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POLISH GYNECOLOGY
GINEKOLOGIA POLSKA
ORGAN POLSKIEGO TOWARZYSTWA GINEKOLOGICZNEGO
THE OFFICIAL JOURNAL OF THE POLISH GYNECOLOGICAL SOCIETY

ISSN: 0017-0011

e-ISSN: 2543-6767

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DOI: 10.5603/GP.a2023.0049

Article type: Research paper

Submitted: 2022-12-15

Accepted: 2023-04-07

Published online: 2023-06-09

ORIGINAL PAPER / OBSTETRICS

The evaluation of serum brain-derived neurotrophic factor levels in pregnant women with hyperemesis gravidarum

Short title: Brain-derived neurotrophic factor (BDNF) and hyperemesis gravidarum

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ABSTRACT

Objectives: The aim of this study was to investigate the relationship between levels of brain-derived neurotrophic factor (BDNF), which is considered a cause of conditions such as depression and eating disorders, and hyperemesis gravidarum (HG).

Material and methods: This study was conducted as a prospective study at Ankara Ataturk Training and Research Hospital in the Department of Obstetrics and Gynecology. The study included 73 pregnant women with singleton pregnancies (32 pregnant women with HG and 41 pregnant women without hyperemesis). Serum BDNF levels were compared between the two groups.

Results: The mean age of the study group was 27.3 ± 3.5 years and the body mass index (BMI) was 22.4 ± 2.7 kg/m^2. There is no statistically significant difference between the study group and the control group in terms of demographic data ($p > 0.05$). The pregnant women

with HG were found to have significantly higher serum BDNF levels compared to the control group (349.1 ± 94.6 pg/mL vs 292. 3± 86.01, p = 0.009)

Conclusions: Serum BDNF levels that are low in psychiatric disorders such as depression or anxiety were found as high in pregnant women with HG.

Key words: hyperemesis gravidarum; psychological factors; brain-derived neurotrophic factor; pregnancy

INTRODUCTION

Pregnancy is an important period in a woman's life, during which somatic, psychological and social changes take place. Hyperemesis gravidarum (HG) is defined as severe nausea and vomiting accompanied by weight loss, nutrient deficiency, and fluid-electrolyte imbalance during the first trimester of pregnancy. Nausea and vomiting are the most common somatic complaints experienced by approximately 75% of pregnant women during the first trimester [1], and these symptoms may continue to occur after the first trimester [1]. HG vomiting is a serious medical problem in pregnancy and remains an important cause of fluid and electrolyte losses, acid-base imbalance, nutrient deficiencies, weight loss, dehydration, anemia, ketonuria, and frequent hospitalizations [1, 2]. HG not only affects pregnant women's physical health, but also their quality of life and affects their psychosocial condition [3]. Endocrine hormones such as human chorionic gonadotropin (HCG), estrogen, progesterone, and thyroid hormones, as well as psychosocial factors, may play an important role in the etiology and pathogenesis of HG [1]. However, the relative roles of psychological and biological factors in the development of this disorder remain controversial [2]. Depressive symptoms in pregnant women have been found to be associated with severe nausea and vomiting during pregnancy [4]. A recent study has shown that there is an association between depression or anxiety scores and the severity of nausea and vomiting in early pregnancy [5]. Although there are a number of studies examining the association between psychiatric disorders and HG, none of these studies are sufficient to clarify the relationship to pathogenesis [6].

Brain-derived neurotrophic factor (BDNF) belongs to the nerve growth factor family, which is important for neuron survival and plasticity. It was originally described in the nervous system but has recently been shown to be present in ovarian tissue as well [7]. There is increasing evidence in the literature that BDNF expression in the limbic structure of the brain decreases with chronic stress, which may lead to an increase in mood disorders in patients with chronic stress [8, 9]. Another study has shown that chronic unpredictable stress

leads to a decrease in the number of harvested oocytes, blastocyst development, and BDNF expression in antral follicles [10]. It has also been reported that increased oxidative stress and inflammation lead to a decrease in serum BDNF levels [11]. A study has shown that HG, which leads to inadequate food intake, suppresses the immune system and plays an important role in antioxidant levels [12].

In addition, there are numerous data suggesting that BDNF may play an important role in determining neuroplasticity in the hippocampus, regulating appetite and eating behavior, and learning and memory behavior [13]. In addition, serum BDNF levels have been found to be decreased in patients with anorexia nervosa [14] and increased in patients with fibromyalgia [15].

The purpose of this study is to discuss depression, anxiety, eating disorders, etc. The aim of this study is to investigate BDNF serum level in pregnant women with hyperemesis gravidarum.

MATERIAL AND METHODS

This study followed the Helsinki Declaration on human subject research and was approved by the Ethics Committee of Ankara Yildirim Beyazit University (Date: 25.03.2013, Approval No: 37).

This study is conducted as a prospective study at Ankara Ataturk Training and Research Hospital in the Department of Obstetrics and Gynecology between February 2013 and July 2013. All participants provided written informed consent. Seventy-three pregnant women participated in the study [32 pregnant women with HG and 41 pregnant women without hyperemesis (control group)]. All participants were selected from pregnant women presenting to our obstetric outpatient clinic during the first trimester of their pregnancy. HG was defined as persistent nausea and the occurrence of three or more episodes of vomiting per day, positive ketonuria (at least 1+) on urine puncture test without identifiable causes, or 5% weight loss during the current pregnancy. Exclusion criteria for all participants were any type of liver, kidney, or thyroid disease, gastritis, pre-existing systemic or infectious diseases, trophoblastic gestational diseases, gastrointestinal disorders, metabolic disorders, collagen vascular disease, inflammatory diseases, fibromyalgia, chronic hypertension, neuropsychiatric disorders, history of diabetes mellitus or gestational diabetes, smoking habits, alcohol consumption, urinary tract infections, and multiple pregnancies. All pregnant women in the study had a history of regular menstrual cycles before conception and no polycystic ovaries, which can alter BDNF serum levels. All participants refused to take antipsychotics or

antidepressants. Patients' characteristic features [age, gravidity, parity, body mass index (BMI), etc.] were recorded. Gestational age was determined for both the study and control groups based on the date of last menstruation and first trimester ultrasound findings. BMI was calculated as weight (in kg) divided by height (in metres) squared. While the patients were sitting upright, blood samples were collected from the antecubital vein between 08:00 and 10:00 after a 12-hour fasting period. Blood samples of 10cc were collected with a tube containing aprotinin and ethylenediaminetetraacetic acid (EDTA)-2Na and immediately centrifuged at 3500 g for 15 minutes at 4°C and stored at –80°C until processing and thawed immediately before analysis.

Determination of brain-derived neurotrophic factor

Maternal plasma concentration of BDNF were determined using sensitive and specific immunoassays (ELISA kit, Boster Immunoleader, catalogue number EK0307). The immunoassay was performed in duplicate and utilized a sandwich enzyme- based technique and had been validated for plasma determinations of the analytes. Serum concentration values were expressed pg/mL.

Statistical analysis

Statistical analysis was performed with the software IBM SPSS 25 (Statistical Package for Social Sciences) (New York, NY, USA). The Shapiro-Wilk test was used to check whether the data conformed to the normal distribution. Continuous variables were expressed as mean and standard deviation or median and minimum-maximum/interquartile range (IQR) for normally and nonnormally distributed data, respectively; categorical variables were expressed in numbers and percentages. For normally distributed data, the independent-samples t test was used, and for nonnormally distributed variables, the Mann Whitney U test was used. All statistical analyzes were performed with two weights, and a p value of < 0.05 was considered statistically significant.

RESULTS

A total of 73 pregnant women (32 women with HG and 41 women without HG) were included in the study. There were no statistically significant differences between patients' age, week of gestation, body mass index (Tab. 1), serum levels of hemoglobin, white blood cell count, platelet count, fasting blood glucose levels, the serum levels of glutamate oxaloacetic transaminase, the serum levels of glutamate pyruvic transaminase, the serum sodium and

potassium levels, urea, creatinine, and the serum levels of thyroid-stimulating hormone between HG and the control groups of the study (Tab. 2) ($p > 0.05$). Table 1 shows the demographic characteristics of the two groups HG and the control group. Serum BDNF levels were higher in the HG group than in the study control group (349.1 ± 94.6 pg/mL vs 292.3 ± 86.01 $p = 0.009$). No correlations were found between BDNF levels, maternal age, BMI, and serum biochemical parameters in the study ($p > 0.05$).

DISCUSSION

In the current study, we found that serum BDNF levels were higher in pregnant women with HG compared with control subjects. BDNF is expressed in many parts of the human brain [16] and plays an important role in various brain functions, such as synapse development, plasticity, neuronal connections, immature neurons, and survival of mature neurons [17]. Based on previous studies, circulating BDNF levels are thought to directly reflect BDNF levels in the brain [18]. Significantly lower serum BDNF levels have been found in neurodegenerative diseases such as Parkinson's disease than in control groups [19]. Inflammation and increased oxidative stress can also lower BDNF levels in patients' blood [11, 12]. In addition, it is well documented that BDNF plays an important role in the proper functioning of the brain and nervous system [17, 20]. A number of studies have shown that BDNF is an important component of the nervous system and acts as a messenger between cells in response to stress [8, 21, 22]. Recent studies have shown that BDNF is associated not only with stress-related mood disorders [9] but also with reproductive disorders such as polycystic ovary syndrome [23] and infertility [24], with infertile women being more prone to depression and anxiety [25, 26]. Serum BDNF levels have been shown to increase in patients taking antidepressants and during remission of depression [27, 28]. Several studies have shown that pregnant women with HG are vulnerable to depression and anxiety [29, 30]. The severity of nausea and vomiting has been found to correlate with the level of anxiety and depression [30]. Simsek et al. [31] studied depression and anxiety scores in pregnant women with HG and found that patients with HG had significantly higher depression and anxiety scores than controls. However, this conclusion has not been confirmed in other studies [32] Although BDNF levels decrease during depression, we found in this study that pregnant women with HG had higher serum BDNF levels. This finding suggests that psychological factors may not be as influential in the etiology of HG as previously thought. Advanced HG may lead to chronic diseases such as Wernicke encephalopathy [33]. We hypothesize that high BDNF levels on HG may have a protective effect on the brain against the development of

central nervous system disorders such as Wernicke encephalopathy, which is associated with severe HG. Another explanation for the high BDNF levels could be the compensatory process of eating habits or loss of appetite during the first trimester in pregnant women with HG. There is ample evidence that BDNF plays an important role in weight control and eating behavior as well as neuroplasticity and memory behavior in the hippocampus [13]. Patients with anorexia nervosa (AN) and those with short-term weight gain were found to have significantly increased serum BDNF concentrations during the remission phase compared with acutely underweight patients AN [14]. Because there were no statistically significant differences in weight and BMI between HG and control groups in the present study, we cannot say with certainty that the increased BDNF levels are related to weight loss, but we hypothesize that the changes in serum BDNF levels may be related to appetite and eating behavior in patients with HG. In addition, BDNF levels may have increased in a compensatory manner to stimulate appetite in pregnant women with HG. However, further studies are needed to support this hypothesis.

Finally, there are some limitations in our study. BDNF levels may change during pregnancy, which may be related to the changes in pregnancy. To compare the status of different gestational weeks, the use of percentiles will lead to more objective conclusions. A larger number of studied populations is necessary not only to draw more concrete conclusions, but also to determine percentile ranks for weeks of gestation and different stages HG.

CONCLUSIONS

In conclusion, BDNF serum levels were higher in pregnant women with HG. This finding might be related to the defense mechanisms of the brain to cope with HG and its complications such as hunger, anorexia, Wernicke encephalopathy, etc. in the early stages and protect the pregnant women from the worsening effects of the disease. As far as we know, the present study is the first on this topic and suggests that psychological factors do not play a major role in the etiology of hyperemesis. However, further controlled studies are needed to support our findings.

Conflict of interests

All authors declare no conflict of interest.

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Table 1. Demographic data of hyperemesis gravidarum (HG) and control groups

	Control group (n = 41)	**HG group (n = 32)**	**p value**
Age (years)	27.3 ± 3.5	26.6 ± 5.5	0.516
Gravida (n)	2.03 ± 1.3	2.17 ± 1.3	0.557
Parity (n)	0.84 ± 1.1	0.76 ± 0.9	0.928
Gestational age (week)	9.2 ± 1.3	9.4 ± 1.3	0.398
Weight (kg)	59.1 ± 9.11	62.5 ± 9.01	0.111
Body mass index (kg/m^2)	22.4 ± 2.7	23.8 ± 3.2	0.059

Table 2. Comparison of the biochemical parameters and BDNF levels of the groups

	Control group (n = 41)	**HG group (n = 32)**	**p value**
Hb (g/dL)	12.6 ± 1.4	12.4 ± 0.9	0.650
WBC (K/uL)	8.5 ± 1.7	9.2 ± 2.9	0.134
PLT (K/uL)	248.4 ± 77.1	268 ± 104.4	0.458
FBG (mg/dL)	84.97 ± 7.02	87.33 ± 11.67	0.310
SGOT (IU/L)	16.54 ± 3.91	18 ± 4.6	0.170
SGPT (IU/L)	12.15 ± 5.65	13.62 ± 6.40	0.730
Sodium (mmol/L)	138.2 ± 0.8	136.11 ± 2.39	0.070
Potassium (mmol/L)	4.1 ± 0.33	4.1 ± 0.59	0.840
Urea (mg/dL)	16.69 ± 4.87	15.23 ± 4.51	0.220
Creatinine (mg/dL)	0.55 ± 0.11	0.51 ± 0.12	0.170
TSH (mU/mL)	1.46 ± 0.88	1.33 ± 1.14	0.090

BDNF (pg/mL)	292.3 ± 86.01	349.1 ± 94.6	**0.009**

Data were expressed as mean ± SD" and Student *t*-test was used for statistical analyses

BDNF — brain-derived neurotrophic factor; FBG — fasting blood glucose; Hb — hemoglobine; HG — hyperemesis gravidarum; PLT — platelets; SGOT — serum glutamic oxaloacetic transaminase; SGPT — serum glutamic-pyruvic transaminase; TSH — thyroid stimulating hormone; WBC — white blood cell count