Serum leptin Levels and Their Correlation with Thyroid Hormones in Women with Hyperemesis Gravidarum

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ABSTRACT:

BACKGROUND:

Leptin is a protein that regulates energy expenditure and food intake. It is found that maternal leptin level increases progressively during gestation. However, in other hypothesis, rapid increase in maternal leptin concentration disproportional to gestational week is a marker for hyperemesis gravidarum.

OBJECTIVE:

To assess the maternal serum leptin , the adjusted leptin levels in first trimester women with hyperemesis gravidarum and with normal pregnancy and to find the correlation between leptin level and thyroid hormones in the two groups.

PATIENTS AND METHODS:

A case-control study conducted in AL- Yarmouk teaching hospital /department of obstetrics and gynaecology for one year from March 2009 to March 2010.

A hundred pregnant women were enrolled in this study. Fifty women with hyperemesis gravidarum and fifty women without hyperemesis gravidarum as a control group were included in the study.The two groups were compared for age, parity, body mass index. Fasting serum thyroid stimulating hormone ,free thyronine hormone, free thyroxine hormone and leptin levels were measured . The adjusted leptin level (ALL) : maternal serum leptin level / gestational week , was calculated in each case.

RESULTS:

Body mass index was found significantly lower in the hyperemesis gravidarum group than in the control group($p = 0.018$) .The mean leptin level in the hyperemsis gravidarum group was14.78 ± 4.46 ng /ml which was significantly higher ($p = 0.035$) than the mean leptin level in the control group which was12.51 ± 4.08 ng/ml.The mean adjusted leptin level in the hyperemsis gravidarum group was 1.86 ± 0.23 which was significantly higher ($p<0.001$) than the mean adjusted leptin level in the control group which was1.38 ± 0.20 . Serum thyroid stimulating hormone was significantly lower ($p = 0.001$) and free thyronine hormone , free thyroxin hormone levels were significantly higher ($p <0.001$, <0.001 respectively) in the hyperemesis gravidarum group than in the control group.

CONCLUSION:

Maternal serum leptin level was significantly higher in the HG group. ALL was also significantly higher in the HG group and there was no significant correlation between leptin level and thyroid hormones.

KEY WORDS : hyperemesis gravidarum , leptin , adjusted leptin level ,thyroid hormones.

INTRODUCTION:

Hyperemesis gravidarum is a significant but underappreciated illness of pregnancy. It is the most common indication for admission to the hospital in the first half of pregnancy and second only to preterm labor as a cause of hospitalization overall.[1]

Nausea and vomiting is a common symptom of early pregnancy, affecting up to 80% of women.[2,3]

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While the reported incidence of hyperemesis gravidarum is 0.5-2.0%.[1,4] Although the pathophysiology for hyperemesis gravidarum is not clear, it has been proposed that hormonal , allergen , genetic , immunological , neuropsychosomatic and metabolic factors play a role in the etiology of hyperemesis gravidarum.[4,5] Leptin is a hormone that is secreted mainly by the adipose tissue to signal the status of body energy stores to the central nervous system. As a signal of energy sufficiency,

adequate leptin levels suppress feeding and permit energy-costly neuroendocrine functions.[6] Circulating leptin levels are elevated during pregnancy, reaching a peak during the second trimester and remain elevated until parturition.[7,8,9] serum leptin concentration in normal pregnancy was determined to be between 7.4 and 19 ng / ml.[8] Leptin may also be involved in modulating the set point of the thyroid axis under physiological conditions.[10]

AIM OF THE STUDY:

1- To assess the maternal serum leptin, the adjusted leptin levels in first trimester women with hyperemesis gravidarum and with normal pregnancy.

2- to find the correlation between leptin level and thyroid hormones in the two groups.

MATERIALS AND METHODS:

A case-control study was conducted in AL-Yarmouk teaching hospital during a period of one year from March 2009 to March 2010. A total of hundred women were included in the study and was divided into two groups:

GroupA:

fifty pregnant patients with hyperemesis gravidarum .

Group B: fifty pregnant women as control.

Patients collection:

The patients were collected from the inpatient and outpatient clinics, all of the patients had single viable pregnancy documented by U/S .The control group were selected as normal pregnant women with gestational age, maternal age, parity that were matched with the case group.

Inclusion criteria:-

1-Singleton pregnancy 2.Viable fetus. 3-First trimester (according to reliable last menstrual period and sonographic confirmation of first trimester), 4- The criteria of observation of at least three vomiting episodes a day with nausea , loss of weight at the beginning of pregnancy , and at least ketonuria [+++] on urine dipstick examination .

Exclusion criteria : 1-Twin pregnancy. 2-Hydatidiform mole.3-Patients with thyroid disease.4-Medical problem like pyelonephritis, pancreatitis, psychological disorder peptic ulcer, diabetes mellitus .

All the participants were subjected to the following: 1-They are told about the nature of the study and only those who agreed to participate in the study were included. 2- Full Information's was taken and complete physical examination including body mass index was done to all patients. 3. An abdominal ultrasound examination was done to all patients to confirm the gestational age, normality of pregnancy and to exclude possible complications likely to cause hyperemesis gravidarum .Every patient had under gone the following investigations in form of:

1.Full blood count,midstream urine examination,serum electrolytes level:sodium,potassium ,chloride and bicarbonate,Renal function test,Liver function test.

2.Thyroid function test [fasting serum thyroid stimulating hormone, free T3 , free T4] were measured by radioimmunoassay.

3-Serum leptin levels was done, measured by enzyme - linked immunosorbent assay (ELISA).

-The adjusted leptin level (ALL) calculated by dividing maternal serum leptin level by gestational week.

Statistical analysis:

Data were analyzed using the computer facility with use of SPSS-15 (statistical package for social sciences version 15) soft ware package. Significance of difference between two quantitative variables was measured using independent t-test. Significance of difference between percentages (for qualititative data) was measured using chi squared test. P value < 0.05 was considered as the level of significance. Pearson's correlation coefficient(r) and p values were obtained. The receiver operator curve (ROC curve) used to found the cut-off value of the adjusted leptin level.

RESULTS:

No significant difference in maternal age between the two groups (P =0.665) and there was no significant difference in parity between the two group (P = 0.358). The mean BMI of patient with hyperemesis gravidarum was significantly lower (P = 0.018) compared to BMI of control group . No significant difference in gestarional age between the two groups (P = 0.096).

Table 1: Characteristics of the patients with and without hyperemesis gravidar (mean ± S.D., median-range).

	H. gravidarum (n = 50)	Control (n = 50)	p-value
Age (year)	24.4 ± 4.38 (17-31)	25.08 ± 4.05 (17-32)	0.665
Parity	1.14 ± 96 (0-3)	0.88 ± 0.96 (0-4)	0.358
BMI (kg/m2)	20.76 ± 1.27 (18.03-22.9)	22.62 ± 1.61 (18.77-27.97)	0.018*
Gestational age (w)	7.78 ± 1.48(5-11)	7.86 ± 1.01(5-12)	0.096

*significant difference at 0.05 level of significance.

The mean ALL in patients with hyperemsis gravidarum was significantly higher ($p < 0.001$) compared to ALL in control group . The mean leptin level in patients with HG was significantly higher ($p=0.035$) than the mean leptin level in control group . The mean TSH level in patients with HG was significantly lower ($p=0.001$) than the mean TSH level in the control group . The mean freeT3 level in patients with HG was significantly higher ($p < 0.001$) than the mean free T3 level in control group. The mean free T4 level was also significantly higher in the HG group ($p < 0.001$) as shown in table 2.

Table 2 : ALL, leptin and other hormonal parameters of HG and control group in the study.

	H. gravidarum (n =50)	Control (n =50)	p-value
Adusted leptin level	1.86 ± 0.23	1.38 ± 0.20	<0.001*
Leptin (ng/ml)	14.78 ± 4.46	12.51 ± 4.08	0.035*
TSH (mIU/ml)	1.18 ± 0.52	1.49 ± 0.39	0.001*
free T3 (ng/ml)	1.63 ± 0.28	1.31 ± 0.24	<0.001*
free T4 (ng/ml)	9.96 ± 1.34	8.78 ± 1.29	<0.001*

*significant difference at 0.05 level of significance.

There was an inverse and statistically significant correlation between leptin and BMI in the HG group ($r = - 0.903$, $p = 0.000$) while there was an inverse but statistically not significant correlation between leptin and BMI in the control group($r = - 0.121$, $p = 0.230$). There was an inverse but statistically not significant correlation between leptin and TSH in the HG group ($r = - 0.206$, $p = 0.151$) and the correlation was also inverse but statistically not significant between leptin and TSH in the control group ($r = - 0.269$, $p = 0.059$). A direct but statistically not significant correlation was found between leptin and free T3,T4 in the HG group($r = 0.094$, $p = 0.516$ and $r = 0.091$, $p = 0.530$ respectively) , also the correlation was direct but statistically not significant between leptin and free T3 ,T4 in the control group ($r = 0.109$, $p = 0.452$ and $r = 0.157$, $p = 0.275$ respectively) as shown in table 3.

Table 3 : The correlation between leptin and the other parameters in the HG and control group as shown in table 3

	HG (NO. = 50)		CONTROL CASES (NO. = 50)	
	r	p-value	r	p-value
BMI (kg/m^2)	-0.903	0.000	-0.121	0.230
TSH (mIU/ml)	-0.206	0.151	-0.269	0.059
freeT3 (ng/ml)	0.094	0.516	0.109	0.452
freeT4 (ng/ml)	0.091	0.530	0.157	0.275

The ALL in HG group was higher than ALL in the control group in all gestational ages which was statistically highly significant (p was < 0.001in all ages; the mean difference is calculated this can be a positive or negative value); A p-value is calculated where p is the probability of a false-positive event as shown in table 4.

Table 4: comparism between ALL in HG group and ALL of control group for the same gestational age .

GESTATIONAL AGE GROUPS	ALL (CONTROL)		ALL (HG)		P-VALUE
	Mean±SD	N	Mean±SD	n	
5-6 w	1.1004	7	1.5620	10	<0.001*
7-8w	1.1047	23	1.8512	27	<0.001*
9-10 w	1.3359	8	2.1232	10	<0.001*
11 -12 w	1.5809	12	2.1030	3	<0.001*

*significant difference using unpaired student's t- test for two independent means at 0.05 level of significance.

DISCUSSION:

Hyperemsis gravidarum (HG) 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 pregnant state. A relationship between leptin and HG was originally based on the notion that leptin was exclusively expressed in white adipose tissue and its main function was to play a crucial role in reducing appetite and raising the consumption of energy.[2].
In our study patients with HG were comparable to women without HG in their maternal age, parity, gestational age in order to avoid possible bias and the effects of these variable on leptin level.
In the current study, the mean maternal serum leptin level in patients with HG was significantly higher (p = 0.035) than the mean maternal serum leptin level in the control group . While in the study carried on 30 patients with hyperemsis gravidarum and 26 control by Arslan E. et al. who investigate the role of leptin in the etiology of hyperemesis gravidarum, he reported that the mean maternal serum leptin level of patients with HG was higher but statistically not significant (p = 0.05) than the mean maternal serum leptin level in the control group[11], this disagree with our result and may be due to small sample size taken in this study. In 2004, Demir et al measured leptin levels in 54 patients with HG and 50 without HG in first trimester and reported that the mean maternal serum leptin level in patients with HG was higher but statistically not significant (p=0.099) than the mean maternal serum leptin level in the control group [12] and this disagree with our result and may be due to different criteria in selection of patients with HG.

Our findings were agreed with a study performed on 18 women with HG and 18 healthy pregnant women in first trimester carried by Aka et al who reported that the group with hyperemesis gravidarum was found to have significantly higher leptin level than the control group (P = 0.037), and on the basis of their results, deposit a role for leptin in the etiology of the disorder .[13]

In the current study ALL of patients with HG was (1.86 ± 0.23) which was significantly higher (p < 0.001) than the ALL of control group which was (1.38±0.20) . this support the hypothesis , that the rapid increase in maternal leptin concentration that is disproportional to gestational age may trigger the development of hyperemsis gravidarum . Demir et al**,** measured the mean maternal serum level of ALL of patients with HG , found to be (4.25 ± 2.34) which was significantly higher (p=0.009) than ALL of the control group which was (3.59 ± 2.31) [12] ,which agree with our result.

Substantial increases in early pregnancy, before the occurrence of any notable increase in body weight with progressive gestation, imply that factors other than increased adiposity mediate maternal leptin levels.[9]

In the current study, the cutoff value for the ALL is 1.66 at sensitivity 82% and specificity 92% (P<0.001), when this value exceeds 1.66 in the first trimester, the hyperemesis will be severe. The aetiology of transient hyperthyroidism of HG is unclear.Some have argued that the hyperthyroidism is the cause of the hyperemesis ,where as others have argued the reverse.[11] In our study serum TSH was significantly lower in HG group than the control group(p=0.001)while T3,T4 levels were significantly higher in hyperemsis gravidarum group than the control group (p=< 0.001,< 0.001) respectively.Our finding was consistent with that of Demir et al who found that Serum TSH was also significantly lower in HG group (p = 0.003) while T3, T4 levels were significantly higher in HG group than in the control group (p = 0.013, 0.012 respectively).[12] The relation between raised ALL and transient hyperthyroidism may be developed via HCG (placental leptin stimulates HCG secretion that stimulates thyroid hormones).[12]

In our study, leptin level was inversely and significantly correlated with BMI in HG group (r = - 0.903 , p = 0.000). this is may be because leptin activates sympathetic nervous system and increases energy expenditure in adults.[12]

Our finding was different from that of Arslan E . et al who found that there was a significant direct correlation between values of BMI and leptin levels in the first trimester (P < 0.01)[11], also Aka et al disagree with our our result and found a significant direct correlation was detected between leptin and BMI (r = 0.711 , P < 0.01).[13] Sivan et al found no correlation between maternal serum leptin and maternal BMI.[14] These different results may arise from different sample sizes as well as methodology.

CONCLUSION:

1-Maternal serum leptin level was significantly higher in the HG group.

2-ALL was significantly higher in the HG group

3-There was no significant correlation between leptin and thyroid hormones.

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