Leptin-Mediated Inflammation and Antioxidant Response in Hyperemesis Gravidarum: Evidence of a Protective Shift in Early Pregnancy

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ABSTRACT

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| **Introduction:** Hyperemesis gravidarum (HG) is a condition of intractable vomiting during pregnancy, leading to fluid, electrolyte and acid–base imbalance, nutritional deficiency and weight loss. Leptin is known to regulate appetite, but its association with oxidative stress and inflammation in HG has not been fully elucidated**Aim:** To assess serum leptin, oxidative stress and inflammatory markers and their correlation in pregnant women with hyperemesis gravidarum**Study design:** This is a cross-sectional case-control study.**Place and Duration of Study:** Ante-Natal Clinic, General Hospital, Ifo, Ogun State, between April and June, 2022.**Methodology:** A total of ninety participants were recruited for the study. This consists of 45 pregnant women with hyperemesis gravidarum and 45 apparently healthy pregnant women (without hyperemesis gravidarum) who served as controls. The serum samples obtained from study participants were assayed for serum leptin, high sensitivity C reactive-protein (hsCRP), Malondialdehyde, Total antioxidant status and Glutathione peroxidase using Enzyme Linked Immunosorbent Assay and Colorimetric methods.**Results:** Mean serum leptin levels were significantly higher in the hyperemesis gravidarum group compared to controls (6.1 ± 1.26 vs. 5.0  ± 1.14 ng/mL; p < 0.01). high sensitivity C-Reactive Protein was also significantly elevated in hyperemesis gravidarum (9.48 ± 2.12 vs. 6.12 ± 1.24 mg/L; p < 0.005), indicating a pro-inflammatory state. Total antioxidant status was higher in the hyperemesis gravidarum group (3.12 ± 0.74 vs. 2.45 ± 0.65; p < 0.05), alongside elevated glutathione peroxidase (110.74 ± 27.1 vs. 93.17 ± 18.9 μ/mL; p < 0.005). No significant difference was observed in Malondialdehyde levels between the groups (7.59 ± 2.8 vs. 8.03 ± 3.05 nmol/mL; p > 0.05).**Conclusion:** Hyperemesis gravidarum is associated with elevated leptin and hsCRP levels, suggesting an inflammatory component. The concurrent rise in TAS and GPx, despite stable MDA levels, indicates a compensatory antioxidant response rather than overt oxidative damage. These findings highlight leptin's possible role in modulating inflammation and redox balance during early pregnancy. |

*Keywords: Leptin, Hyperemesis Gravidarum, Oxidative Stress, Antioxidants, C-Reactive Protein, Early Pregnancy, Inflammation*

1. INTRODUCTION

The first trimester of pregnancy is commonly associated with nausea and vomiting. This has been reported in up to 70% of pregnant women (Fejzo *et al*., 2019). Its onset is usually around the fifth week of pregnancy, reaching a peak by the tenth week with a spontaneous resolution and disappearance between the 16th and 20th week (Austin *et al*., 2019). Hyperemesis gravidarum (HG) in its severe form, is accompanied by weight loss, nutritional deficiency, dehydration, electrolyte and acid-base imbalance with ketonuria and reported in 0.3 – 10.8% of pregnancies (Jennings and Mahdy, 2023).

The aetiology of HG is not entirely clear, however, the roles of endocrine, gastrointestinal and genetic factors in its pathophysiology have been documented (ACOG, 2018; Jennings and Mahdy, 2023). Moreso, the involvement of chorionic gonadotropin, oestrogens, pituitary adrenal axis, thyroxine, prostaglandin E2, prolactin, leptin, adrenocorticotropin, testosterone, serotonin, *Helicobacter pylori*, immune system, neuromuscular, anatomic, and psychological phenomena have been elucidated (Hussein, 2017; Pakniat *et al*., 2018; Aleem *et al.,* 2021). Additionally, accumulating research evidence suggests that the development of HG involves growth/differentiation factor 15 (GDF15) and its receptor - GDNF receptor alpha like (GFRAL) (Zdravkovic *et al*., 2015; Turco *et al*., 2018; Fejzo *et al*., 2019; Fejzo *et al*., 2024). This has been attributed to the impact of GDF15 on maternal appetite regulation. GDF15, a hormone produced by the placenta, becomes expressed as early as the 8-10 cell blastocyst stage and moves from the placenta into the maternal circulation (Fejzo *et al*., 2024). Mechanistically, GDF15 regulates appetite by binding to its receptor (GFRAL), found in the area postrema and nucleus of the solitary tract in the medulla oblongata. This interaction sets off a cascade of events leading to reduced appetite, taste aversion, and ultimately weight loss (Frikke-Schmidt *et al*., 2019). Consequently, HG is deemed to be associated with the hyperactivation of the GDF15-GFRAL pathway.

Leptin, a prototype adipocytokine plays significant roles in energy metabolism, reproduction, immunity and inflammation (Perez-Perez *et al*., 2020). It basically acts as an afferent satiety signal through its crucial role in reducing appetite and raising the consumption of energy by interacting with other factors such as cortisol, thyroid hormones and insulin; thus, regulating body weight (Park and Ahima, 2015; Shih *et al*., 2022). When fat cells release leptin into the bloodstream, it travels to the hypothalamus, and acts on specific receptors to suppress appetite and increase energy expenditure (Obradovic *et al*., 2021). As a pro-inflammatory mediator, leptin promotes the secretion of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) (Rehman and Akash, 2016). These cytokines create a chronic low-grade inflammatory state, which has been implicated in the pathophysiology of HG. In addition to this, leptin modulates the balance between Th1 and Th2 immune responses, favoring a pro-inflammatory Th1 response (Perez-Perez *et al*., 2020). This shift exacerbates inflammation in HG, contributing to systemic effects such as nausea and vomiting through interactions with the hypothalamic centers regulating appetite and emesis. Elevated leptin levels correlate with increased high-sensitivity C-reactive protein (hsCRP), a biomarker of inflammation. In HG, higher hsCRP levels observed in affected women further highlight leptin’s contribution to the inflammatory cascade.

Studies show mixed results regarding malondialdehyde (MDA) levels, a marker of lipid peroxidation, in HG. However, elevated leptin levels are known to influence antioxidant defenses by regulating enzymes like glutathione peroxidase (GPx) and catalase. It is however unclear if this elevation is a cause or consequence. Previous studies have reported that increased leptin levels is associated with oxidative stress and inflammation via the activation of NADPH oxidase leading to ROS generation (Kleinridders *et al*., 2018) and activation of NF-KB and JAK-STAT signaling pathways which can further contribute to ROS generation (Pérez-Pérez *et al*., 2020). Thus, the role of leptin in appetite regulation, its involvement in oxidative stress and inflammation, makes it a suitable candidate for the present study.

 We have previously described the relationship between oxidative stress and inflammatory responses in preeclampsia (Adediji *et al*., 2017). Oxidative stress and inflammation seem to go ‘hand in hand’ in many conditions. HG could therefore be expected to have some association with inflammation. Furthermore, a number of studies have demonstrated the association of leptin with HG (Kuo *et al*., 2010; Kaygusuz *et al*., 2013; London, 2017), no report was however found on its relationship with oxidative stress or inflammatory markers in pregnant women with HG. Therefore, our hypothesis revolves around the potential correlation between serum leptin levels in women experiencing Hyperemesis gravidarum (HG) and the presence of inflammation and oxidative stress. To this end we assessed serum levels of leptin, high sensitivity C reactive-protein (hsCRP)- a selected inflammatory marker, and oxidative stress markers including total antioxidant status (TAS), Glutathione peroxidase (GPx) and malondialdehyde (MDA) – in pregnant women with HG and control subjects

2. material and methodS

**2.1 Study design**

This study was carried out as a hospital based, cross-sectional and case-control study, carried out between April and June, 2022.

**2.2 Participants**

Study participants were recruited from among pregnant women who presented at the antenatal clinic of General Hospital, Ifo, Ogun State, located in the South-Western region of Nigeria. They include 45 women who presented with hyperemesis gravidarum during the first trimester, and 45 pregnant women of a similar gestational age who did not have any vomiting at all, as control group.

**2.2.1 Inclusion criteria**

Participants with singleton pregnancy, gestational age between six and 14 weeks and having persistent nausea and vomiting were recruited for the study. The control group includes pregnant women with similar characteristics but without any history of vomiting.

**2.2.2 Exclusion criteria**

Pregnant women with multiple gestation, known thyroid disease, trophoblastic disease, eating disorders, known psychiatric disorder, smokers, and women having any known inflammatory conditions were excluded from this study.

**2.3 Sample collection**

Five milliliters (5ml) of venous blood sample was collected aseptically from each participant into a plain bottle, and centrifuged at 3500rpm for 5 minutes, after which the serum was separated into plain bottles and stored at -20°C until the time of analysis for leptin, hsCRP, total antioxidant status, malondialdehyde and glutathione peroxidase.

**2.4 Biochemical analysis**

Serum Leptin and hsCRP levels were determined using ELISA technique with kits supplied by Calbiotech Inc. (California, USA). Briefly, a monoclonal antibody specific for Leptin has been coated onto the wells of the microtiter strips provided. Twenty five microlitres of samples/standard/controls were pipette into these wells, followed by addition of 100μL of HRP conjugate. The plate was swirled for 20 seconds and incubated at room temperature for 60 minutes. This was then washed and followed by addition of 100 μL of TMB substrate. At exactly 15 minutes, 50 μL of stop solution was added to each well and the optical density was measured with Caretium KC-100 micro GrapH reader at wavelength of 450nm. Sample concentrations were read off the calibration curve prepared with the concentration of standards.

Serum MDA was measured as an index of lipid peroxidation by the thiobarbituric acid (TBA) reaction method as previously carried out (Adelakun *et al*., 2014). This method is based on the principle that presence of acid, MDA reacts with TBA to produce a colored end product that absorbs light maximally at 532 nm which corresponds to the concentration of MDA in the sample.

Serum activity of GSH-Px was measured in serum using ELISA technique, with kits supplied by Northwest Life Science Specialties (Vancouver, Canada) as previously carried out (Adelakun *et al*., 2014).

Total antioxidant status was determined using TAS colorimetric kit supplied by Randox Laboratories Ltd. (UK). The procedure has been previously described (Adediji *et al*., 2017).

**2.5 Statistical analysis**

Demographic data was reported as mean ± standard deviation and number (percentages) as appropriate. Data obtained from the biochemical analysis was analysed using the Statistical Package for Social Sciences (SPSS) and reported as mean ± standard error of mean (SEM) for the two groups. Difference between the means was analyzed using Student’s t-test with. P-values < 0.05 were considered statistically significant. Linear correlation analysis was done to determine the relationship between each of the age, serum leptin, serum hsCRP, TAS, MDA and GSH-Px

3. results and discussion

Table 1 shows demographic data of study participants. Participant groups (tests vs controls) were observed to be identical in terms of age, gravidity, parity, gestational age, educational status and occupation.

**Table 1: Demographic data of the patients with HG and the control group**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **HG**  | **Controls** | ***P*** |
| Age | 33.5 ± 4.7 | 31.7 ± 6.3 | .26\* |
| Gravidity | 3 (1 – 6) | 3 (1 – 5) | .62† |
| Parity | 1 (0 – 3) | 1 (0 – 4) | .76† |
| Gestational age | 8.6 ± 2.0 | 8.7 ± 1.9 | .93\* |
| Educational status |  |  | .69‡ |
|  | No formal education | 1 (2.2%) | 1 (2.2%) |  |
|  | Primary | 3 (6.7%) | 5 (11.1%) |  |
|  | Secondary | 12 (26.7%) | 11 (24.4%) |  |
|  | Tertiary | 29 (64.4%) | 28 (62.2%) |  |
| Occupation |  |  | 0.59‡ |
|  | Civil servant | 8 (17.8%) | 11 (24.4%) |  |
|  | Self employed | 36 (80.0%) | 32 (71.1%) |  |
|  | Student | 1 (2.2%) | 2 (4.4%) |  |
| BMI | 23.0 ± 3.5 | 24.8 ± 4.2 | 0.04\* |

**\*** Independent samples t-test

† Mann–Whitney U test.

‡ Chi-square

 Table 2 shows the comparison of Leptin, hsCRP and oxidative stress makers between test and controls. The test group has a higher leptin (p < 0.01), hsCRP (p < 0.005), TAS (p < 0.05) and GPx (p < 0.005) compared to control, while there was no significant difference in the mean value of MDA between the two groups.

**Table 2: Comparison of biochemical parameters between test and control group**

|  |  |  |  |
| --- | --- | --- | --- |
|  | HG§  | Control | *P* (Student’s t-test) |
| Leptin (ng/ml) | 6.1 ± 1.26 | 5.0 ± 1.14 | .005 |
| hsCRP (mg/L) | 9.48±2.12 | 6.12±1.24 | .004 |
| TAS | 3.12±0.74 | 2.45±0.65 | .03 |
| MDA(nmol/ml) | 7.59±2.8 | 8.03±3.05 | .28 |
| GPx (μ/ml) | 110.74±27.1 | 93.17±18.9 | .001 |

Table 3 shows the linear correlation among age, serum leptin, hsCRP, MDA, TAS and GPx values in the HG group. Leptin showed a positive correlation with hsCRP and TAS while it showed a negative correlation with MDA. Also, a negative correlation was observed between MDA and TAS, as well as between MDA and GPx; while a positive correlation was observed between GPx and hsCRP as well as between GPx and TAS.

**Table 3: Linear correlation of Age, Leptin, hsCRP and oxidative stress makers**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Age (r; *P*) | Leptin(r; *P*) | hsCRP (r; *P*) | TAS (r; *P*) | MDA(r; *P*) | GPx (r; *P*) |
| Age | 1 | 0.065; .67 | 0.183; .62 | 0.212; .53 | -0.079; 0.61 | -0.054; 0.73 |
| Leptin | 0.065; .67 | 1 | 0.436; .03\* | 0.224; .01\* | -0.165; .047\* | 0.059; 0.07  |
| hsCRP | 0.183; .62 | 0.436; .03\* | 1 | 0.254; .06 | -0.121; 0.11 | 0.209; 0.04\* |
| TAS | 0.212; .53 | 0.224; .01\* | 0.254; .06 | 1 | -0.865; .009\* | 0.924; 0.006\* |
| MDA | -0.079; .61 | -0.165; .047\* | -0.121; .11 | -0.865; .009\* | 1 | -0.243; 0.02\* |
| GPx | -0.054; .73 | 0.059; .07  | 0.209; .04\* | 0.924; .006\* | -0.243; .02\* | 1 |

Nausea and vomiting of pregnancy affect majority (70%) of women with onset at 6 to 8 weeks of gestation and resolving by 16 to 20 weeks (Fejzo *et al*., 2019). Its severe form, hyperemesis gravidarum (HG) has been reported in 0.3 to 10.8% of pregnant women (Jennings and Mahdy, 2023), and associated with serious maternal and prenatal complications such as dehydration, electrolyte imbalance, ketoacidosis as well as increased risks for low birthweight (LBW), preterm birth (PTB), small-for-gestational-age (SGA) and perinatal death (Gabra, 2018; Vikanes *et al*., 2013).

In this study, we observed that serum leptin concentration was increased among test subjects compared with the control group, this agrees with the study of Elzeneny *et al*. (2017), who reported that serum leptin was higher among patients with hyperemesis gravidarum. Leptin inhibits hunger and regulates energy balance. A decrease in leptin concentration triggers an increase in appetite and food cravings, while its increase inhibits the desire for food (Picό *et al*., 2003). Since a two-fold risk of anorexia nervosa has been reported among women with hyperemesis gravidarum (Mantel *et al*., 2020), it therefore suggests that the observed elevated serum leptin is responsible for decreased appetite in patients with HG. Increase in leptin concentration in HG has been associated with small for gestational age infants (SGA) and prematurity as well as adverse birth outcomes (McCarthy *et al*., 2014; Hu *et al*., 2017). This emphasizes the role of hyperleptinaemia in maternal nutritional inadequacy.

Additionally, the findings of this study showed that the body mass index in the HG group was significantly lower when compared with the control. This further showed the increased in leptin level in the study subjects is responsible for the low weights seen in pregnant women with Hyperemesis gravidarum. Chortatos *et al*. (2015) and the committee on practice bulletin-obsterics (2018) reported that the consequences of nausea and vomiting in pregnant women correlate with the severity of the symptom and ranges from reduced quality of life and depressive symptoms to preeclampsia, malnutrition, weight loss and dehydration. Thus, hyperemesis gravidarum can be seen as a condition requiring urgent medical attention due to its higher chances of resulting in an adverse birth outcome and the burden on maternal well-being.

Furthermore, this study found no significant difference between serum MDA levels in hyperemesis gravidarum patients compared with controls, despite the significant elevation of other oxidative stress and inflammatory markers such as glutathione peroxidase (GPx), total antioxidant status (TAS), leptin, and hsCRP in HG patients. This observation contrasts with previous studies which reported increased serum MDA levels in patients with hyperemesis gravidarum (Abdul-Barry *et al*., 2010; Biberoglu *et al*., 2016). This disparity might be due to the gestational age of study participants. In our study, all participants were within the first trimester of pregnancy, whereas in the study of Abdul-Barry *et al*. (2010), participants were spread across the three trimesters during which oxidative stress and lipid peroxidation might increase progressively due to cumulative metabolic demand and placental maturation. Furthermore, there is possibility of compensatory antioxidant response with elevated TAS and GPx levels in the HG group suggesting an enhanced antioxidant defense effectively neutralizing lipid peroxidation, thereby stabilizing MDA levels. This supports the idea of a protective shift rather than overt oxidative damage in early pregnancy.

Serum level of MDA has been used as a marker of lipid peroxidation and an important expression of oxidative stress (Nesma *et al*., 2021). Our finding therefore suggests that excessive lipid peroxidation is not associated with hyperemesis gravidarum in the first trimester.

The lack of elevated MDA in HG, despite evidence of inflammation and increased antioxidant activity, indicates that oxidative stress in early pregnancy may be balanced by upregulated antioxidant mechanisms, particularly in women with hyperemesis gravidarum. Thus, MDA alone may not be a reliable indicator of oxidative stress in early HG and should be interpreted alongside TAS and GPx.

The lack of equilibrium between reactive oxygen species (ROS) and the antioxidant defense systems causes oxidative stress. This study also showed an increased level of glutathione peroxidase (GPx) in test subjects compared with controls. This finding implies oxidative stress is not associated with this condition. This is also in disagreement with studies done by Abdul-Barry *et al*., (2010). Various researchers have evaluated the relationship between oxidative stress and hyperemesis gravidarum, but conflicting results have been reported on this relationship. Various studies have reported that plasma level enzyme antioxidants and non-enzymatic antioxidants are decreased, increased, or unchanged (Vidal et al., 2014). The total antioxidant status in this study was found to be significantly higher in the study subjects when compared with the control. The elevated GPx levels and TAS in the study subject, might be responsible for the reduced MDA or prevent its accumulation, thus masking lipid peroxidation.

Immune dysregulation and inflammation have been suggested to play an important role in the aetiopathogenesis of HG (Yoyshio et al., 2002). In this study, a significant increase in hsCRP was seen in the study subjects when compared with the control group. HsCRP has been reported to be a major biochemical parameter used in various studies to depict hyperemesis gravidarum as an inflammatory process. The findings of the present study agree with Ozlen *et al*. (2020) who reported a significant high hsCRP level in pregnant women with hyperemesis gravidarum when compared with women without HG. However, Yilmaz *et al*. (2016) reported no significant difference in hsCRP level in women with HG and control. Furthermore, other proven indicators of inflammation such as C-reactive protein, Vaspin, interleukin-6 (IL-6) and tumour necrosis factor (TNF-α) have been reported to be elevated in women with HG, thus underscoring the role of inflammation in the pathogenesis of HG (Engin-Ustin *et al*., 2013).

4. Conclusion

Hyperemesis gravidarum is associated with elevated leptin and hsCRP levels, suggesting an inflammatory component. The concurrent rise in TAS and GPx, despite stable MDA levels, indicates a compensatory antioxidant response rather than overt oxidative damage. These findings highlight leptin's possible role in modulating inflammation and redox balance during early pregnancy.

Consent

All authors declare that ‘written informed consent was obtained from the patients. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

Ethical approval

Ethical consideration: Ethical approval was obtained from Babcock University Health Research Ethics Committee (BUHREC) with approval number - BUHREC638/21. All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

**Disclaimer (Artificial intelligence)**

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, manuscript, etc.) have been used during the writing or editing of manuscripts.

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