during pregnancy is a typical occurrence throughout early pregnancy, HG is distinguished by an excessive and severe form of nausea and vomiting that can result in dehydration, loss of weight, and imbalances in electrolyte levels [1]. Women suffering from HG endure severe and protracted nausea, frequently characterized as incapacitating. Nausea may last continuously and is not restricted to specific day periods [1]. Dehydration is a significant risk with HG due to frequent vomiting. Indications of dehydration encompass a parched mouth, urine with a dark color, infrequent urination, and a sensation of dizziness [2]. Women suffering from HG may have substantial weight loss during pregnancy as a result of their inability to retain food. This weight loss is problematic and may necessitate medical attention. Women experiencing HG may develop intense aversions to specific foods or odors, resulting in difficulty finding food they can tolerate [3]. Fatigue and weakness might result from the concurrent presence of persistent nausea, vomiting, and dehydration. The desiccation and disturbances in electrolyte levels induced by HG can result in dizziness and syncope, particularly when assuming an upright position or engaging in rapid movements. Hypersalivation, sometimes referred to as sialorrhea, is the condition where excessive production of saliva occurs. This symptom is observed in certain women who have HG. This can lead to sensations of nausea and unease [4]. HG incidence is predicted to occur in 0.3% to 2.0% of all pregnancies [5, 6]. Pathogenesis and factors associated with hyperemesis in pregnancy include maternal factors like olfaction [7, 8], Body mass index [9, 10], and being younger [10, 11] immunological changes [12-14];

gestational transient thyrotoxicosis [14-15]; high estrogen level [16]; high progesterone level [17]; leptin, adreno-cortical hormones, and serotonin [18], and oxidative stress [19, 20]. Liver function abnormalities are common in hyperemesis patients and may be associated with the onset and severity of the condition [21, 22]. Elevated alanine aminotransferase levels (ALT) in the bloodstream suggest liver damage or inflammation [22]. Dehydration and electrolyte abnormalities may manifest in instances of intense and protracted vomiting linked to HG. The presence of these variables, in conjunction with the metabolic alterations that occur during pregnancy, might strain the liver and potentially result in moderate hepatic impairment [23] Consequently, ALT levels may increase. Notably, the extent of ALT increase in HG is typically moderate and temporary. As the symptoms of HG ease and hydration and electrolyte imbalances are treated, the levels usually return to normal [24]. Additional Liver Enzymes: Although ALT is the predominant liver enzyme linked to hepatic involvement in HG, other liver enzymes can also be assessed to examine liver function. These include aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT). The enzyme AST, similar to ALT, is mainly localized in the liver [25]. However, it also exists in other organs, including the heart and skeletal muscle. Elevated levels of AST can serve as an indicator of liver injury. However, they can also be affected by muscle damage or other variables. ALP and GGT are enzymes principally linked to the functioning of the bile duct. An increase in the concentrations of ALP and GGT may indicate the presence of cholestasis, a medical disease characterized by compromised bile flow [26]. It is imperative to remember that although liver enzyme abnormalities may manifest in HG, they often manifest as mild and ultimately resolve spontaneously. Nevertheless, it is imperative to do a thorough assessment of persistent or severe liver abnormalities to exclude alternative liver disorders or consequences [27]. This study aims to estimate the prevalence and extent of liver dysfunction among pregnant women diagnosed with HG.

Methods

A retrospective study was conducted at Basrah Maternal and Child Teaching Hospital from October 1, 2023, to October 1, 2024. The study involved 100 pregnant women diagnosed with HG who were admitted to the obstetrical ward and emergency unit. These women received daycare treatment for HG and were included in the analysis. The study focused on women with severe vomiting necessitating hospital admission. Patient information, including age, parity, gestational age, occupation, educational level, and body mass index (BMI) ($BMI = Weight\,(kg)/Height2\ (m2)$), was collected through history-taking and clinical examination. Women with pre-existing liver diseases or other causes of nausea and vomiting, such as gastric ulcers, thyroid disease, or diabetes, were excluded from the study.

A blood sample of 5 mL was drawn from each woman and sent for liver enzyme assays, specifically focusing on liver function tests and hemoglobin levels, white blood cell count, and urine ketone assessment. The blood samples were processed in the laboratory, where serum was separated from the cellular components through centrifugation. Liver enzymes, including ALT and AST, were measured using automated analyzers. The results were reported in units per liter (U/L) or international units per liter (IU/L) and compared with reference values for pregnant women. In addition, urine samples were collected and analyzed for the presence of ketones.

For statistical analysis, the data were processed using the Statistical Package for Social Sciences (SPSS) version 26. Quantitative data were expressed as mean values with standard deviations, while qualitative data were presented as frequencies and percentages. A significance level of $p<0.05$ was considered for all statistical tests to determine the presence of statistically significant differences between variables.

Results

Table (1) provides a clear summary of the demographic and obstetrical characteristics of the study population. The participants were relatively young, with a mean age of 24.2 years, and had a healthy mean BMI of 21.4 kg/m². The mean gestational age of 9.8 weeks suggests that most participants were in the first trimester of pregnancy. The parity range, spanning from 0 to 5, reflects a diverse obstetrical history among the participants, encompassing both first-time mothers and those with multiple prior pregnancies.

Table 1: Demographic, anthropometric, and obstetrical history of the study population

Variable	Mean ± SD	Range
Age (Year)	24.2±5.93	16-35
Body Mass Index (kg/m²)	21.4±2.10	18-30.6
Gestational Age (Week)	9.8±1.43	8-13
Parity (number of babies)	1.9±1.41	0-5

The laboratory findings in Table (2) offer a comprehensive assessment of key hematological and biochemical parameters in the study population. The mean hemoglobin level of 10.5 g/dL suggests that mild anemia is common. White blood cell counts fall within normal limits, indicating standard immune function. Liver function tests reveal some variability, with Total Serum Bilirubin averaging 0.98 mg/dL, and liver enzymes such as ALT and AST showed a broad range of values. While most participants exhibit normal liver function, some may be experiencing mild hepatic involvement.

Table (3) provides a summary of the frequency distribution of key metabolic and liver function indicators in the study population. Ketonuria levels reveal that a significant portion of participants exhibit moderate (33.0%) to severe (42.0%) ketonuria, suggesting that many may be experiencing metabolic imbalances or inadequate nutritional intake. Total Serum Bilirubin (TSB) levels are predominantly 1.2 mg/dL or lower (89.0%), reflecting generally normal bilirubin metabolism, with only a small proportion showed elevated levels. AST and ALT levels indicate that most participants have normal liver enzyme levels (81.0% for AST and 80.0% for ALT).

Table 2: The laboratory findings distribution among the studied population

Variable	Mean ± SD	Range
Hemoglobin (gm/dL)	10.5±1.55	7.1-14.0
White Blood Cell Count (cells/µL)	8.2±1.62	5.6-15.5
Total Serum Bilirubin (mg/dL)	0.98±0.58	0.6-3.2
Alanine Aminotransferase (Units/L)	30.4±32.1	8-161
Aspartate Aminotransferase (Units/L)	32.6±22.9	13-98
Alkaline Phosphatase (Units/L)	61.3±33.0	10-176

Table 3: Frequency distribution of ketonuria and liver function markers among the study population

Variable		Frequency	Percent
Ketonuria Level	Mild Ketonuria (+)	25	25.0
	Moderate Ketonuria (+ +)	33	33.0
	Severe Ketonuria (+ + +)	42	42.0
Total Serum Bilirubin (TSB) Levels	1.2 mg/dL or less	89	89.0
	1.3-2 mg/dL	3	3.0
	2.1-3 mg/dL	6	6.0
	3.1-4 mg/dL	2	2.0
AST Level	40 Units/L or less	81	81.0
	41-100 Units/L	19	19.0
ALT Level	40 Units/L or less	80	80.0
	41-100 Units/L	17	17.0
	101-200 Units/L	3	3.0

Table (4) shows that the most prevalent liver function abnormality is in serum AST at 19.0%, followed by ALT at 20.0%. elevated total TSB has a prevalence of 11.0%, while elevated ALP is the least prevalent, at 2.0%. AST and ALT are the most common abnormalities in this population. Meanwhile, 21% of the cases had at least one liver function test abnormality.

Table 4: Liver function positivity prevalence among the studied cases

Variable	Frequency	Percentage
TSB	11	11.0%
ALT	20	20.0%
AST	19	19.0%
ALP	2	2.0%
Total cases showed at least one positive findings	21	21.0%

Table (5) compares key liver function indicators between primigravida and multigravida groups. The results indicate no significant differences in TSB and ALT levels between the two groups, suggesting that liver function remains relatively stable regardless of obstetric history. However, the near-significant difference in AST levels, with higher averages in the multigravida group, may point to increased hepatic strain or differing physiological adaptations between the two groups.

Table 5: Comparison of mean total serum bilirubin, aspartate aminotransferase, and alanine aminotransferase levels between primigravida and multigravida

Variable	Primigravida (Mean ± SD)	Multigravida (Mean ± SD)	P-value
Total Serum Bilirubin (mg/dL)	0.91±0.42	1.00±0.61	0.554
Alanine Aminotransferase (Units/L)	30.44±24.45	30.48±33.63	0.997
Aspartate Aminotransferase (Units/L)	26.28±13.55	34.07±24.33	0.068

Discussion

HG is a severe form of nausea and vomiting during pregnancy, characterized by persistent symptoms that can lead to dehydration, weight loss, and malnutrition. Affecting approximately 0.3-2% of pregnancies, it is more severe than typical morning sickness [28].

Regarding demographic data, the mean age of the study participants was 24.2 years, with a mean BMI of 21.4 kg/m², indicating that the population consisted of relatively young women with normal body weight. This is inconsistent with the findings of Alonso *et al.* [29]. The mean gestational age was 9.8 weeks, aligning with the typical presentation of HG [30]. This differs from a study by Gaba *et al.* which reported a mean gestational age of 13.27±2.4 weeks, slightly later than our findings [31].

The mean hemoglobin level in the study population was 10.5 g/dL, and the mean WBC count was 8.2 cells/µL. suggesting mild anemia, common in pregnancy due to the increased plasma volume of 40-50% [32]. Mild anemia is common in women with HG, as persistent vomiting leads to poor nutritional intake [33]. The WBC count, though on the higher level of normal, possibly reflects a mild stress response or subclinical inflammation due to vomiting and dehydration in HG, consistent with findings by Tunc *et al.* and Oglak *et al.* [34]. Oglak *et al.* noted an increase in neutrophils and a decrease in lymphocyte count, indicating a systemic inflammatory response in HG [35].

Liver function tests revealed that the participants had a mean TSB level of 0.98 mg/dL, with 89% of participants showing TSB levels of 1.2 mg/dL or less. This indicates that significant hyperbilirubinemia was rare. The normal bilirubin levels suggest that, despite HG, there was no significant cholestasis or hemolysis, consistent with existing literature stating that elevated bilirubin levels are not typical in HG [47]. Rarely, mild jaundice can result from cholestasis, with bilirubin levels rising to 4 mg/dL [36].

Liver enzyme profiles showed mean ALT levels of 30.4 U/L, AST levels of 32.6 U/L, and APh levels of 61.3 U/L. These are slightly elevated but not indicative of severe liver dysfunction. Notably, 81% of participants had AST levels of 40 U/L or less, and 80% had ALT levels of 40 U/L or less, suggesting that mild elevations in liver enzymes are common in HG, but usually not concerning unless accompanied by other symptoms. This mirrors findings from studies where abnormal liver function tests occurred in up to 60% of HG cases [37]. The mild elevation of liver enzymes in women with HG has been documented in several studies [38]. This is believed to result from the liver's response to prolonged fasting, dehydration, and stress due to persistent vomiting [39]. The extent of liver function test (LFT) abnormalities may correlate with the severity of vomiting, and they resolve on cessation of vomiting [40].

A significant finding in this study is the high prevalence of ketosis, with 42% of the participants having + + + ketone bodies in their urine. This indicates that a large proportion of the study population was experiencing significant nutritional deprivation, leading to fat breakdown and ketone production. There is a positive correlation between ketonuria levels and inflammatory markers in patients with HG [41]. Inadequate carbohydrate intake, which is a notable risk in HG, can lead to the production of ketone bodies, resulting in ketonemia or ketonuria. These elevated ketone levels negatively affect embryogenesis [42]. Ketone levels in urine are frequently used in the diagnosis of HG and are

reported as a criterion in approximately 60% of clinical studies [43]. The relationship between ketonuria and illness severity is debated in the literature [44]. Derbent *et al.*, found that ketonuria levels are higher in HG patients compared to healthy pregnancies and that these levels correlate with the length of hospital stay [45]. Moreover, Aslan *et al.* found a positive correlation between ketone positivity levels and inflammatory markers such as neutrophil count, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio in HG. This suggests that the severity of ketonuria may correlate with the severity of inflammation in HG [46]. On the contrary, Koot *et al.* found that a higher degree of ketonuria at admission was not associated with the severity of HG in terms of nausea, vomiting, quality of life, maternal weight loss, or readmission rates. The only significant finding was that women with higher ketonuria levels were hospitalized for a longer duration [47].

The comparison between primigravida and multigravida women revealed no significant differences in TSB, ALT, and AST levels ($p = 0.554$, $p = 0.997$, and $p = 0.068$, respectively). This suggests that parity does not significantly influence the liver enzyme levels or bilirubin levels in women with HG. A prospective study of 135 women with HG conducted by Gaba *et al.* found no statistically significant difference in LFTs between primigravida and multigravida women [48]. This finding is consistent with the present study.

The lack of significant difference between these groups is important because it indicates that the physiological response to HG, as measured by liver enzymes and bilirubin levels, is consistent regardless of the number of previous pregnancies, as discussed by Nadeem *et al.* in their study on 106 pregnant women with HG [49]. This finding is supported by the literature, which generally shows that the biochemical markers of liver function in HG are not strongly influenced by parity [50]. While the exact reasons aren't widely discussed in the literature, liver function abnormalities in HG are generally attributed to severe vomiting, leading to malnutrition, dehydration, and metabolic stress, as mentioned above. These factors similarly impact the liver in both primigravida and multigravida women. Since the underlying cause of HG isn't directly tied to the number of previous pregnancies, the effect on liver function tests remains consistent regardless of gravidity.

Conclusion

This study provides valuable insights into the biochemical and hematological profiles of pregnant women with HG. The findings demonstrate that while mild elevations in liver enzymes and ketonuria are common in HG, they do not generally indicate severe hepatic dysfunction. The study also shows that parity does not significantly influence these biochemical markers, suggesting a consistent physiological response to HG across different groups.

Study limitations

1. Being conducted at a single center with a retrospective analysis, making the findings less generalizable to other populations or settings.
2. The relatively small sample size of the study may reduce its statistical power, limiting the ability to detect subtle differences or relationships between variables.

Recommendations

1. Future studies should include larger, multicenter populations to improve statistical power and generalizability.
2. Track biochemical changes over time to understand the progression and resolution of HG.
3. Assess a broader range of nutritional and inflammatory markers to better capture the metabolic impact of HG.

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