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Original Research Article

ASSOCIATION OF ANXIETY, DEPRESSION, FOLATE AND VITAMIN B12 LEVELS WITH HYPEREMESIS GRAVIDARUM

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Abstract: Objective: The aim of this study was to determine the relationship between Hyperemesis Gravidarum (HG) and serum folate/vitamin B12 levels and Beck score of anxiety/ depression.
Methods: This is a case control study conducted at Obstetrics and Gynecology outpatient clinic between June 2013 - January 2014. The study group consisted of 80 with HG and 80 controls matched for age, gestational age. Age, education, occupation, family type, residence, status of pregnancy, body mass index (BMI) and smoking were questioned in all patients. Blood samples were drawn for complete blood count and calcium, magnesium, folic acid and vitamin B12 measurements. Beck Anxiety Inventory (BAI) and Beck Depression Inventory (BDI) were applied to all patients.
Results: No significant difference was found in age and gestational week between patients and controls. HG was higher in patients at rural areas. BMI was found to be significantly lower in HG group ($p<0.001$). BAI and BDI scores were found to be significantly higher in patients with HG. Both folic acid and vitamin B12 levels were found to be lower in cases with HG ($p<0.001$).
Conclusion: In our study, it was found that anxiety and depression were more common while serum folic acid and vitamin B12 levels were significantly lower in pregnant women with HG.

Keywords: Hyperemesis gravidarum, anxiety, depression, folic acid, vitamin B12

Introduction: Nausea and vomiting are commonly seen symptoms in pregnancy by 80%, which affect family experience, social life and career. However, hyperemesis gravidarum (HG) is a condition characterized by excessive and persistent vomiting, which onset prior to gestational week 22. It is seen in approximately 0.3-2% of all pregnancies, comprising most frequent cause of hospitalization in the first half of pregnancy [1, 2]. In pregnancy, nausea and vomiting occur through two possible mechanisms. First mechanism involves activation of unknown pathways via direct stimulation, while second mechanism involves decrease in nausea and vomiting thresholds

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mediated by vestibular and intestinal systems [3].

In the literature, it has been proposed that HG is a syndrome that results from complex interplay between environmental, familial and genetic factors, although etiology isn't fully elucidated [2, 3]. There are theories indicating importance of psychological factors, although there are reasonable biological theories [4]. HG may have maternal and fetal life-threatening consequences including weight loss, malnutrition, electrolyte imbalance, ketosis, fetal loss, premature birth, stillbirth, intrauterine growth retardation, congenital malformations and Wernicke's encephalopathy [4,5]. There is no standard therapy in HG and complete recovery is rarely achieved in these patients [1]. Current standard care relies on rehydration and anti-emetic therapy; however, these measures fail in many patients. Thus, meeting social, psychological and physical requirements in an individualized manner may be more effective in these patients [6]. Currently, etiology hasn't been fully elucidated in HG, although there are studies on risk factors for HG. Folate and Vitamin B12 play a role in synthesis of neurotransmitter in the central nervous system and regulating mode. Low levels of folate and vitamin B12 cause anxiety and depression [7,8].

The relationship between HG and anxiety/ depression was expressed in the literature[9,10]. Watanabe H et al. showed that was no relationship between HG and folate, vitamin B12 levels in early pregnancy [11]. There are few studies in the literature on this subject. For this reason, this study was planned. The aim of this study was to determine the relationship between HG and serum folate / vitamin B12 levels and Beck score of anxiety / depression.

Patients and Methods

Study design: This is a case control study conducted at Obstetrics and Gynecology outpatient clinic between June 2013 - January 2014. The study group consisted of 80 with HG and 80 controls matched for age, gestational age. The study was approved by Ethics Committee of Medicine School. All patients gave written informed consent. The study conducted in accordance to Helsinki Declaration. Data were recorded by using data sheet. Turkish versions of Beck Depression Inventory and Beck Anxiety Inventory were applied by a psychiatrist [12, 13].

Patient selection: Inclusion criteria included: 1) pregnancy at first trimester; 2) presence of a single, healthy pregnancy on sonography; 3) HG diagnosis based on 3 or more severe vomiting episodes per day, failure in oral intake, weight loss of at least 3 kg and at least 1+ ketonuria; 4) establishing sufficient cooperation that would not affect test results; 5) lack of psychiatric or medical disease before pregnancy; The patients not meeting above-mentioned criteria were excluded. Control group were selected among pregnant women with a single, healthy pregnancy, each were matched with a control who was at same age and gestational age.

Age, education (primary school, secondary school, college, university), occupation, family type (nuclear family or extended family), residence (urban or rural), status of pregnancy (planned or unplanned), body mass index (BMI) and smoking status were questioned in all patients.

Blood samples were drawn at presentation after 8-hours fasting for complete blood count, and electrolyte (Na, K, Cl, Mg), folate and vitamin B12 measurements. Urine samples were obtained for ketone analysis. Sonography was performed for fetal assessment. The patients diagnosed as HG were admitted to hospital and standard intravenous fluid therapy and anti-emetic treatment were given. The patients were assessed according to oral intake and clinical condition. The patients were discharged after rehydration and sufficient oral intake.

Biochemical assay: Serum B12, folate, Ca, Mg, Na, K, Cl were measured on Abbott ci8200 automated analyser (Abbott laboratories, Chicago, IL, USA). Blood cells were counted sing the HMX (Beckman Coulter, USA) analyser.

Statistical Analyses: Statistics were run with Software package STATA 11.0 (College station, Texas, USA). Continuous variables were expressed as mean ± Standard deviation (SD) or median and categorical variables were

expressed as percentage. Risk factors for HG were assessed. A p-value of <0.05 was considered statistically significant. The Chi-square test was used to compare proportions. Continuous variables were compared using an independent-groups Student's test informality assumptions were met; otherwise, groups were compared using the Wilcoxonranksum test. An analysis of normality of the continuous variables was performed with the Kolmogorov-Smirnov test. Logistic regression was used to model assess the risk factors associated HG. For multivariate analysis, only variables with a p value<0.05 were entered in to model and selected using a step wise selection procedure.

RESULTS

Analysis of demographic data: Table 1 presents demographic characteristics of patients. No significant difference were found regarding age, education, occupation, family type (nuclear family or extended family), status of pregnancy (planned or unplanned) and smoking status.BMI was found to be significantly lower in the HG group (p<0.001). Proportion of patients living in rural areas was higher in the HG group when compared to controls.

Comparison of laboratory results: Leukocyte counts and sodium levels were found to be significantly lower in HG group (p<0.001). Folic acid levels were found as 15.2±4.2 and 12.1±2.5 ng/mL in control and HG groups, respectively. Vitamin B12 levels were found as 277.4±87.7 and 202.3±53.6 pg/mL in control and HG groups, respectively. Both folic acid and vitamin B12 levels were found to be lower in cases with HG (p<0.001). Table 2 presents laboratory results in cases included.

Analysis of risk factors by results of anxiety and depression: Both anxiety and depression scores were found to be significantly higher in cases with HG when compared to controls (p<0.001).

In logistic regression analysis, depression, anxiety, rural residence, BMI, and low folic acid and vitamin B12 levels were identified as risk factors for HG.

In logistic regression analysis, depression, anxiety, rural residence, BMI, and low folic acid and vitamin B12 levels were identified as independent risk factors for HG. Depression, anxiety, living in rural areas were associated with a high rate of HG. Low BMI, serum folate and vitamin B12 levels have been associated with a high rate of HG. The results of logistic regression analysis were presented in table-3.

Discussion: In our study, it was found that anxiety and depression were more common while serum folic acid and vitamin B12 levels were significantly lower in pregnant women with HG. Although many psychological and behavioral reasons including lack of communication between pregnant woman and partner, stress in home life and inadequate knowledge about pregnancy have been proposed for the etiology of HG, it is difficult to make discrimination among these. In the present study, no significant difference was detected between patient and control groups regarding education level, occupation, family type, status of pregnancy (planned or unplanned) and smoking status. In our study, HG incidence was 2.7 fold higher among pregnant women living at rural areas. In addition, it was seen that anxiety and depression rates were higher in cases with HG. In the literature, it is suggested that anxiety and depression rates are higher in cases with nausea and vomiting during pregnancy. This can be due to insufficient nutrition, energy deficiency and severe fatigue, failure in socialization, hopelessness about relief of vomiting after pregnancy, and concerns that it is impossible to provide sufficient feeding to developing fetus [4, 14, 15]. In a study on 284 patients with HG by Tan PC et al., it was suggested that depression could be an independent risk factor for development of HG [9]. In agreement with literature, it was seen that both depression and anxiety were identified as independent risk factors for HG in logistic regression analysis in our study. Similarly, in the study on patients with HG, Annagür *et al.* reported that psychiatric disorders might play role in HG etiology [10]. Another etiological factor is perceived body image by pregnant woman. In a study on this topic by Cedergen *et al.*, it was found that need for treatment and hospitalization due to HG was higher in underweight pregnant women, while it was less

common in obese pregnant women[16]. In another study, it was suggested that both obesity and being underweight are associated with HG symptoms [17]. In our study, BMI appeared as an independent risk factor in HG etiology.

Folic acid has a role in the synthesis of neurotransmitters such as serotonin in central nervous system. Increased homocystein levels, a marker of folic acid and vitamin B12 deficiency, lead oxidative stress that may result in neurotransmitter failure, cerebrovascular and neurological injury [18, 19]. There are several studies defining relationship between folic acid and vitamin B12 deficiency and neuropsychiatric disorders since discovery of folic acid in 1945 and vitamin B12 in 1948 [7]. In a meta-analysis on relationship between folic acid and depression, Gilbody et al. reported that there is a relationship between low folic acid levels and depression, but it is difficult to document that it is a causal relationship [19]. In addition, authors suggested that there are many controversial aspects in this topic. Folic acid and vitamin B12 deficiency may result from several reasons such as insufficient dietary intake, malabsorption and increased requirement during stress. It has been suggested that folic acid and vitamin B12 is important in mood regulation. Serum folic acid and vitamin B12 levels were found to be low in patients with depression [8]. In the present study, low serum folic acid and vitamin B12 levels in patients with anxiety and depression. Also, folic acid and vitamin B12 were found as independent risk factor for HG development. However, in a study on 86 pregnant women by Watanabe et al., it was reported that there was no association between depression incidence and serum folic acid or homocystein levels in first trimester of pregnancy; thus, folic acid supplementation would not be protective against depression [9]. Similarly, in a study on postmenopausal women, Sengül et al. reported that there was no relationship between depression and serum folic acid or vitamin B12 levels [20]. In another study by Watanabe et al., it was suggested that there might be a relationship between folic acid intake and depression in women at reproductive age; thus, folic acid supplementation could be effective in decreasing depression incidence [21]. In another study, it was suggested that relationship between folic acid and vitamin B12 might involve different mechanisms and depression could result from B12 [22].

In conclusion, Depresion, anxiety, patients living in rural areas and low BMI were more frequent in HG. Likewise, low serum folic acid and vitamin B12 levels were found as independent risk factors in the etiology. Thus, it is important to perform psychological assessment and to measure serum folic acid and vitamin B12 levels in pregnant women with HG. Also, we think that individualizing management and providing folic acid and vitamin B12 supplementation as well as psychological support would play an important role in the success of treatment.

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We declare that we have no conflict of interest.

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Table-1: Demographic data of the patients

		Control group(n:80)		HG group (n:80)		P value
Age		25.4±4.7		26.4±6.1		0.247
BMI at admission		26.1±3.1		23.8±2.7		<0.001
Pregnancy week		10.1±1.8		10.1±1.8		0.930
		n	%	n	%	
Education status	Primary-middle school	38	47.5	48	60	0.112
	High school	31	38.8	25	31.3	0.320
	College	11	13.8	7	8.8	0.316
Employment	Paid	21	26.3	15	18.8	0.256
	Housewife	59	73.8	65	81.3	
Living of family	Nuclear	70	87.5	63	78.8	0.140
	Extended	10	12.5	17	21.5	
Place of residence	Village	33	41.3	51	63.8	0.004
	City	47	58.8	29	36.3	
Pregnancy	Planned	61	76.3	56	70	0.373
	Un-planned	19	23.8	24	30	
Smoking	Non-smoker	73	91.3	67	83.8	0.151
	Smoker	7	8.8	13	16.3	

HG: Hyperemesis Gravidarum, BMI: Body Mass Index

Tablo-2: Comparison of laboratory values of the Control and HG groups.

	Control group (mean±SD)	HG group(mean±SD)	p
WBC (10^3/ml)	10.2±2.8	8.9±1.8	<0.001
Hb (g/dl)	12.1±1.4	12.1±1.3	0.892
Platelet (10^3 /ml)	247.9±64.1	246.8±61.7	0.913
Na (mmol/L)	139.2±2.9	138.1±2.7	0.020
K (mmol/L)	4.1±0.3	4.1±0.3	0.534
Cl(mmol/L)	101.6±5.3	101.9±2.9	0.617
Ca (mg/dL)	9.4±0.5	9.4±0.4	0.368
Mg (mg/dL)	2.1±0.3	1.9±0.2	0.052
Folate(ng/mL)	15.2±4.3	12.1±2.5	<0.001
B12 vitamin(pg/mL)	277.4±87.7	202.3±53.6	<0.001

WBC: White blood cell, Hb: hemoglobin, Na:sodium, K:potassium, Cl:chloride, Ca:calcium, Mg: magnesium, HG: Hyperemesis Gravidarum, SD: Standard Deviation

Table-3:Analysis of risk factors for HG.

Independent risk factors	Odds Ratio	%95 Confidence interval (CI)	p
Depression	1.07	1.003-1.147	0.040
Anxiety	1.06	1.006-1.111	0.030
Rural residence	2.76	1.052-7.221	0.039
BMI	0.763	0.636-0.913	0.003
Folate	0.801	0.694 – 0.925	0.002
Vitamin B12	0.979	0.971-0.988	<0.001

BMI: Body Mass Index

Figure-1: Comparison of folate levels between control and HG groups.(p<0.001)

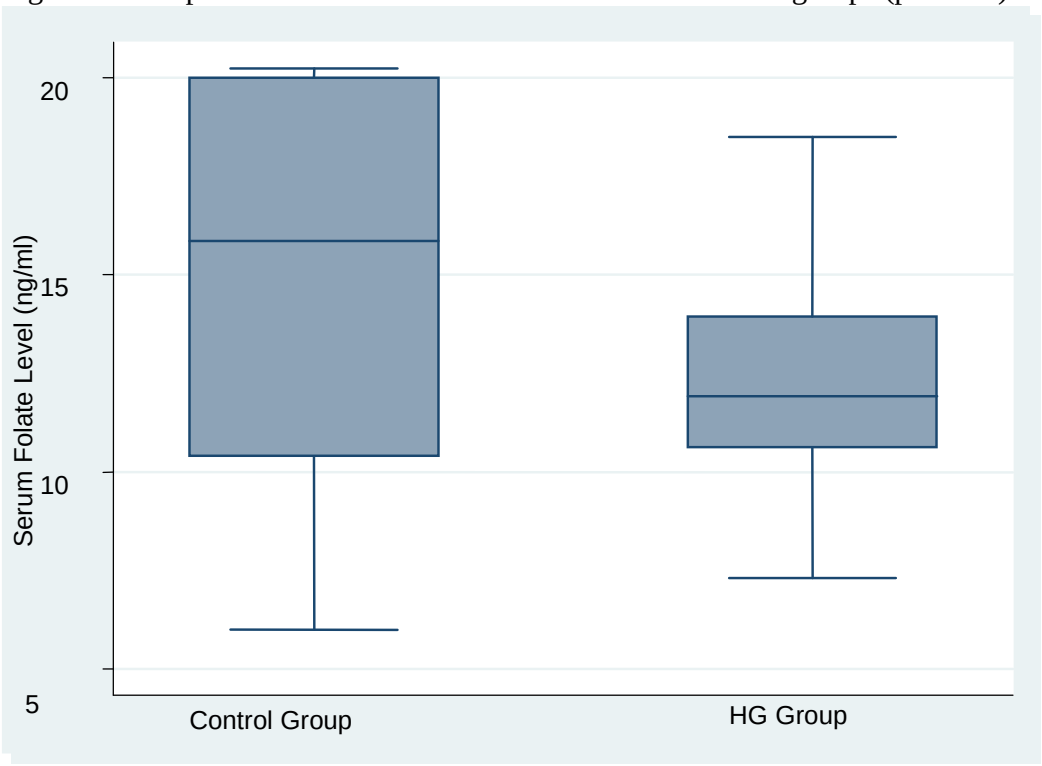

Figure-2: Comparison of Vitamin B12 levels between control and HG groups.($p<0.001$)