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MATERNAL SERUM C-REACTIVE PROTEIN AS A PREDICTIVE MARKER FOR HYPEREMESIS GRAVIDARUM: A CASE-CONTROL STUDY

***Lahaib Sadiq Al Bosaeeda**

Diploma of Gynecology and Obstetrics.

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***Corresponding Author: Lahaib Sadiq AlBosaeeda**
Diploma of Gynecology and Obstetrics.

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ABSTRACT

Background: Hyperemesis gravidarum is a severe form of nausea and vomiting during pregnancy that leads to considerable maternal morbidity, with mechanisms believed to include systemic inflammation marked by elevated biomarkers such as C-reactive protein (CRP). **Patients and Methods:** An analytic case-control study was conducted in Baghdad, Iraq, from August 2024 to March 2025, involving 100 first-trimester pregnant women diagnosed with hyperemesis gravidarum and 100 matched controls. Comprehensive demographic, clinical, and laboratory assessments were performed, and women with confounding medical conditions, multiple pregnancies, or recent drug use were excluded. Data analysis included t-tests and ROC analysis to evaluate the diagnostic performance of CRP. **Results:** Women with hyperemesis gravidarum were significantly younger and more likely to be nulliparous compared to controls ($p < 0.001$ and $p = 0.029$, respectively). Significantly higher CRP levels (0.75 ± 0.15 mg/dL vs. 0.27 ± 0.12 mg/dL, $p = 0.003$) and pronounced disturbances in sodium, chloride, potassium, and liver enzymes were reported in the case group. ROC analysis identified a CRP cut-off of 0.46 mg/dL, yielding 75% sensitivity and 79.4% specificity for predicting hyperemesis gravidarum (AUC = 0.780, $p < 0.001$). **Conclusion:** Serum CRP is significantly elevated in first-trimester women with hyperemesis gravidarum and serves as a reliable, accessible marker for diagnosis. A threshold of 0.46 mg/dL demonstrates good sensitivity and specificity, supporting the use of CRP measurement in clinical evaluation and management of hyperemesis gravidarum.

KEYWORDS: Serum CRP is significantly elevated in first-trimester women with hyperemesis gravidarum and serves as a reliable, accessible marker for diagnosis.

INTRODUCTION

Hyperemesis gravidarum signifies the extreme manifestation of nausea and vomiting during pregnancy, a syndrome that impacts most pregnant persons to differing extents. In contrast to the mild nausea and vomiting associated with pregnancy, which generally commences shortly after a missed menstrual period, peaks between 8 and 12 weeks of gestation, and ameliorates as the pregnancy advances into the second trimester, hyperemesis gravidarum is distinguished by relentless vomiting, substantial weight loss (typically ≥5% of prepregnancy weight), dehydration, and metabolic imbalances, making it a predominant cause of early pregnancy hospitalization.[1][2] Although up to 90% of pregnant individuals globally experience nausea and vomiting of pregnancy (NVP), hyperemesis gravidarum (HG) is believed to affect between 1%–3% of pregnancies.[3][4] A history of HG is the single largest risk factor for (recurrent) HG.[5] Recurrence rate estimates range from 15% to 89%.[5][6] Positive family history for HG, multiple pregnancy, primiparity, female fetal sex, younger maternal age, and over- or underweight are each associated with an increased risk of HG.[7]

While fatalities due to nausea and vomiting in pregnancy are seldom documented nowadays, considerable morbidity, including Wernicke encephalopathy, splenic avulsion, esophageal rupture, pneumothorax, and acute tubular necrosis, has been observed.[8] Wernicke encephalopathy, resulting from vitamin B1 deficiency and coupled with hyperemesis gravidarum, has been linked to maternal mortality or irreversible neurological impairment[9–11] In addition to increased hospital admissions[12][13], Certain women endure considerable

psychological morbidity due to nausea and vomiting during pregnancy, leading to the choice of pregnancy termination. A thorough evaluation of psychological morbidity associated with hyperemesis gravidarum revealed substantially elevated sadness and anxiety scale scores in affected women.

Recent studies show that inflammatory reactions may play a pivotal role in the onset and advancement of HEG, as evidenced by increased levels of interleukin-6 (IL-6) and C-reactive protein (CRP) in afflicted individuals.[14][15] These markers, obtained from haemograms, are easy, economical, and dependable indicators of systemic inflammation, providing insights into a patient's inflammatory condition without requiring sophisticated tests.[15]

PATIENTS AND METHODS

Study place and time

This is an analytic case control study that has been conducted in Baghdad/ Iraq. The data was collected from the 1st of August 2024 to the 1st of March 2025. The study included a total number of 100 first-trimester pregnant women with hyperemesis gravidarum (and 100-matched controls) were included in the study sample.

2.3.2 Exclusion criteria

1. Presence of other medical conditions: such as infections (respiratory, urinary tract), autoimmune diseases (e.g., rheumatoid arthritis), endocrine disorders (thyroid disorders, diabetes, Addison's disease, hyperparathyroidism), heart disease, or chronic inflammatory conditions.
2. Multiple or complicated pregnancies.
3. Recent drug use: women on medications such as antibiotics, iron supplements, or corticosteroids, which can alter CRP and symptom presentation.
4. Significant comorbidities: women with significant comorbidities requiring special therapies unrelated to HG, such as preexisting diabetes, hypertension, or other chronic diseases.

Ethical Consideration

Verbal consent has been obtained from all participants before data collection.

Data Collection

A detailed history was collected, including demographic and clinical characteristics, using a semi-structured questionnaire. General examinations included vital signs, weight, height, BMI, signs of dehydration, jaundice, and generalized weakness. Before starting treatment, group I underwent blood group and Rh tests, full blood count, fasting blood sugar, liver function tests, renal function tests, serum electrolytes, thyroid function tests, urine analysis, and ultrasound to exclude H.mole and multiple pregnancy. Group II routine investigations were performed during an obstetric check at a consultant clinic. The patient's condition was evaluated for signs of dehydration, jaundice, and generalized weakness.

Data entry and analysis

Data entry was done using Microsoft Excel 2019. Data was recorded into different quantitative and qualitative variables for the purpose of analysis.

Analysis was done using statistical package for social sciences (SPSS version 26).

Data was summarized using measures of frequency (mean), dispersion (standard deviation), tables and graphs. Independent sample t-test was used to test for statistical significance between continuous variables. Fischer's exact test was used for categorical variables. A two-tailed p value of less than or equal to 0.05 was assigned as a criterion for declaring statistical significance.

RESULT

Table (1) shows that hyperemesis gravidarum cases are significantly younger (28.4 ± 5.2 years) than controls (33.6 ± 7.1 years) with $p < 0.001$. There was no significant difference regarding mean BMI (23.4 ± 4.7 vs. 23.2 ± 3.8. $p = 0.519$). Residence distribution shows no significant difference between urban and rural settings ($p = 0.624$). Regarding parity, a significantly higher proportion of cases are nulliparous (36%) compared to controls (14%), with a significant p-value of 0.029, and cases have fewer multiparous women (38% vs. 58%).

Table (1): Comparison of basic characteristics between both study groups.

Variables	Cases (N=50)	Controls (N=50)	P value
Age (years)			
Mean ± SD	28.4 ± 5.2	33.6 ± 7.1	<0.001
BMI (Kg/m^2)			
Mean ± SD	23.2 ± 3.8	25.4 ± 4.7	0.519
Residence			
Urban	41	38	0.624
	82.0%	76.0%	
Rural	9	12	
	18.0%	24.0%	
Parity			
Nulliparous	18	7	0.029
	36.0%	14.0%	

Primiparous	13	14	
	26.0%	28.0%	
Multiparous	19	29	
	38.0%	58.0%	

Comparison of serum electrolyte levels between both study groups

Table (2) shows that serum sodium, chloride, and potassium levels are significantly lower in the hyperemesis gravidarum cases compared to controls, with p-values of 0.002, 0.001, and less than 0.001, respectively, indicating strong statistical evidence of electrolyte imbalances in affected patients. In contrast, serum calcium levels are slightly lower in cases but the difference is not statistically significant (p = 0.302).

Table 2: Serum electrolyte levels in the study groups.

Variable	Cases (N=50)	Controls (N=50)	P value
Serum Na (mEq/L)	134.5 ± 4.5	138 ± 3.2	0.002
Serum Cl (mEq/L)	96.3 ± 5	101.2 ± 4	0.001
Serum K (mEq/L)	3.1 ± 0.6	3.8 ± 0.5	<0.001
Serum Ca (mg/dL)	8.4 ± 0.8	8.9 ± 0.6	0.302

Comparison of serum biochemical parameters between both study groups

Table (3) demonstrates statistically significant differences between hyperemesis gravidarum cases and controls in several key laboratory parameters. Cases have significantly higher WBC, ALT, AST, and CRP levels ($p \leq 0.003$), indicating an inflammatory and hepatic response, while hemoglobin levels are significantly lower (p = 0.005).

Table 3: Comparison of laboratory investigations between both study groups.

Variable	Cases (N=50)	Controls (N=50)	P value
WBC (x10^3/µL)	13.2 ± 4.5	8.9 ± 3.1	0.001
Hb (g/dL)	10.4 ± 1.2	11.6 ± 1.0	0.005
Platelet (x10^3/µL)	245.1 ± 55	253.3 ± 48	0.45
ALT (U/L)	42.0 ± 15.3	22.5 ± 10.2	0.0001
AST (U/L)	38.1 ± 12.2	20.4 ± 7.3	0.0001
ALP (U/L)	110.7 ± 40.4	95.1 ± 35.9	0.1
Fasting blood sugar (mg/dL)	85.3 ± 12.5	93.5 ± 15.8	0.08
CRP (mg/dl)	0.75 ± 0.15	0.27 ± 0.12	0.003

Role of CRP in diagnosing hyperemesis gravidarum

To determine the diagnostic performance of CRP, Receiver operator characteristics (ROC) analysis was employed. The analysis revealed that CRP was a significant predictor of hyperemesis gravidarum (AUC = 0.780, P value <0.001); as shown in figure (1). The optimum cut-off point with the highest (sensitivity + specificity) was determined to be 0.46 md/dL; as it had a sensitivity of 75.0% and specificity of 79.4%.

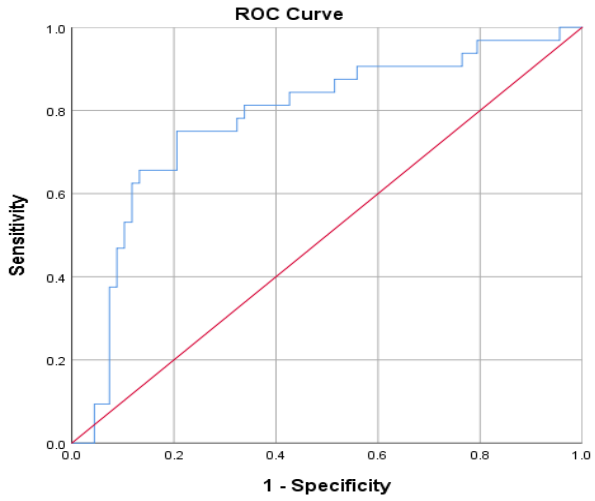

Figure 1: ROC analysis diagnostic indices of CRP for diagnosis of hyperemesis gravidarum.

DISCUSSION

The present study found that CRP levels were significantly higher in cases than controls. Moreover, a cut-off value of 0.46 md/dL had a 75% sensitivity and 79.4% specificity. Our findings are in concordance with the study by **Kan et al.** who found that CRP levels were significantly higher in HG patients compared to controls (0.85 mg/dL vs. 0.19 mg/dL) with CRP correlating with disease severity. The study also found that a CRP cut off value of 0.32 mIU/mL had 69% sensitivity and 61% specificity.[17]

Emekçi Özay et al. observed significantly higher CRP and other inflammatory markers in HEG patients than controls, confirming CRP as a better indicator for predicting diagnosis and severity but did not specify cutoff points.[18]

Engin-Ustun et al. found that women with HEG had significantly higher levels of CRP than the control group [10.1 (5-20) vs. 9 (1.4-14) mg/l].[19]

In discordance with our study, the study by Rosiyana et al. reported that the mean CRP level of blood in normal pregnant women (10.13 mg/L) does not differ greatly from the mean blood CRP in pregnant women with HG (10.34 mg/L), where the average difference between the two groups is 0.21 mg/L.[20]

C-reactive protein (CRP) is elevated in hyperemesis gravidarum (HG) primarily due to an underlying inflammatory process triggered during pregnancy. The condition is associated with a systemic subclinical inflammation marked by activation of immune cells and release of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which stimulate the liver to produce acute-phase proteins including CRP. This inflammatory response may be triggered by factors related to pregnancy itself, such as placentation or human chorionic gonadotropin secretion, or by a subclinical inflammatory state inherent to HG. The elevated CRP thus reflects this ongoing inflammation, which contributes to the pathophysiology of HG, as observed in multiple studies showing higher CRP levels in affected women compared to healthy pregnant controls.[18]

The present study also found that cases had significantly younger maternal age than controls. A large 2020 study by Nurmi et al. showed that higher maternal age (31 years or older) was associated with a lower risk of HG compared to a younger reference group (26-30 years), suggesting older age may be protective rather than a risk factor.[7]

The current study also found that nulliparity was significantly associated with hyperemesis gravidarum. A large hospital-based study reported that nulliparity increased the risk of HG nearly fourfold (OR 3.76) compared to women who had previous births.[21] Another study by Seid et al. indicated that nulliparous women have a higher risk of admission for HG compared with parous women, supporting nulliparity as a risk factor.[22]

CONCLUSION

This study demonstrates that maternal serum C-reactive protein is significantly elevated in first-trimester pregnancies complicated by hyperemesis gravidarum, supporting its role as a marker of systemic inflammation in affected women. The research identifies a CRP cut-off value of 0.46 mg/dL, yielding a sensitivity of 75% and specificity of 79.4% for predicting hyperemesis gravidarum.

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