The Association between Maternal Ghrelin Hormone Levels and Hyperemesis Gravidarum

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ABSTRACT:

BACKGROUND:

Ghrelin hormone (Hunger hormone) is one of the appetite hormones that either secreted from adipose tissue (leptin, adiponectin and resistin), or mainly secreted from GI tract (ghrelin, obestatin, cholecystokinin, peptide YY and glucagon—like peptide –1). These hormones may be responsible for hyperemesis gravidarum.

OBJECTIVE:

To evaluate the role of ghrelin hormone in the etiopathogenesis of hyperemesis gravidarum

PATIENTS AND METHODS:

A case control study was performed in Gynecology and Obstetrics Department/ Baghdad teaching hospital(medical city complex) from the 1st of Sep. 2014 to the end of August 2015 including 100 women 50 women were the cases and 50 women were the control group.

RESULTS:

Mean age of cases was 24±8 years; prevalent age group was 20-29 years (48%).there was no significant difference in both groups regarding to the age, gestational age, gravidity and BMI between cases and controls ($p>0.05$). no significant differences were observed in TSH between cases and controls ($p>0.05$). But a significant association was observed between cases and low ghrelin level ($p<0.001$).

CONCLUSION:

there is a relation between the low level of ghrelin and hyperemesis gravidarum.

KEY WORD:hyperemesis, ghrelin hormone, TSH.

INTRODUCTION:

Hyperemesis gravidarum is a condition of intractable vomiting occur during pregnancy, leading to fluid, electrolytes and acid-base imbalance, nutritional deficiency and weight loss often severe enough to require hospital admission [(1)].

Nausea and vomiting in pregnancy is the most common symptoms, where about 70 to 85% of pregnant mother suffering from it. 0.3%-2.3% of all pregnancies suffering from the hyperemesis.[(2)]

In Egypt 2000 BC, nausea and vomiting described as the symptoms of early pregnancy, during the 2nd century AD hyperemesis was probably first described in one particular papyrus exhibited currently at the Petrie Museum of Egyptian Archeology in London. [(3)] Through historical time the causes of nausea and vomiting in pregnancy speculated by many authors.

Between 4-6 weeks of gestation the symptoms of hyperemesis gravidarum usually appear and may peak between 9-13 weeks. Majorities of pregnant women receive some relief between weeks 14-20, while up to 20% of them may require care for hyperemesis gravidarum until the end of their pregnancy. There is no known prevention of Hyperemesis gravidarum but you can take comfort in knowing that there are ways to manage it. [(4)]

Women with hyperemesis in the first pregnancy observed to have a high risk of recurrence and the risk reduced by a change in paternity. For women with no previous hyperemesis, a long interval between births slightly increases the risk of hyperemesis in the second pregnancy. [(5)]

Ghrelin represents a crucial endocrine link connecting physiological processes regulating nutrition, body composition and growth. But how does ghrelin orchestrate this connection? Ghrelin might ensure that sufficient amounts of energy are available for growth hormone to stimulate growth and repair. A positive energy balance is one of ghrelin's most powerful physiologic actions and it appears that ghrelin signals the brain when energy must be consumed or stored.

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The observed physiological actions of ghrelin are increasing food intake, decreasing fat oxidation and suppression of body core temperature. [7]
The effect of Ghrelin on pregnancy and lactation is that the ghrelin is abundantly expressed by the placenta, and in vitro the ghrelin can stimulate GH release by human fetal pituitary cells. In rat Immunoneutralization of maternal ghrelin diminishes fetal body weight, raising the possibility of maternal-fetal exchange of ghrelin. In human maternal ghrelin and placentally derived variant-GH concentrations peak at about 18 and 34 weeks of the gestation, respectively, fall thereafter, and reach a nadir approximately 3 days postpartum. in the third trimester of pregnancy the decline in ghrelin is inversely related to resistin, blood pressure, and TNF-alpha levels. [8]

PATIENTS AND METHOD:

ACase control study performed in the Department of obstetrics and gynecology/ Baghdad teaching hospital (Medical city complex) During the period from the 1st of September 2014 to the end August of 2015 (one year duration) in which a total of one hundred pregnant women were included in this study and divided in two groups:
Group A: 50 pregnant patients with hyperemesis gravidarum (cases).
Group B: 50 pregnant women without hyperemesis gravidarum (control).

All patients attending to the inpatient and outpatient at the time of the study agreed to participate within the selected criteria were considered eligible. For the control group selected in the current study they were normal pregnant women with maternal age, gestational age, and gravidity that were comparable with the case group. All patients were informed about the nature of the current study and only those who agreed to participate were included. Verbal consent was obtained from all the respondents.

Inclusion criteria:

Pregnant women at first trimester (according to reliable last menstrual period and confirmed by ultrasound) with Viable Singleton pregnancy. With history of admission of ≥ two times to the hospital at the present pregnancy. The Patients should be having at least three vomiting episodes a day with nausea, significant loss of weight at the beginning of pregnancy and Ketonuria [+++] on urine dipstick examination with no other detectable cause.

Exclusion criteria:

Twin pregnancy, Hydatidiform mole pregnancy. Surgical problem like intestinal obstruction, appendicitis, torted ovarian cyst, Medical problem like: Diabetes mellitus, hypertension, gastritis, thyroid disease, hepatic disease (viral hepatitis, liver cirrhosis, etc.) and or renal disease (nephrotic syndrome, renal failure, etc) and psychological disorder. Patients on drugs that could contribute to nausea and vomiting for example iron-containing compounds, hormonal therapy, and Patients with +ve H. pylori

All the participants subjected to the following:

Socio-demographic Information: about the age, gestational age and gravidity for all the participants included in this study.
Detailed past medical and surgical history was obtained from them, Physical examination was performed to all patients include:
Assessment of vital signs: looking for signs of dehydration (hypotension, low grade fever, and tachycardia).Abdominal examination: peritoneal signs (guarding, rigidity, rebound tenderness), distention with tympany, focal tenderness, absent or high-pitched tinkling bowel sound, flank tenderness to percussion, uterus too large for dates).Neurological examination: nystagmus, photophobia, focal weakness, stiffness to passive neck flexion (meningismus).
Body mass index was calculated to all participants: this was done by measuring both weight and height of patients and calculate the BMI by dividing the weight (kg) of the participant over the square of the height in meters (kg/m^2).An abdominal ultrasound examination was done to all patients to confirm the normality of pregnancy, gestational age and to exclude multiple pregnancies and other diseases (torted ovarian cyst, degenerating uterine fibroid, trophoblastic disease, renal stone, cholecystitis, pyelonephritis, and gallstone). In the hospital all participants had under gone the following investigations in the form of: FBC, Serum electrolytes level, Urinalysis and midstream urine examination, Liver function test, Renal function test, Fasting serum thyroid stimulating hormone was measured, Detection of fasting serum Ghrelin level, Serum for H. pylori.

Sample collection:

Sample of the fasting serum ghrelin and thyroid stimulating hormone (TSH) levels, in between 08.30 and 10.00 A.M. the samples of the blood were collected in tubes containing EDTA-Na and aprotinin. At 4 C^0 centrifuged immediately and then frozen at -80 C^0 for a maximum of 3 months before processing. Serum ghrelin levels were determined using ELISA methods (enzyme linked immunosorbent assay) we use human ghrelin Eliza kit of Mybiosource Company in USA (for reseach use only. Not for use in diagnostic or therapeutic procedures),while TSH was determined by chemiluminometric assay

using an ADVIA centaur XP immunoassay system made by Siemens AG company, Germany.

Statistical analysis

Data were analyzed using Statistical Package for Social Science (SPSS) version 20 by specialists (statistician), after coding and assigning a serial identified number for each questionnaire. Continuous variables presented as mean and standard deviation and discrete variables presented as numbers and percentages. Chi square test and T test were used to verify the significance of observed findings. Findings with P value less than 0.05 considered statistically significant.

RESULTS:

A total of 100 pregnant women were included in present study, 50 pregnant women with HG (cases) and 50 with no HG (controls). Mean age of cases was 24±8 years; prevalent age group was 20-29 years (48%), and the mean age of pregnant women without HG (controls) was 25±7.9 years; prevalent age group was 20-29 years.

Mean gestational age of patients (cases) was 8±2 weeks, 68% of them had gestational age ≥8 weeks. Mean gravidity of cases was 3±1, 38% of them were gravida 2. While the mean gestational age of controls was 8±1.8 weeks, 64% of controls had gestational age ≥8 weeks. Mean gravidity of controls was 3±1, 40% of them were gravida 2.

The mean BMI of pregnant women with HG (cases) was 26.5±5.1 Kg/m^2, 50% of them were overweight and 26% of them were obese. While mean BMI of controls was 27.5±4.9 Kg/m^2, 52% of them were overweight and 26% of them were obese (table 1).

Table 1: Socio-demographic characteristics of the studied groups (cases and control).

Variable	cases		co	χ^2		p
	No.	%	No	%		
Age						
<20 years	13	26.0	12	24.0	1.2	0.7 (NS)*
20-29 years	24	48.0	25	50.0		
30-39 years	12	24.0	10	20.0		
≥40 years	1	2.0	3	6.0		
Total	50	100.0	50	100		
mean±SD	(24±8 years)		(25±7.9)			
Gestational age						
<8 weeks	16	32.0	18	36.0	0.18	0.67 (NS)*
≥8 weeks	34	68.0	32	64.0		
Total	50	100.0	50	100		
mean±SD	(8±2 weeks)		(8±1.8 weeks)			
Gravidity						
1	18	36.0	18	36.0	0.09	0.9 (NS)*
2	19	38.0	20	40.0		
3	8	16.0	7	14.0		
>3	5	10.0	5	10.0		
Total	50	100.0	50	100		
mean±SD	(3±1)		(3±1)			
BMI						
Normal	12	24.0	11	22.0	0.06	0.9 (NS)*
Overweight	25	50.0	26	52.0		
Obese	13	26.0	13	26.0		
Total	50	100	50	100		
mean±SD	(26.5±5.1 Kg/m^2)		(27.5±4.9 Kg/m^2)			

* Not significant.

Mean duration of vomiting for cases was 5±4 weeks, 52% of them had HG for duration less than two weeks. Mean frequency of vomiting for HG group was 5±3 times/day, 58% of them had vomiting frequency ≤5 times/day (table 2 and figure 1).

Table 2: Hyperemesis gravidarum characteristics of cases (HG).

Variable	No.	%
Duration of vomiting		
<2 weeks	26	52.0
≥2 weeks	24	48.0
Total	50	100.0
mean±SD	(5±4 weeks)	
Frequency of vomiting in HG		
≤5 times/day	29	58.0
>5 times/day	21	42.0
Total	50	100.0
mean±SD	(5±3 times/day)	

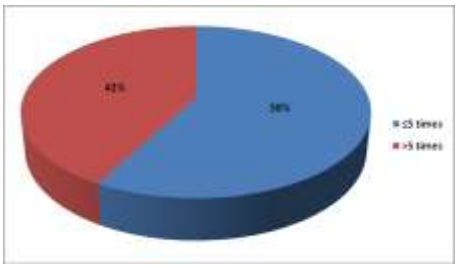

Figure 1: Frequency of vomiting in HG group (cases).

Mean TSH of cases was 0.9±0.2 mIU/L, all case had normal TSH level, while mean TSH of controls was 1.0±0.3 mIU/L, and all control had normal TSH. Mean ghrelin level of cases was 46±21.9 ng/ml, 84% of cases had low ghrelin level. And the mean ghrelin level of controls was 63.4±18.2ng/ml, 26% of controls had low ghrelin level and 58% of them had high ghrelin level. No significant differences were observed in TSH between cases and controls ($p>0.05$). A significant association was observed between cases and low ghrelin level ($p<0.001$) (table 3).

Table 3: Distribution of investigation results according to the studied group (cases and control).

Variable	Cases		Control		χ^2	P
	No.	%	No.	%		
TSH (0.4 - 4.0 mIU/L)					0.0	1.0
Normal	50	100	50	100.0		
Abnormal	0	0.0	0	0.0		
mean±SD	0.9±0.2		1.0±03			
Ghrelin					38	<0.001*
Normal	6	12.0	8	16.0		
Low	42	84.0	13	26.0		
High	2	4.0	29	58.0		
mean±SD	46±21.9		63.4±18.2			

*significant association

No significant differences were observed in means of age, gestational age, gravidity, BMI and TSH between cases and controls (p>0.05). Moreover there was significantly lower ghrelin level among cases than controls (p<0.001) (table 4).

Table 4: Distribution of age, gestational age, gravidity, BMI and hormones means according to the studied group (cases and control).

Variable	Cases	Control	t-test	P
	Mean±SD	Mean±SD		
Age (years)	24±8	25±7.9	0.6	0.5
Gestational age (weeks)	8±2	8±1.8	0.001	1.0
Gravidity	3±1	3±1	0.00	1.0
BMI (Kg/m^2)	26.5±5.1	27.5±4.9	1.1	0.3
TSH (mIU/L)	0.9±0.2	1.0±0.3	0.4	0.6
Ghrelin (ng/ml)	46±21.9	63.4±18.2	4.3	<0.001*

DISCUSSION:

Ghrelin cells in the gastrointestinal tract produce the ghrelin hormone which acts as a neuropeptide in the central nervous system. [9, 10] Beyond regulating hunger, ghrelin also plays a significant role in regulating the distribution and rate of use of energy. [11] The secretion of the ghrelin is stopped when the human is eating and the stomach is stretched. The hormone acts on the cells of the hypothalamus both to increase secretion of the gastric acid and GI motility this to prepare the body regarding intake of food. [12]

In the present study, the mean BMI of pregnant women with HG (cases) was 26.5±5.1 Kg/m^2, half of them were overweight and 26% of them were obese and the mean BMI for controls was 27.5±4.9 Kg/m^2, 52% of them were overweight and 26% of them were obese. This is similar to that revealed by Vikanes A. [3] in Norway, 2010 in his thesis were the overweight and obese women were more likely to develop hyperemesis gravidarum than normal-weighted women. And more than that registered by Kaygusuz, Ikbal, et al. [13] in 2013 where the mean BMI of pregnant women with HG (cases) was 23.2 ± 3.2 Kg/m^2 and the BMI of controls was 23.5 ± 4.1Kg/m^2. This may be attributed to the differences in the food habits between the communities in addition to absence of sport and physical activity by most of the women in our society.In the current study, it had been found that the mean age of cases was 24±SD years, which is less than that revealed by OruçAyla et al. [14] in 2013 in Turkey, concluded that the mean age of cases was 26.4±SD years. This may be attributed to that the women in our society married younger.

Regarding to the Ghrelinin the past, several study groups supported the concept of ghrelin as an endogenous regulator of energy homeostasis. Energy balance is achieved when energy intake is equal to energy expenditure. A positive energy balance, leading to weight gain, occurs when calories ingested, digested and reabsorbed exceed calories expended. Ghrelin administered to rodents influences both energy intake and metabolism. It stimulates food intake in a dose dependent manner mainly through central mechanisms [15]

In the current study the level of ghrelin in cases is less than that for the control in which the mean ghrelin hormone level of cases was 46±SD ng/ml and for the control was 63.4 ±SD ng/ml, which is similar to that found by Kaygusuz, Ikbal, et al. [13] in 2013 in his study revealed that the mean ghrelin level was less for cases group than that for control (Kaygusuz, Ikbal attributed this low ghrelin levels found for the HG group may be a trigger for nausea and vomiting, through elevated progesterone levels). But it is inconsistent with OruçAyla et al. [14] in 2013, where the ghrelin levels were significantly increased in patients with HG compared to normal pregnant women, this conclusion suggesting that this finding may be related to the need of the maternal organs to react with the a compensatory mechanism to restore the energy balance of the pregnant women and guarantee nutrients for the growing fetus.

Maggiore, Umberto and Simone Ferrero [16] (2013) in their study read with the interest the OruçAyla[14] article and he attributed the increase of ghrelin in this study is because the OruçAyla [14] used a commercial polyclonal antibody

(phoenix pharmaceuticals, Belmont, USA) for measuring plasma ghrelin levels; this antibody does not discriminate octanoylated and non octanoylated ghrelin, and, therefore, the total ghrelin level was measured. Antibodies specific for the active form of ghrelin (with the octanoyl group on serine 3) are commercially available. The dosage of active ghrelin needs precautions since this form is particularly unstable and labile in plasma. Moreover not consistent with Albayrak, Mustafa, et al [17] (2013) on his study To assess the serum levels of gut and adipocyte-derived metabolic hormones that control appetite, adipocity, weight gain and energy hemostasis, namely total ghrelin (TG), acylated ghrelin (AG), leptin and PYY-3 in hyperemesis gravidarum (HG) conclude that the ratio between the acylated and total ghrelin was significantly lower in the HG group compared to control groups ($p \leq 0.017$).

In the present study the woman with HG, plasma ghrelin levels was significantly lower than in women without hyperemesis gravidarum, which mean plasma ghrelin levels and reduced oral intake correlated positively. Despite that level of ghrelin increase before eating and decrease after meal which means plasma ghrelin and oral intake correlate negatively. This suggests the lower levels are not the result of, but are rather the cause of reduced oral intake during HG.The proposed mechanism for hormone to cause hyperemesis gravidarum may be a fluctuation of ghrelin levels circulating in relation to meal intake and its effects on appetite, causing nausea and vomiting to become more severe.

In the current study serum TSH was lower in HG group than that in the control group. But there is no significant difference between them. This is consistent with that found by Masiukiewicz in 1999 where the Serum TSH levels were significantly lower in the HG group. This may be because transient hyperthyroidism is common in pregnancy. Most likely, increased levels of hCG, a known stimulator of the TSH receptor, play an important role. [18] Also it is similar to that found by OruçAyla et al.[14] in 2013, where the serum TSH levels were lower in the HG group than that for control group.

Conclusions and Recommendations

There is a relation between low level of ghrelin and hyperemesis gravidarum.

There is a need for prospective studies with a large sample size to find out the possible role of the Ghrelin hormone in the pathogenesis, development, and management of HG.

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