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Assessment of Thyroid Function and Leptin Hormone in Women with Hyperemesis Gravidarum

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Abstract. **Background.** Several studies have suggested that hyperemesis gravidarum in early pregnancy is related to women's levels of thyroid hormones, human chorionic gonadotropin (hCG), and serum leptin. To ascertain this relationship, we investigated 50 pregnant women in the first trimester. Twenty subjects had morning sickness, 20 had hyperemesis gravidarum, and 10 were healthy pregnant women who served as control subjects. **Methods.** The enzyme immunoassay method was used to measure all subjects' serum levels of T_3 (pg/mL), T_4 (ng/dL), TSH (µIU/mL), antithyroid peroxidase (anti-TPO) antibodies (IU/ml), and leptin (ng/-mL). Serum β hCG was quantitatively assayed. **Results.** There was a statistically significant difference between the three studied groups as regards serum free T_4 ($p < 0.05$), but there was no difference as regards serum free T_3, TSH, anti-TPO, and serum β-hCG ($p > 0.05$). Serum leptin was significantly higher ($p < 0.001$) in the hyperemesis gravidarum and vomiting group compared to the healthy control group, with a non-significant difference between pregnant women with hyperemesis gravidrum and those with vomiting ($p > 0.05$). Correlation analysis showed that the only significant positive correlation was between serum T_3 and serum leptin ($p < 0.05$) in hyperemesis gravidarum. No significant correlation was found between β-hCG and thyroid hormones, antithyroid antibodies, and serum leptin in pregnant women with morning sickness and hyperemesis gravidarum ($p > 0.05$). **Conclusion.** Our results suggest that serum leptin levels are involved in the pathogenesis of hyperemesis gravidarum. No significant role was detected for thyroid hormones, serum β-hCG, or anti-TPO in patients with hyperemesis gravidarum.

Keywords • Hyperemesis gravidarum • hCG • Leptin • Pregnancy • T_3 • T_4 • Thyroid hormone

INTRODUCTION

Hyperemesis gravidarum is a condition of intractable vomiting during pregnancy, leading to fluid, electrolyte and acid–base imbalance, nutritional deficiency, and weight loss often severe enough to require hospital admission.[1] Hyperemesis gravidarum is most prevalent during, but certainly not limited to, the first trimester of pregnancy when both the placenta and the corpus luteum are producing hormones and the body is adapting to the pregnancy state.[2]

Estimates of the incidence of hyperemesis gravidarum vary from 0.3 to 1.5% of all live births, with most authors reporting an incidence of 0.5%.[3,4] It is said to be higher in multiple pregnancies, hydatidiform mole, and other conditions associated with increased pregnancy hormone levels.[2]

Up to 80% of all pregnant women experience some form of nausea and vomiting during their pregnancies.[5] Because the great majority of pregnant women experience discomfort due to nausea and vomiting, a functional role of nausea and vomiting is often considered. Despite decades of research, the cause of these conditions remains unknown, and the relationship between nausea and vomiting during pregnancy and hyperemesis gravidarum is still unclear.[2] Many

etiopathogenic factors have been considered for hyperemesis gravidarum, including endocrine factors, hepatic dysfunction, changes in lipid metabolism, upper gastrointestinal system dysmotility, and psychological factors. However, no specific causative factor has been established.[6] Theories on how pregnancy hormones could cause hyperemesis gravidarum assert that patients who develop the condition may be exposed to higher levels of hormones during early pregnancy, especially progesterone and hCG. Also, irrespective of the gestational week, the rapid increase in the leptin concentrations in the first trimester may be a factor and also an early marker for hyperemesis gravidarum.[6]

Sometimes, thyroid hormone values deviate from the reference range, leading to a state referred to as gestational transient thyrotoxicosis (GTT). This has been observed in up to two thirds of women suffering from hyperemesis gravidarum.[7]

The etiology of transient hyperthyroidism of hyperemesis gravidarum is unclear. Some have argued that the hyperthyroidism is the cause of hyperemesis, whereas others have argued the reverse. The aim of this study was to evaluate the thyroid function, serum β-hCG, and serum leptin in women with hyperemesis gravidarum.

Materials and Methods

A case-control study was conducted involving 50 pregnant women in their first trimester of pregnancy. The women were selected from the outpatient clinic of Maternity Clinic and the in-patient wards of the Hospital of Obstetric and Gynecology at Ain Shams University Hospitals. The patients were divided into three groups. The first group was patients with emesis (vomiting); the second group was patients with hyperemesis gravidarum [defined as persistent nausea and vomiting associated with ketosis and weight loss > 5% of pre-pregnancy weight];[8] and the third group was healthy pregnant women who served as controls.

All groups were adjusted for age, parity, and BMI. All included women were subjected to the following: full history taking, thorough clinical examination; measurement of serum TSH (μIU/mL) by electrochemiluminescence immunoassay (ECLIA); serum FT_3 (pg/mL), serum FT_4 (ng/dL), and anti-thyroid peroxidase (Anti-TPO)(IU/mL) by micro particle enzyme immunoassay (MEIA); serum β-human chorionic gonadotrophins (serum β-hCG) quantitatively by the Sandwich principle; serum leptin (ng/mL) by ELISA technique (normal value of serum leptin level is: < 50 ng/ml);[9] and blood urea (mg/dL), serum creatinine (mg/dL), serum sodium (mmol/l), serum potassium (mmol/L), and complete blood picture to detect the severity of emesis.

A blood sample of 15 cc was withdrawn from each subject and the blood sample was divided in the following way:

(a) 5 cc were used for a thyroid profile (TSH, FT_3, FT_4, and Anti-TPO);
(b) 5 cc were were collected and stored as serum in an aliquot at -20°C till time of assay for serum leptin.
(c) 5cc were used for blood electrolytes and urea, and serum creatinine and β-hCG (quantitative).

Also, ketones in a morning urine sample were measured with urine stripes.

Statistical Analysis. Data were collected, revised, verified, and then edited on a PC. Then data were analyzed statistically using SPSS statistical package, version 15. Data were expressed as mean ± SD for quantitative measures. The following tests were done:

1. The Student's-t test for independent variables and was used to assess significant differences between values in various groups of patients where appropriate.
2. ANOVA test was used for comparison between more than two independent groups as regard studied variables.
3. *Post hoc* test was used for comparison of quantitative variables.
4. Pearson correlation coefficient (*r*) was done for correlations between different studied parameters.
5. Sensitivity, specificity, and diagnostic accuracy at different cut-off levels and ROC-curves were analyzed.

The results were considered to be statistically significant at a p value of < 0.05, highly significant at p value of < 0.001, and insignificant at a p value of > 0.05.

Results

As shown in Table 1, the only statistically significant differences between the three studied groups were in regard to the free T_4 and serum leptin ($p < 0.05$). The β-hCG level was higher in patients with hyperemesis gravidarum than in women with emesis and healthy controls, but the difference was not significant ($p > 0.05$). *Post hoc* testing for comparisons

of the three studied groups showed a significantly higher mean free T_4 level for group 2 compared to group 1 and group 3 ($p < 0.05$). But as shown in Table 2, the difference in the free T_4 level between

Table 1. The comparative data of all studied groups by ANOVA test.

Parameters	Group (1) (Pregnant with emesis)	Group (2) (Pregnant with hyperemesis gravidum)	Group (3) (Healthy pregnant control)	F	P	Sig
	N = 20	N = 20	N = 10			
FT_3 (pg/mL)	2.5 ± 0.5	2.6 ± 0.6	2.4 ± 0.5	0.6	> 0.05	NS
FT_4 (ng/dL)	***1 ± 0.1***	***1.3 ± 0.5***	***1 ± 0.2***	***4.1***	***< 0.05***	***S***
TSH(µIU/mL)	2.1 ± 1	1.4 ± 1.5	1.8 ± 0.9	1.9	> 0.05	NS
Anti-TPO (IU/mL)	6.4 ± 4.8	15.2 ± 29.2	5.1 ± 2.6	1.5	> 0.05	NS
β-hCG (mIU/mL)	79.7 ± 54.6	93.4 ± 57.8	69.5 ± 60.2	0.8	> 0.05	NS
Leptin (ng/mL)	***37.5 ± 28.8***	***43.6 ± 6.1***	***16.2 ± 9.2***	***9***	***< 0.00***	***HS***

NS=non significant, S= significant, HS= highly significant, N= number

group 1 and group 3 was not significant ($p > 0.05$). Also, the difference in leptin levels between the the emesis group and the hyperemesis gravidarum group was not significant ($p > 0.05$). However, the leptin levels in both the emesis group and hyperemesis gravidarum group were highly significantly higher than the level in the healthy control group ($p < 0.00$).

Pearson correlation tests for the emesis group and the healthy control group, respectively, showed no significant correlation of serum leptin and serum β-

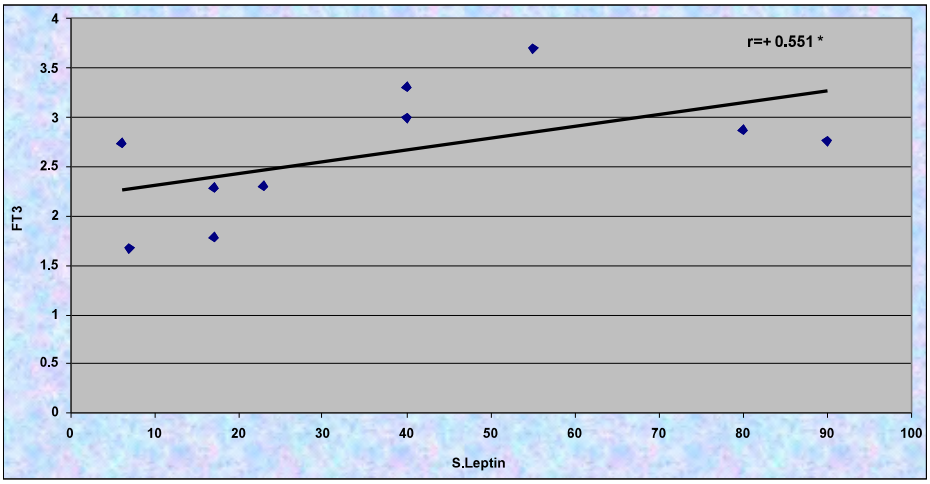

Figure 1. Correlation between serum leptin and FT3 in hyperemesis gravidarum.

hCG (*r*: 0.107) (*r*: 0.198), anti-TPO (*r*: 0.029) (*r*: -0.590), free T_4 (*r*: 0.145) (*r*: 0.287), and free T_3 (*r*: 0.322) (*r*: -0.374) ($p > 0.05$). In the hyperemesis gravidarum group, the serum leptin level was positively correlated with the free T_3 with an *r* value of 0.551 (Figure 1).

In the healthy control group, the leptin level was significantly negatively correlated with the serum TSH ($r = -0.737$, $p < 0.05$). Also, in this group, the serum β-hCG level was positively correlated with the free T_3 level ($r = 0.755$, $p < 0.05$).

In the emesis group and the hyperemesis gravidarum group, respectively, no correlation ($p > 0.05$) was found between the levels of serum β-hCG and anti-TPO (*r*: -0.146) (*r*: 0.021), serum leptin (*r:* 0.367((*r*: 0.107) [Figure 2], TSH (*r*: 0.344) (*r*:

-0.212), free T_4 (*r*: -0.248) (*r*: -0.312), and free T_3 (*r*: 0.050) (*r*: -0.359). Serum anti-TPO was positively correlated only with the free T_3 (*r*: 0.587) and the free T_4 (*r*: 0.938) in hyperemesis gravidarum group ($p < 0.01$) and the TSH (*r*: 0.447) in the emesis group ($p < 0.05$).

For the hyperemesis gravidarum group, the ROC curve detected the best cutoff point for the free T_4: 1.06 ng/dL, with a sensitivity = 80% and a specificity = 80 % and an area under the curve of 0.743 with a

Table 2. A multiple comparison study between all studied by *post hoc* test.

Parameters	Group (1) vs Group (2)			Group (1) vsGroup (3)			Group (2) vs Group (3)		
	LSD	P	Sig.	LSD	P	Sig.	LSD	P	Sig.
FT_3 (pg/mL)	-0.113	> 0.05	NS	0.111	> 0.05	NS	0.224	> 0.05	NS
FT_4 (ng/dL)	***-0.268***	***< 0.05***	***S***	-0.011	> 0.05	NS	***0.257***	***< 0.05***	***S***
TSH (µIU/mL)	0.719	> 0.05	NS	0.357	> 0.05	NS	-0.362	> 0.05	NS
Anti-TPO (IU/mL)	-8.82	> 0.05	NS	1.315	> 0.05	NS	10.135	> 0.05	NS
β-hCG (mIU/mL)	23.96	> 0.05	NS	13.765	> 0.05	NS	-10.195	> 0.05	NS
Leptin (ng/mL)	-6.100	> 0.05	NS	***-21.300***	***< 0.00***	***HS***	***-27.400***	***< 0.00***	***HS***

NS=non significant, S= significant, HS= highly significant, N= number

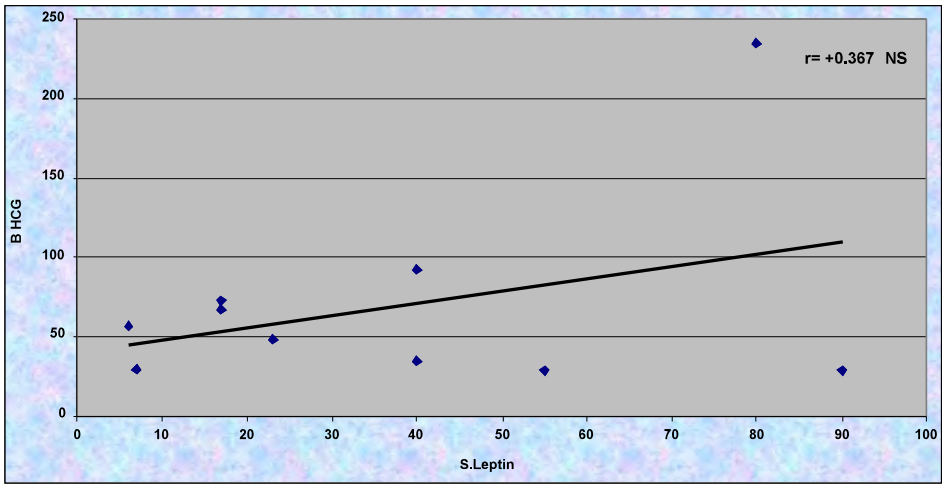

Figure 2. Non-significant correlation between serum leptin and β hCG in hyperemesis Gravidarum.

p value of < 0.004. But there was not a significant cut off point for serum leptin with a *p* value of > 0.05, a sensitivity = 60%, and a specificity = 53.3%.

Discussion

Hyperemesis gravidarum is defined as excessive vomiting during pregnancy, which may lead to sever outcomes including weight loss, dehydration, fasting acidosis, alkalosis due to hydrochloric acid loss, and hypokalemia.[10] Both the etiology and pathogenesis of hyperemesis gravidarum remain unknown.[2] The potential role of pregnancy-related hormones such as progesterone, estrogen, and hCG has been widely studied; however, various other hormones such as leptin, placental growth hormone, prolactin, thyroid hormone, and adrenal-cortical hormones have been implicated in the etiology of hyperemesis gravidarum.

The presence of an association between hyperemesis gravidarum and the rapid increase in leptin of placental origin, particularly in the first trimester, may be considered.[6] This study aimed to study thyroid hormones, serum β-hCG, anti-TPO, and serum leptin in women with hyperemesis gravidarum, and to detect any possible role of these parameters in the pathogenesis of hyperemesis gravidarum.

Our study revealed that there was no significant difference between the three studied groups as regards the free T_3, TSH, and anti-TPO ($p > 0.05$). Only the

free T_4 was significantly higher in the hyperemesis gravidarum group compared with the emesis group and the healthy control group ($p < 0.05$). However, the higher free T_4 was still within reference range.

The higher reference range free T_4 level in the hyperemesis gravidarum group can be explained by the characteristic pattern of serum free T_4 changes during normal pregnancy.

This pattern includes a slight and temporary rise in the free T_4 during the first trimester (due to the thyrotropic effect of hCG) and a tendency for serum free T_4 values to decrease progressively during later gestational stages.[11] But, although we found that the serum β-hCG level was higher in the hyperemesis gravidarum group than in the emesis group and the healthy control group, the level was not significantly different ($p > 0.05$).

This finding agrees with Al-Yatama et al.[12] They found that the serum free T_4 level was higher in hyperemesis gravidarum patients than in healthy controls ($p < 0.0001$), but no patients showed signs of thyrotoxicosis. We detected that the best significant cut off point of free T_4 for women with hyperemesis gravidarum was 1.06 ng/dL with a sensitivity = 80% and a specificity = 80% with a p value of < 0.004), which is still within the reference range for the free T_4. Panesar et al.[13] found by logistic regression analysis that the free thyroxine level was an independent variable. In addition, they found no significant difference between the free T_4 levels of healthy pregnant women and those with emesis ($p > 0.05$). Kimura et al.[14] found that serum free T_4 and free T_3 levels were higher in pregnant women with emesis and hyperemesis gravidarum ($p < 0.01$) and that the serum TSH was suppressed to less than 0.1mU/L in both groups. They also found, as we did in this study, that the serum β-hCG level did not significantly differ between the emesis group, hyperemesis gravidarum group, and the healthy control group. Also, Wilson et al.[15] reported no significant difference between the thyroid hormone and hCG levels of healthy controls and hyos peremesis gravidarum patients. In addition, Panesar et al.[13] observed that hGC is not independeetiology of hyperemesis gravidarum. In contrast, however, Al-Yatama et al.[12] reported that the total β-hCG level was significantly higher in hyperemesis gravidarum patients than in healthy control subjects.

Tan et al.[16] found that hyperemesis gravidarum patients were not clinically overtly thyrotoxic and thyroid antibodies were usually absent. But Taskin et al.[17] reported that the serum TSH and serum β-hCG levels were higher in women with hyperemesis gravidarum than in healthy pregnant women, while there was no significant difference between the groups as regards free T_3 and T_4 levels. However, Asakura et al.[18] found that free T_3 and free T_4 levels were significantly higher in hyperemesis gravidarum patients than in healthy controls; the levels were higher in the hyperemesis gravidarum patients with milder symptoms of morning sickness ($p < 0.05$). Also, Leylek et al.[19] found that the mean serum hCG, free T_3, and free T_4 levels were significantly higher in hyperemesis gravidarum patients than in healthy controls ($p < 0.05$), with a non-significant difference in serum TSH levels ($p > 0.05$). They also found that for hyperemesis gravidarum patients, the serum hCG significantly negatively correlated with the TSH and positively correlated with the free T_3 and free T_4. They found no relationship between β-hCG and thyroid function test levels in the control group ($p > 0.05$).

Our study did not show a significant correlation between serum β-hCG and serum TSH, free T_3, and free T_4 levels in hyperemesis gravidarum patients. In healthy controls, only the β-hCG level was positively correlated with the free T_3 ($r = 0.755$, $p < 0.05$). Tareen et al.,[20] demonstrated that serum T_4 and β-hCG were significantly increased in hyperemesis gravidarum, while the TSH significantly declined in the same group. They also found a direct relationship between the serum T_4 and β-hCG levels and an inverse relationship between the TSH and β-hCG levels in pregnant women with morning sickness.

Goodwin et al.[21] observed that the hCG level correlated directly with the free T_4 level and inversely with the TSH level ($p < 0.001$) in women with hyperemesis gravidarum. They also found that patients with hyperemesis gravidarum had significantly higher mean levels of free T_4, hCG, and total T_3, and a lower TSH level compared to control subjects. From these results, it was suggested that hyperemesis gravidarum may be caused by some not-yet-identified circulating stimulator. Abell and Riely,[22] suggested that there is a circulating hormone or hormone-like substance that may stimulate the thyroid gland and render it temporarily unresponsive to the control of the pituitary. This suggests that thyroid hormones are stimulated by something other than the TSH. By the time this substance subsides in later pregnancy, both the hyperemesis gravidarum and the hyperthyroidism resolve.

The serum leptin levels significantly differed ($p < 0.00$) between our three studied groups: the emesis and hyperemesis gravidarum groups had higher leptin levels than the healthy control group. However, the difference between women with emesis and hyperemesis gravidarum was not significant ($p > 0.05$). This agrees with Nurettin et al.[6] who found that their

group with hyperemesis gravidarum had significantly a higher serum leptin level ($p = 0.037$) than healthy pregnant women. But thyroid hormones and hCG levels in the two groups did not significantly differ.

In the hyperemesis gravidarum group in our study, only the serum leptin level positively correlated with the free T_3 level ($p < 0.05$). But three prospective cohort studies that compared the serum leptin levels between hyperemesis gravidarum patients and controls did not show a statistically significant difference.[23,24,25] Supporters of the leptin theory stated that this could be a false negative finding due to a negative energy balance in hyperemesis gravidarum patients, a dramatic decrease in leptin levels being observed in other condition with a negative energy balance, such as fasting.[26,27,28]

Our data show that patients with hyperemesis gravidarum had a significantly higher free T_4 level, but the level was within the reference range and the patients had no clinical manifestations of thyrotoxicosis. The group therefore had no underlying thyroid abnormality. It appears that neither thyroid hormones nor hCG contribute to the pathogenesis of hyperemesis gravidarum. Serum leptin, however, may play a role in the pathogenesis of hyperemesis gravidarum. Larger studies are needed to confirm this role.

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