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Comparison of Serum Ykl-40 and Ischemia Modified Albulmin Levels Between Pregnant Women with Hyperemesis Gravidarum and Normal Pregnant Women

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ABSTRACT

Introduction: The etiopathogenesis of HG is still unclear. Aim: The aim of this study was to investigate the levels of YKL-40 protein as an inflammatory marker and evaluate the levels of IMA as an oxidative marker in hyperemesis gravidarum women. Materials and Methods: Totally 35 patients with hyperemesis gravidarum and 35 healthy pregnants were included in the study. Singleton pregnancies between 6+0 week and 13+6 weeks of gestation, with normal fetal anatomy were included in the study. Complete blood count, complete urine analyze, biochemical tests and thyroid function tests were done. Results: There was no significant difference between groups for demographical features (age, gravidity, gestational age, body mass index). Also, there was no statistically significant difference between groups for IMA levels ($p>0.05$). The median level of YKL-40 was higher in pregnants with hyperemesis gravidarum than normal pregnants but the difference was not statistically significance ($p>0.05$). Conclusion: Further comprehensive studies with more number of patients are needed to show the efficacy of YKL-40 and IMA levels for predicting hyperemesis gravidarum and even monitoring of the treatment.

Keywords: Hyperemesis gravidarum, inflammation, Ischemia modified albumin, oxidative stress, YKL-40.

1. INTRODUCTION

Nausea and vomiting in the first trimester of pregnancy is a common condition, which affects approximately 85% of women. Hyperemesis gravidarum (HG), a disorder that occurs 0.3-2% of all pregnancies, is more severe nausea and vomiting that leading to weight loss, dehydration, electrolyte imbalance and ketonuria (1, 2).

Although the etiopathogenesis in HG is not clear, the disease is thought to be associated with maternal endocrinologic and immunological function, placental growing-function and pregestational gastrointestinal condition (2).

Oxidative stress is an instability of oxidant molecules and antioxidant defenses in living organisms and this imbalance may result a lot of pathological and physiological situation that include pregnancy and the complications about pregnancy (3).

In ischemic events, the albumin molecule undergoes modifications on its amino terminal portion and losing metal binding capacity thus the variant metabolic protein occur. This change is named as ischemia-modified albumin (IMA) and is used as an oxidative marker in recent years (4).

At the process of pregnancy, some modifications happen to protect the fetus and decidua from maternal immunity and we know that some disorders can occur if these physiological immune responds change (5). Chitinase like protein, YKL 40, is a glycoprotein that is secreted by the *CHI3L1* gene that is approximately 40 kDa in size (6). YKL 40 is an inflammatory marker, which is related with acute and chronic inflammation, extracellular remodeling, and angiogenesis and has prognostic importance of many cancers (7).

The relation of inflammatory disorders and increased oxidative stress

with HG has been appraised but the findings are inconsistent (5, 8-11).

2. AIM

We aimed to evaluate the levels of YKL 40, which is used as inflammatory marker, and to evaluate the levels of IMA, which is used as oxidative marker in HG patients.

3. MATERIAL AND METHODS

The research was carried out at the University Hospital between April and December 2015. The population consisted of 35 pregnant women with HG (patients group) and 35 healthy first trimester pregnant women (control group). The research was approved University Ethics Committee and was taken written informed consent to take in the study from all women.

Inclusion criterias for HG were singleton pregnancy, gestational age between 6 and 14 weeks, ketonuria (>1 positive ketone in random urine specimen), severe vomiting and nausea (>4 times per day) and weight loss (>%5 of body weight) (1, 12). Exclusion criterias were multiple pregnancy, fetal congenital malformation, known gastrointestinal, audiovestibular, endocrinological, infectious or psychological disorders which can cause nausea and vomiting, systemic diseases which may effect ketonuria or blood electrolytes like diabetes mellitus and kidney failure. We determined gestational age by crown rump length measurement in sagittal plane with transabdominal ultrasound probe.

Medical (age, complaint, height and weight, cigarette use) and obstetric history (gravity, parity, abortus, weight loss in pregnancy) of each participant was recorded and, all physical-obstetric examination was done by same person to eliminate the difference between observers. Gestational age was detected by using the first date of last menstrual period and verified by crown rump length measurement in sagittal plane with transabdominal ultrasound probe (Voluson P8, GE Ults, 2013, Korea-GE 4C -RS). BMI was calculated by dividing weight in kilograms by the square of the height in meters.

2.1. Blood Sample Collection

Blood samples were taken from antecubital vein with a 10-gauge needle in the early morning after overnight fasting. Complete blood counts with automated differential counts and biochemical parameters, which included urea, creatinine, serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), thyroid stimulating hormone (TSH) were measured using analyzers (Mindray BC 6800 and Cobas 6000).

2.2. Measurement of YKL-40 and IMA

Blood samples were taken to non-heparin tube for measurement of IMA and YKL 40, the samples was centrifuged with the speed of 1500 rotation per minute for 15 minutes. Supernatant serums was put into eppendorf pipettes and stored up -80 C until assay. Plasma concentrations of YKL 40 and IMA were detected by a commercially available ELISA kit (YH Biosearch IMA-YKL-40 EIA Kit).

2.3. Statistical Analysis

SPSS 15.0 for Windows program was used for analyzing the data. Distribution of data was performed analyzing with Kolmogorov–Smirnov test. The data was presented as mean ± standard deviation for numerical variables and as percentage for categorical variables. Independent sample test and Mann Whitney U test were used for analyzing data with a normal distribution and non-normally distributed data. Categorical variables were evaluated using Chi-square test. $P < 0.05$ value was considered statistically significant.

4. RESULTS

There was no significant difference in basic demographic properties (age, gravity, parity, gestational age, BMI) between the groups (Table 1).

	HG (n=35) (Mean ± SD)	Control (n=35) (Mean ± SD)	p
Age (year)	26.8±4.5	26.8±4.2	1.000
*Gravity (med-min-max)	2 (1-5)	2 (1-6)	0.634
*Parity (med-min-max)	1 (0-3)	1 (0-3)	0.614
Gestational Age (week)	9.7±2.3	10.4±2.3	0.212
BMI (kg/m2)	24.2±3.7	25.4±4.7	0.230

Table 1. Demographic data of the patients with HG and the control group, Independent Sample T test, *Mann Whitney U test. Comparison of laboratory parameters, potassium, urea and creatinine were higher than control group in HG group but there was no statistically difference (p>0.05).

Comparison of laboratory parameters, potassium, urea and creatinine were higher than control group in HG group but there was no statistically difference (p>0.05) (Table 2).

	HG (n=35) (Mean ± SD)	Control (n=35) (Mean ± SD)	p
Hb (g/dl)	11.7±1.3	11.8±1.3	0.770
Htc (%)	36.1±2.3	37.2±2.5	0.113
WBC (×103/µl)	8.6±1.4	8.4±1.7	0.738
SGPT (µ/l)	14.2±6.5	14.2±6.2	1.0
SGOT (µ/l)	14.8±4.6	16.3±4.3	0.158
TSH (µIU/ml)	1.7±0.8	2.0±1.1	0.123
*BUN (mg/dl)	16 (8-26)	13 (8-23)	0.07
Creatinine (mg/dl)	0.48±0.13	0.41±0.13	0.205
Na (mmol/L)	137±3.5	137±3.9	0.636
K (mmol/L)	3.87±0.63	3.72±0.64	0.14
Ca (mmol/L)	8.77±0.47	8.70±0.43	0.529

Table 2. Biochemical parameters of patients with HG and the control group. Independent Sample T test. *Mann Whitney U test (med-min-max).

Median IMA value is in control group, median YKL 40 is in HG is higher but there was no significant difference found (Table 3).

	HG (n=35) (Mean ± SD)	Control (n=35) (Mean ± SD)	p
IMA (ng/dl)	69.6 (40.3-400.4)	92.5(41.8-465.4)	0.136
YKL-40 (ng/dl)	28.0 (12.0-353.7)	23.3 (8.8-269.5)	0.147

Table 3. Comparison of IMA and YKL-40 levels patients with HG and the control group. Mann Whitney U test was used.

Smoking habit and parity analyzes were done. The incidence of nulliparity and not smoking is higher in HG group but there was no statically significant difference (non smoking rate: 91,4% in HG group versus 77,1% in control group, Chi-Square test - p=0,103).

5. DISCUSSION

Pregnancy is a physiologic condition that is predominated by oxidative stress because of increased metabolic turnover and oxygen consumption (9). Many researches have concluded the effects of increased oxidative stress on infertility and hyperemesis gravidarum (10, 13).

Many biomarkers related to oxidant/antioxidant status have been investigated, with controversial results (9, 11, 14, 15). Reduced glutathione, an antioxidant marker, has been detected lower among pregnant women with hyperemesis gravidarum than normal pregnant women (11). Additionally, Aksoy et al. have reported that the oxidant/antioxidant balance has been shifted to oxidant side and serum malondialdehyde level (MDA) has increased which represent the total antioxidant level (TAS-TAL) decrease (15). Another research has showed TAS and TOS levels increase the nausea and vomiting during pregnancy and these may be used as an early predictive biomarkers. Results were statistically significant (16).

Another research (17) has pointed that decreased PON-1 activity is related to oxidative stress and inflammation among pregnant with hyperemesis gravidarum. Although it has been proved that decreased PON-1 activity increases the oxidative stress and inflammation (17) there are also some studies hypotheses that total antioxidant activity does not change at pregnant with hyperemesis gravidarum (14) and this situation is not a cause but a result (18).

There are some mechanisms that may cause oxidative stress at hyperemesis gravidarum. First of these is insufficient intake of antioxidant foods like vitamin C and vitamin E, in spite of an increasing nutritional need (19). Another possible mechanism is mucosal injury caused by H. pylori infection related to oxidative stress (20).

In the literature, even though a lot of studies have shown that oxidative activity may change at pregnant women with hyperemesis gravidarum (15, 16), there is one study on IMA levels as an oxidative marker among pregnant women with hyperemesis. In this cross-sectional study design, Sari et al. found that IMA levels increase women with HG (21). In our study, serum IMA levels were similar between the groups.

It is thought that physiological immune response that protects the fetus and decidua from the maternal effect may also have a pathogenetic role (22). In another study, immune response have been observed and it has been detected that activation of granulocytes, natural killer cells and extrathymic cells are necessary for progression of pregnancy (5). It has been stated that cytokines that play role at inflammation have role at physiopathology of hyperemesis gravidarum as well (23, 24). Additionally, serum immunoglobulin, complement and lymphocyte levels are higher at pregnant women with hyperemesis gravidarum than healthy pregnant women (25). In another study consisting 55 HG patient and 50 healthy pregnant, neutrophil lymphocyte ratio (NLR) and high sensitivity CRP (hsCRP) levels have been found quite high according to healthy pregnant women and it has stated that hyperemesis gravidarum is a disease related to inflammation (26).

To our knowledge, this is the first report that investigates level of YKL-40 among pregnant women with hyperemesis gravidarum. In this study, YKL-40 levels have been detected at higher levels among patient group although there was no statistically significance (p> 0.05). This condition may be related to our limited sample size and cross-sectional study design.

Different studies state that body mass index is lower pre-pregnancy at hyperemesis gravidarum than control pregnant and obesity is protective for hyperemesis gravidarum (27). On the other hand, obesity and visceral adipose tissue may be risk factors (28). In our study, although BMI was lower at patient group than control group there was no statistically significant difference (p=0.23).

Clinical thyrotoxicosis has been emphasized as a cause of hyperemesis but this situation is more likely based on higher serum hCG levels. Generally, serum free thyroxine levels normalize with hydration and emesis treatment. (2). In our study, convenient to inclusion criteria, the patients were euthyroid and there was no significant difference between groups' thyroid function tests (p=0.123).

Some studies have stated that advanced maternal age, multiparity and smoking are protective for hyperemesis gravidarum (29). At this study, there was no difference between patient and control groups for maternal age. Furthermore, despite of high percentage of nulliparity and being non-smoking there was no significant statistical difference.

6. CONCLUSION

There was no difference in the levels of IMA as an oxidative marker between the groups. On the other hand, levels of YKL-40 as an inflammatory marker protein were higher in pregnant women with hyperemesis gravidarum, but this increase wasn't statistically significant. However, there is a need for large scale, prospective and long-term studies that evaluate the effects of these parameters in hyperemesis gravidarum.

- **Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms.
- **Author's contribution:** MB, NS gave a substantial contribution to the conception and design of the work. MB gave a substantial contribution of data. MB, NS, UK gave a substantial contribution to the acquisition, analysis, or interpretation of data for the work. MB, NS, CDS, IY had a part in article preparing for drafting or revising it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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