

1-1-2013

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Available at: <https://journals.tubitak.gov.tr/medical/vol43/iss5/19>

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Association between maternal ghrelin levels and hyperemesis gravidarum

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Received: 05.09.2012 • Accepted: 01.01.2013 • Published Online: 26.08.2013 • Printed: 20.09.2013

Aim: To investigate serum levels of ghrelin in pregnant women as a potential early marker for hyperemesis gravidarum (HG).

Materials and methods: A cross-sectional study was carried out at Fatih University Hospital. Included in the study were 35 women with HG and 31 pregnant women without HG as a control group. The groups were compared in terms of age, gravidity, body mass index (BMI), and fasting serum thyroid-stimulating hormone (TSH) and ghrelin levels.

Results: Ghrelin levels of the patients with HG were found to be significantly lower than those in the control group ($P = 0.03$). No intergroup differences could be found in serum TSH or BMI values.

Conclusion: Ghrelin might serve as a reliable marker in the etiopathogenesis of HG.

Key words: Hyperemesis gravidarum, pregnancy, ghrelin, etiopathogenesis, thyroid-stimulating hormone, body mass index

1. Introduction

Hyperemesis gravidarum (HG), a pregnancy-related condition marked by extreme nausea and vomiting, occurs in 0.5%–2% of all pregnancies. This condition usually begins between the 4th and the 10th weeks of gestation and disappears spontaneously at the 20th week of gestation (1). Fluid, electrolyte and acid–base imbalance, nutritional deficiencies, and weight loss are the expected important side effects (1). For these reasons, hospitalization and intravenous hydration therapy or parenteral nutrition may be necessary. This period may lead to depression and decrease in the patient's quality of life. The financial burden on the health system due to hospitalization and on the patient due to time lost from work is another significant problem (2). Furthermore, it is associated with adverse pregnancy outcomes such as low birth weight and preterm birth (2).

Although endocrinological, psychoneurotic, environmental, and genetic factors are considered as potential causes for HG, the extant literature on this issue does not offer a definitive answer pertaining to the potential cause (3).

Ghrelin, a gastric-derived peptide, is known as an appetite-stimulating hormone (4). It regulates food intake, energy metabolism, and growth hormone secretion both by central and peripheral action (5,6). The level of ghrelin increases before eating and decreases after a meal (7). Moreover, ghrelin influences sleep; controls gastric motility, acid secretion, pancreatic secretion, glucose and lipid metabolism, and cell proliferation; and exerts cardiovascular and antiinflammatory effects (8,9). It has recently been reported that ghrelin plays an important role in reproductive functions, such as the regulation of gonadal function, gonadotrophin secretion, embryo development, implantation, and prenatal growth (9–11). Maternal ghrelin concentration begins to increase in the first trimester, reaches the highest level at mid-pregnancy, and reduces to the lowest level in the third trimester (12).

The observed high ghrelin levels in the first trimester of pregnancy raises the question as to whether this hormone can serve as a distinctive marker for HG. To answer this question, we examined the relationship between HG and ghrelin levels in pregnant women.

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2. Materials and methods

This cross-sectional study was performed at the Medical School of Fatih University, Ankara, Turkey. Included in the study were 35 pregnant women with HG and 31 pregnant women in the first trimester without any symptoms whose age, prepregnancy weight, and gravidity matched those of the women in the study group, for a total of 66 cases.

HG was defined as severe nausea and vomiting, positive ketonuria (++++ in urine samples with no other detectable causes, and 2 or more hospitalizations during the present pregnancy because of electrolyte imbalance.

Any patient known to have hepatic and/or renal dysfunction, gastritis, or thyroid diseases was excluded from the study.

This study was approved by the Fatih University Ethics Committee and complied with the Helsinki Declaration, including current revisions and Good Clinical Practice guidelines. All the women signed written informed consent forms before the start of the study.

Both the study and the control groups were examined with respect to age, parity, and body mass index (BMI). The gestational age of the pregnancy in weeks was determined according to the last menstruation date and first trimester ultrasonographic measurements for both groups. BMI was calculated as weight in kilograms divided by the square of height in meters for all subjects.

To determine fasting serum ghrelin and thyroid-stimulating hormone (TSH) levels, blood samples were collected in tubes containing EDTA-Na and aprotinin between 0830 and 1000 hours, centrifuged immediately at 4 °C, and then frozen at -80 °C for a maximum of 3 months before processing. Plasma ghrelin levels were determined using enzyme linked immunosorbent assay (ELISA) methods (ELISA, Phoenix Pharmaceuticals, Belmont, CA, USA). TSH was determined by chemiluminometric assay using an ADVIA Centaur XP immunoassay system (Siemens Healthcare Diagnostics, Deerfield, IL, USA).

Statistical analyses were performed using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were first inspected for normality of statistical distribution graphically and by Shapiro–Wilk test. Data were reported as mean \pm standard deviation (SD) or median with interquartile ranges (IQRs), as appropriate. The nonparametric Mann–Whitney U test was used to analyze the significance of the differences between the control and HG groups. $P \leq 0.05$ was used to define significance in all statistical comparisons.

3. Results

The study included 66 pregnant women between the 6th and 10th gestational weeks. There were 35 pregnant women diagnosed with HG, who were classified as the study group, and the remaining 31 women constituted the control group. Characteristics of the patients are summarized in the Table. The 2 groups showed similarities in terms of age, gravidity, preconception body mass index, and gestational age, as shown in the Table. There were no differences in TSH levels between the groups. Ghrelin levels were statistically lower in the HG group (47.0 ± 22.9 ng/mL) than in control subjects (62.4 ± 17.0 ng/mL) ($P = 0.026$). The Figure shows the ghrelin levels for the groups.

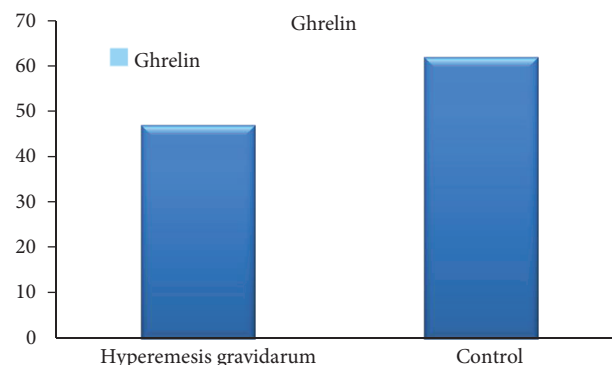


Figure. Levels of ghrelin between the groups (ng/mL).

Table. Characteristics of patients and levels of ghrelin between the groups.

	HG (n = 35)	Control (n = 31)	P-value
Age (years)	29.4 \pm 5.6	29.3 \pm 4.6	0.87
Gravidity	2.0 (1.0)	2.0 (1.0)	0.77
P-BMI (kg/m ²)	23.2 \pm 3.2	23.5 \pm 4.1	0.86
Gestational age (weeks)	8.2 \pm 1.4	8.8 \pm 1.5	0.89
Ghrelin (ng/mL)	47.0 \pm 22.9	62.4 \pm 17.0	0.03*
TSH (mIU/L)	1.1 \pm 1.4	1.0 \pm 0.9	0.45

Data are mean \pm SD or median with IQR. *: Statistically significant.

Abbreviations: HG, hyperemesis gravidarum; P-BMI, preconception body mass index; TSH, thyroid stimulating hormone.

4. Discussion

Although some endocrine factors are often cited as the primary cause for HG, its exact cause still remains unknown. Several placental products, such as human chorionic gonadotropin (hCG), estradiol, and thyroid hormones, are considered to be related to this condition. HG has a higher incidence when the hCG levels peak, and in twin and molar pregnancies, which are associated with elevated hCG levels, HG is more common (13). Similarly, the symptoms of HG coincide with high progesterone levels in the first trimester of pregnancy. In addition, slower intestinal transit and gastric emptying time, distension of the upper gastrointestinal tract, trace element and vitamin deficiency, *Helicobacter pylori* infection, and environmental and genetic factors are considered as causes of HG (3). HG has been suggested to be related to the activity of pyridoxine and Wibowa et al. found significantly lower concentration levels of total plasma vitamin B₆ in pregnant women with nausea and/or vomiting. They revealed that vitamin B₆ supplementation significantly affected the clinical symptoms of nausea and vomiting (14). In a study by Chittumma et al. (15), 650 mg of ginger or 25 mg of vitamin B₆ was given to women with hyperemesis 3 times per day for 4 days and Rhodé's score implemented to quantify patients' nausea. Both ginger and vitamin B₆ were effective for the treatment of nausea and vomiting in pregnancy. Moreover, ginger was more effective than vitamin B₆.

Because of inconsistent findings, a consensus about the cause and mechanism of HG has not yet been reached. Some studies looked over the other peptides that affect food intake and appetite, such as leptin. They examined the relationship between the severity of nausea and vomiting and the alterations in the levels of leptin and found higher serum leptin levels in pregnant women with HG than in women without nausea and vomiting (16,17). Although numerous research studies have been carried out to elucidate the relationship between maternal serum leptin levels and HG, this study is, to the best of our knowledge, the first to investigate the relationship between maternal serum ghrelin levels and HG. In the present study, maternal serum ghrelin levels were found to be significantly lower in the study group than in the control group. Ghrelin is an orexigenic hormone identified as an endogenous ligand of the growth hormone secretagogue receptor (ghrelin receptor) (6). It stimulates food intake (5) and triggers a positive energy balance through central and peripheral action (6,7). The level of ghrelin increases before eating and decreases after a meal (7), which means plasma ghrelin and oral intake correlate negatively. However, in the present study, plasma ghrelin levels and reduced oral intake correlated positively. This suggests that the lower ghrelin levels are not the result of, but are rather the cause

of, reduced oral intake during HG. In the study by Shintani et al. (6), a single intracerebroventricular injection of ghrelin caused a significant and dose-related increase in cumulative food intake in rats. They demonstrated that ghrelin, a novel orexigenic peptide, activates the hypothalamic neuropeptide Y/Y1 receptor pathway and this effect results in antagonizing leptin action in the body. In another study, Yakabi et al. (18) demonstrated a significant increase in hypothalamic ghrelin levels in rats fasted for 24 h and a significant decrease in cisplatin-treated rats during the early stage of anorexia, although their plasma ghrelin levels were comparable. On the other hand, Hiura et al. (19) found lower plasma ghrelin levels and feeding activity with cisplatin-based chemotherapy and reported that the extent of ghrelin reduction correlated well with adverse events, especially with neutropenia and anorexia. Furthermore, administration of intravenous ghrelin improved oral feeding and was effective against weight loss after total gastrectomy in cancer patients.

Ghrelin is mainly produced in the stomach, but it is also produced in the central nervous system, kidneys, heart, parathyroid glands, salivary glands, pituitary, small intestine, pancreas, hypothalamus, and placenta (20). It has been reported that both mRNAs for ghrelin and its functional receptor are present in the human placenta (primarily in cytotrophoblasts) during normal pregnancy, and ghrelin levels increase in the first trimester of pregnancy but not in the third trimester (12). This suggests a role for this hormone as an autocrine/paracrine factor for the growth and maintenance of the placenta during pregnancy.

Ghrelin has an inhibitory effect on human myometrial contractility in vitro. Low levels of ghrelin in the third-trimester myometrium are thought to prepare the uterus prior to labor (21). However, in term pregnancy, the placental ghrelin-ghrelin receptor system in the intrauterine growth restriction of rat models is speculated to continue to operate for the compensation of fetal development and fetoplacental circulation (22). It was proposed that chronic treatment of mothers with ghrelin during the last stage of pregnancy prompts fetal growth through stimulation of cell proliferation (23). Moreover, in small-for-gestational-age neonates, umbilical cord ghrelin plasma concentrations were higher than in appropriate- and large-for-gestational-age neonates (24). In another study, Aydin et al. (25) found higher maternal serum, arterial, and venous cord blood ghrelin levels in preeclamptic pregnant women than in healthy controls. They commented on this increase as a compensatory response to preeclampsia in an effort to contribute fetal growth, as ghrelin was detected to be involved in several growth-related processes. Physiological properties of ghrelin are thought to be a consequence of its relationship with human placental

growth hormone, which alters maternal metabolism during pregnancy by raising maternal insulin resistance, in order to increase nutrient availability for the fetoplacental unit (21). Ghrelin induces hyperglycemia and decreases plasma insulin concentrations, and ghrelin concentrations decrease with hyperglycemia and hyperinsulinism (25). Tham et al. (26) found markedly low acylated ghrelin levels during pregnancy, likely because of a decrease in the acylation process, and high desacyl ghrelin levels in gestational diabetes, possibly reflecting resistance to the inhibitory effect of insulin on ghrelin secretion.

In the present study we found significantly lower maternal serum ghrelin levels in the HG group than in the control group. Recent studies have reported a negative correlation of serum ghrelin levels with food intake in normal conditions. However, in the present study, plasma ghrelin levels and reduced oral intake correlated positively. This suggests that the lower ghrelin levels are not the result of, but are rather the cause of, reduced oral intake during HG. However, whether the origin of the ghrelin is placental or it is secreted from the stomach, hypothalamus, or other tissues is presently unknown. If we had examined the source of ghrelin, we could have more easily interpreted whether the decrease in ghrelin level was due to a decreased production by the placenta or gastric mucosa, which was affected by *H. pylori* infection. Recently a metaanalysis concluded that circulating ghrelin is significantly lower in *H. pylori*-positive subjects (27). Another limitation is that we did not analyze ghrelin levels in the prepregnancy period, during the course of pregnancy longitudinally, after delivery, and in the cord blood. With these analyses, the effects of ghrelin on the fetus and the ways in which it affects other pregnancy complications could have

concluded. Another limitation was that we did not analyze any other etiopathogenic factors that could have affected ghrelin levels. To have surveyed the level of leptin or to have determined the presence or absence of *H. pylori* infection could have enriched our interpretation. It would be understandable if there were a balance between leptin and ghrelin in order to maintain the normal physiology of pregnancy.

The proposed mechanism for ghrelin to cause HG may be a fluctuation of circulating ghrelin levels in relation to meal intake and its effects on appetite, causing nausea and vomiting to become more severe. Another hypothesis is that ghrelin may decrease progesterone levels, as suggested by Rak-Mardyla et al. (28). In the present study, the low ghrelin levels found for the HG group may be a trigger for nausea and vomiting, through elevated progesterone levels.

Many pathogenic mechanisms and causes have been hypothesized and studied to identify the pathogenesis of HG. However, no consensus on its cause and mechanism has been reached. Until the etiology and pathogenesis of HG are known, treatment or patient care will remain empirical and therefore will be suboptimal. Our study contributes to this strand of literature by reporting a significant negative relationship between ghrelin levels and HG during pregnancy. Prospective studies with a larger sample size are needed to find out the possible role of these hormones in the pathogenesis, development, and management of HG.

Acknowledgment

This work was supported by the Scientific Research Fund of Fatih University under project number P53011109_B (1563).

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