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Serum oxidative markers and delta neutrophil index in hyperemesis gravidarum

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ABSTRACT

Objectives: To evaluate the relationship between different serum oxidative markers and the delta neutrophil index and hyperemesis gravidarum.

Methods: One hundred pregnant women were enrolled in the study and divided into two groups. Group 1 included 50 women with hyperemesis gravidarum, while Group 2 (control group) included 50 pregnant women similar in age, gestational week, and body mass index. Serum oxidative markers and complete blood count inflammatory markers were compared.

Results: Native thiol and total thiol were significantly lower in the Group 1 when compared with the control group (P=0.029 for native thiol; P=0.035 for total thiol). Moreover, ischemia-modified albumin (IMA) and catalase values were significantly higher in the Group 1 than in the control group (P=0.023 for IMA; P=0.021 for catalase). Index1% shows the disulfide/native thiol percent ratio and means that the Group 1 oxidant load is increased but not statistically significant. Myeloperoxidase, ferroxidase, and the delta neutrophil index did not differ significantly between the two groups (P=0.591, P=0.793, and P=0.52; respectively).

Conclusions: According to our study, contrary to the literature, although there are differences in some values, when evaluated individually hyperemesis gravidarum does not impose an extra burden on maternal oxidant-antioxidant balance.

Keywords: Oxidative hemostasis, hyperemesis gravidarum, delta neutrophil index

Hyperemesis gravidarum (HG) is an important reason for hospitalization in the early stages of pregnancy and is seen in approximately 0.3-3% of pregnancies. Its definition according to the American College of Obstetricians and Gynecologists (ACOG) guidelines in 2015 is still unclear. Constant nausea and vomiting not associated with other causes, ketonuria, dehydration, electrolyte disturbances, and monitoring of approximately 5% of pre-pregnancy weight loss are frequently determined criteria for the diagnosis of HG [1]. There are different studies in the literature on the etiology of HG, which is not elucidated. Psychological causes, pregnancy hormones, gastritis, and genetic causes were investigated, but the main cause remains unclear [2-5]. One investigated etiology is imbalance between oxidant and antioxi-

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dants. When healthy pregnancies were examined, it was found that antioxidant activity was higher than in the non-pregnant ones [6]. Many studies have reported that antioxidants decrease in HG and the situation shifts towards oxidants [7].

Oxidative stress (OS) is a condition that causes cellular and molecular damage resulting from an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense system that buffers oxidative damage. In many pathological conditions associated with pregnancy such as HG, it has been found that antioxidant activity decreases and the balance shifts to the oxidant side [2, 8, 9].

There are oxidant and antioxidant mechanisms in the human body that act against stressors. An enzyme found in the antioxidant defense system is ferroxidase, which converts toxic iron to less toxic ferric iron to reduce cellular and molecular oxidative damage [10, 11]. Another intracellular antioxidant is catalase (CAT). Its main purpose is to neutralize intra- and extracellular hydrogen peroxide, so its level increases in cases of OS [12]. Myeloperoxidase (MPO) is another intracellular enzyme found in neutrophils and is involved in the antioxidant system [13]. Thiols are protective organic components that are specified against ROS [14]. Thiols contain sulfhydryl (SH) groups, which react with oxidant molecules and change as a result of oxidation. Proteins mutate due to the changes in thiol groups, resulting in structural and functional changes [15]. Ischemia-modified albumin is a biochemical marker that increases in some situations such as ischemia, acidosis, or hypoxia. A somewhat hypoxic intrauterine environment occurs in the physiology of pregnancy. Reperfusion and OS that occur afterward are important for trophoblast development. In previous publications, IMA elevation was found in the early pregnancy period [16-18].

The delta neutrophil index (DNI) is a marker showing the number of immature granulocytes in human serum. In a limited number of studies, the DNI was used in patient groups with inflammatory processes [19]. The number of studies investigating whether it is associated with hyperemesis is limited.

To the best of our knowledge, our study is the first to evaluate many more oxidant and antioxidant active parameters in the same patient with a somewhat larger number of patients compared to previous studies. The main aim of our study was to determine the direction of serum oxidation balance in pregnancy nausea and vomiting, to clarify the literature, and to give a clear answer to pregnant women who are very concerned about themselves and their babies during this process.

METHODS

This case-control study was conducted in the Obstetrics and Gynecology clinic of our tertiary hospital between December 2022 and March 2023. One hundred pregnant women who were referred to the Obstetrics Department of our hospital were enrolled. The Ethical Committee of our hospital approved the study protocol (No: E2-22-2647, date: 26.10.2022). Informed consent was obtained from each participant. The diagnostic criteria for HG were determined by the ACOG Practice Bulletin No. 153: nausea and vomiting of pregnancy. All the pregnant women were in the first trimester (≤14 weeks). Fifty patients with a diagnosis of HG who were admitted to the hospital for the first time and had not received any medication for emesis

Table 1. Demographic parameters in HG and control groups

Parameters	Control	HG	P value
Age (years)	27.47±3.81	26.94±5.04	0.560
Gravidity	1.81±0.77	1.96±1.02	0.762
Parity	0.79±0.75	1.12±1.52	0.215
Gestational week	9.74±2.28	10.12±2.25	0.667
BMI (kg/m^2)	25.49±4.99	26.94±4.42	0.265

Data are shown as mean±standard deviation, HG=hyperemesis gravidarum, BMI=body mass index. Independent sample t-test was applied.

Table 2. Levels of serum oxidative markers in HG and control groups

Parameters	HG	Control	P value
Native thiol (µmol/L)	375.35±96.64	414.6±73.14	**0.029***
Total thiol (µmol/L)	416.69±106.34	458.04±79.13	**0.035***
Disulfide (µmol/L)	20.67±7.49	21.72±6.6	0.474
IMA (ABSU)	0.81±0.17	0.72±0.19	**0.023***
Index1 (%)	5.64±2.11	5.28±1.47	0.336
Myeloperoxidase (U/L)	91.08±19.64	93.4±22.55	0.591
Catalase (U/L)	197.19±39.11	180.01±31.71	**0.021***
Ferroxidase (U/L)	448.37±59.5	445.1±62.68	0.793

Data are shown as mean±standard deviation, HG=hyperemesis gravidarum, IMA= ischemia-modified albümin, index1=disulfide/native thiol percent ratio. Independent sample t-test was applied

*P<0.05 was considered significant.

before were compared with 50 pregnant women similar in age, gestational week, and body mass index (BMI). The number of ketones in the urine of all pregnant women in the HG group was the same. Although the pregnant women in both groups did not have any chronic disease, the patient group with HG did not have any additional medical problems other than pregnancy to explain their nausea, vomiting, and weight loss. All participants had intrauterine fetuses with normal heart rates. The maternal age, BMI, parity, gravidity, and gestational weeks of all the pregnant women were recorded.

Fasting blood samples from all volunteers before medication was placed into plain tubes. Sera were separated after centrifugation at 1600 × g for 10 minutes and stored at -80 °C until the time of analysis.

Thiol/disulfide homeostasis tests were performed using an automated spectrophotometric method as described by Erel and Neselioglu [15]. The albumin cobalt binding test was used to detect the presence of IMA [19]. Ceruloplasmin levels were measured by the method described by Erel [21]. This method is automated, colorimetric, and based on the enzymatic oxidation of ferrous ions to ferric ions. Serum MPO activity was measured by a modification of the o-dianisidine method [22]. CAT activity was measured by Goth's method [23].

Statistical Analysis

The statistical analysis was performed using SPSS for Windows 18.0 (IBM, Chicago, IL, USA). The mean and frequency values of the variables were calculated. The Kolmogorov–Smirnov test was used to detect whether the numerical values were normally distributed. Student's t-test was used to compare normally distributed values and the Mann–Whitney U test was used to compare non-normally distributed values. P<0.05 was considered statistically significant.

RESULTS

Table 1 contains the demographic features of the study participants including age, gravidity, parity, gestational week, and BMI. Comparison of the two groups shows that the participants have a similar distribution in terms of demographic features.

Table 2 shows the differences between the two groups in terms of thiol hemostasis, IMA, MPO, CAT, and ferroxidase. The differences between the groups were analyzed. Native thiol, total thiol and catalase levels were lower in the HG group (P=0.029, P=0.035, and P=0.021; respectively) while the level of IMA was higher compered to in the control group.

In Table 3, inflammatory markers in complete blood parameters, especially the DNI, which is associated with the severity of the disease in inflammatory events in recent years, was also compared. No statistically significant difference was found in any of the complete blood parameters between the groups.

Table 3. Complete blood count inflammatory markers in HG and control groups

Variables	HG	Control	P value
Neutrophil count ($\times 10^9$/L)	6.40±2.18	6.57±1.86	0.632
Lymphocyte count ($\times 10^9$/L)	1.91±0.62	2.06±0.58	0.142
Monocyte count ($\times 10^9$/L)	0.44±0.17	0.40±0.11	0.463
Plateletcrit (%)	0.22± 0.05	0.22±0.05	0.889
Platelet distribution width (fL)	51.15±7.21	51.95±7.25	0.615
Platelet count ($\times 10^9$/L)	278.42±74.03	264.46±66.39	0.309
Hemoglobine(g/dL)	12.8±1.21	12.61±1.07	0.173
Neutrophil/lymphocyte ratio	13.51±58.9	3.34±0.99	0.357
Delta neutrophil index (%)	0.32±0.97	0.52±1.81	0.52
Large unstained cell count ($\times 10^9$/L)	0.12±0.54	0.11±0.03	0.30

Data are shown as mean±standard deviation, HG=hyperemesis gravidarum. Mann-whitney u test was applied. *P<0.05 was considered significant.

DISCUSSION

In many studies on oxidants and HG, it has been stated that oxidant and antioxidant balance shifts towards the oxidant side. Contrary to the literature, we believe that HG may not have caused extra oxidative load for the mothers.

In thiol/disulfide balance, native and total thiol levels show antioxidant status while the index1% value shows the balance between oxidants and antioxidants. According to our study, the level of antioxidants in terms of thiol/disulfide was lower in the HG group (P=0.029 and P=0.035, respectively). The literature also supports this situation and studies have found a decrease in total antioxidant activity in HG [6, 8, 24]. In a previous study the balance was shifted to the oxidant side with the decrease in antioxidants in 26 pregnant women with HG [24]. Index1% shows the disulfide/native thiol percent ratio and the oxidative balance. In our study, although there was a decrease in antioxidant activity, it was not statistically significant between the two groups in terms of oxidative balance (index1%, P=0.336). Therefore, in studies conducted with thiol/disulfide balance to date, considering that the number of participants is higher than in previous studies, we can conclude that the oxidative balance does not make a significant difference when HG patients and pregnant women without HG are compared.

IMA is a rapidly increasing biomarker in clinical response conditions such as hypoxia, acidosis, and myocardial ischemia. In previous studies, increased levels of IMA have been reported in complicated pregnancies involving fetal growth retardation, recurrent pregnancy loss, first-trimester miscarriages, and preeclampsia [25-29]. Papageorghiou *et al*. found that serum IMA levels are higher in defective endovascular trophoblast invasion. They argued that the trophoblast may trigger improper development because of the high degree of intrauterine hypoxia and subsequent reperfusion-related oxidative damage [16]. There are also different studies in the literature stating that IMA levels increase physiologically in early gestational weeks [17, 18]. Recently, Uckan *et al*. [30] found high IMA levels in 137 women with pregnancies complicated by HG. Although the level of IMA was significantly higher in our study, it is not clear whether this marker, which was already determined to be high in the first period of pregnancy, increased even more due to HG or its high level played a role in the etiopathogenesis of HG.

MPO is a lysosomal enzyme secreted from leukocytes in response to OS. It was reported that the levels of MPO, which was determined at increased levels in complicated pregnancies like preeclampsia and idiopathic intrauterine growth restriction, did not differ significantly in the three trimesters in healthy pregnancies [31, 32]. There is one study in the literature

conducted on the relationship between HG and MPO in 30 women and the results are consistent with those of our study. They found statistically significant low levels of MPO in HG [33]. However, in our study, although low MPO levels were observed, there was no statistically significant difference compared to control group. This indicates that HG does not cause extra oxidative load.

The vast majority of circulating copper is transported by an oxidase enzyme called ceruloplasmin, which has antioxidant properties. Ferroxidase enzymatically shows the active state of ceruloplasmin [34, 35]. Various researchers investigated ferroxidase and reported that although it is more dramatic in severe preeclampsia it is higher in preeclamptic pregnancies than in normal pregnancies [36, 37]. Another study states that ceruloplasmin and cholesterol levels can be used to predict the development of preeclampsia in the second trimester. Studies investigating the relationship between OS, antioxidant enzymes, and preeclampsia attribute the increase in ferroxidase activity to increased OS in preeclampsia [36, 37]. As in other studies related to HG and ferroxidase, no significant difference was found in ferroxidase activity when compared to in pregnant women without HG [8, 33]. Ferroxidase level was not significantly different in pregnant women without HG than in the HG group in our study, so this may be one more sign that the oxidant balance is not disturbed.

CAT is an intracellular antioxidant that plays a role in enzymatic defense. It increases during OS to balance the redox reactions. ROS play an important role in pregnancy. However, excessive amounts can override the antioxidant systems and can cause oxidative damage. In the 10th-12th weeks of gestation, ROS levels increase physiologically in pregnant women and this increase is directly proportional to the increase in CAT levels, which is one of the main endogenous antioxidants. However, if there is insufficient antioxidant production, the oxidative balance is disturbed and oxidative damage may contribute to the development of pregnancy disorders [38, 39]. Guney *et al*. found that the CAT level was lower in the group with HG. They reported that it can be explained by the deficiency of antioxidants taken with nutrients [2]. According to Ege *et al*. [33], CAT levels were significantly higher in the HG group and they state that the level of CAT increases during OS to prevent the increase in oxidative radicals. Although CAT levels were significantly higher in the HG group in our study, in light of this information, considering that the pregnant women in the study were at 10-12 weeks, it cannot be concluded that there was extra oxidative load.

The DNI is a marker showing the number of immature granulocytes in human serum. In a limited number of studies, it was used in patient groups with inflammatory processes such as sepsis, acute appendicitis, meningitis, decompensated heart failure, acute gout attack, and acute pancreatitis, and it was thought that it could guide physicians in determining disease severity [19]. In a study published recently, it was mentioned that the DNI was not different in the HG group, but there was an increase in the neutrophil count and neutrophil/lymphocyte ratio in the HG group [40]. No significant change was found in any of the complete blood parameters in our study.

Limitations

Like other studies in the literature, our study has some limitations. The pre-pregnancy oxidative status of the HG group and the control group is not known. In addition, the fetal and neonatal consequences of decreased antioxidants in the HG group are unknown.

CONCLUSION

According to the study, contrary to the literature, HG does not impose an extra burden on maternal oxidative balance. Although there is a decrease in antioxidant levels in terms of thiol/disulfide, we believe that the physiological mechanisms are trying to protect both mother and fetus from possible oxidative complications by keeping the oxidative balance stable. The relationship between oxidative balance and HG complications can be revealed more clearly with fetal/neonatal outcomes.

Ethics approval and consent to participate

All participants signed informed written consent before being enrolled in the study. The study was reviewed and approved by the ethics committee of Republic of Turkey Ministry of Health Ankara City Hospital (Ethics approval reference number: E2-22-2647 and date: 16.10.2022). All procedures were performed according to the Declaration of Helsinki.

Authors' Contribution

Study Conception: GY; Study Design: GY; Supervision: GY, HA, DŞ, ASÖE; Funding: N/A; Materials: GY, SN, GG, ÖE; Data Collection and/or Processing: GY, DO, SN; Statistical Analysis and/or Data Interpretation: GY, DO, SN, GG, ÖE; Literature Review: GY, DO, HA; Manuscript Preparation: GY, DO and Critical Review: DŞ, HA, ÖE, ASÖE.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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