

Investigation of the Relationship between Serum Leptin levels and Nausea and Vomiting of Pregnancy

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Abstract

Background: Worldwide, half of women suffer from nausea and vomiting in early pregnancy which generally continues to the 20th week of pregnancy. Although pathogenesis of nausea and vomiting of pregnancy as well as hyperemesis gravidarum are still unknown, some believe that nausea and vomiting of pregnancy is likely related to maternal serum leptin level.

Objectives: This study aimed to examine the relationship between leptin and pregnancy nausea and vomiting.

Methods: In this case-control study, 45 pregnant women at first and second trimesters were selected through convenient sampling. Mothers' blood samples were taken in the 6th, 12th, 15th, and 20th weeks of pregnancy. The participants were divided into healthy, without nausea, (24) and with nausea and vomiting groups (21). The relationship among the variables was analyzed using independent t-test, Pearson correlation, regression tests, and Lambda statistic (P value <0.05).

Results: The mean age of the participants was 27.47±5.55 years, and Body Mass Index (BMI) was found to be 24.58±26.57. There was no significant difference between groups in this regard. Based on results, changes in maternal serum leptin had significant correlation with nausea and vomiting of pregnancy (p<0.04), meaning that the mean of leptin changes in patients with nausea and vomiting was significantly lower. Moreover, serum leptin at first and second trimesters of pregnancy did not have significant correlation with nausea and vomiting (p=0.5 and 0.3, respectively).

Conclusion: With regard to leptin peak level at second trimester of pregnancy, leptin changes at first and second trimesters can be a good index to predict the nausea and vomiting of pregnancy. Thus, further domestic studies are required in this respect.

Keywords: *leptin, pregnancy, nausea, vomiting*

Introduction

According to World Health Organization reports, more than 200 million pregnancies annually occur throughout the world, and providing health and care services for this group is among the main and

important objectives of socioeconomic developments. Physiologic changes of pregnancy involve all body systems including digestive system. Digestive disorders are among prevalent problems in pregnancy among which nausea and

vomiting are the most dominant cases [1-3]. Half of women suffer from nausea and vomiting in early pregnancy (50-90%) and 25% suffer from daily nausea which is light and auto-disappearing and can be controlled with preventive treatments. This condition usually occurs between the 5th and 18th weeks of pregnancy and generally disappears in the 20th week. However, nausea and vomiting symptoms remain until the end of pregnancy in 10% of mothers [4-6].

Despite the fact that morning sickness is more prevalent, 80% of women suffer from this problem all day long, and merely 1.8% of its symptoms are limited to morning. Thus, the term "morning sickness" does not seem to be appropriate [2,7]. In some patients, symptoms become too severe and result in dehydration, weight loss, and hospitalization [8-10]. This is referred to as fatal severe pregnancy nausea and vomiting. The prevalence of Severe nausea and vomiting of pregnancy (hyperemesis gravidarum) is about 0.32%, and its symptoms are continuous vomiting, weight loss more than 5%, ketonuria, electrolytic disorders (hypokalemia), and dehydration (high urine specific gravity) [3,8, 11]. Fatal pregnancy vomiting is accompanied with several problems including gullet laceration, Mallory Weiss syndrome, pneumothorax, environmental neuropathy caused by B6 and B12 vitamins deficiency, and preeclampsia [7,12].

Although the pathogenesis of nausea and vomiting of pregnancy and hyperemesis gravidarum are unknown, they are related to hormone, autonomic, liver, and stomach functions [1,12, 13]. Chorionic gonadotropin, estrogen, pituitary adrenal axis, thyroxin, prostaglandin E2, prolactin, leptin, adrenocorticotropin, testosterone, serotonin, helicobacter pylori, immune system, neuromuscular, anatomic, and psychological aspects are among the highlighting factors in this regard [2,14,15]. Moreover, the nausea and vomiting of pregnancy history, female fetus, race, family background, motion sickness history, socioeconomic class, education, migraine, pregnancy nausea, and vomiting history while using anti-pregnancy tablets including estrogen, low age, obesity, stress, multiple pregnancy, first pregnancy, and molar pregnancy have previously been documented as nausea and vomiting of

pregnancy risk factors [4,6,16]. Nausea and vomiting of pregnancy prevalence is reported to be lower in addicts that can be related to lower size of placenta, while it is 1.5 times higher in female fetus [1,7]. With regard to the incidence of this condition in molar pregnancy, its origin appears to be placenta and is not related to fetus [7].

Although the prevalence of weight loss at giving birth, abortion, preterm delivery, limited fetus growth, and stillbirth is higher in pregnancy nausea and vomiting, this does not increase congenital anomalies [2,7,17]. However, a recent study revealed that fetus neural tube dysfunction as a function of early nausea and vomiting of pregnancy cannot be its cause [18]. Previous studies showed that this is accompanied with a decreased job performance, energy loss, exhaustion, irritability, unenjoyably life, problematic marital relationships, financial burden, and depression which altogether affect the life quality of mothers [2,19,20]. These factors subsequently lead to distress, disgruntle, and sleeping and feeding problems, and excretion in infants. These infants may face other problems such as improper learning, delay in puberty, irritability, and distraction in childhood [21].

Leptin is a non-glycosylated protein with 167 amino acids which was detected by Zank et al. in 1994 [22]. This hormone is the product of ob gene which is released mainly by adipocytes [23]. Leptin regulates the body weight and appetite via providing negative feedback on appetite center and having direct effect on cerebral anorectic neurons [8,13]. In fact, it has lower levels at midnight and in the morning and has higher concentration in obese people [24,25]. Leptin decreases appetite via preventing the effects on neurons through Y neuropeptide in arcuate nucleus of hypothalamus [25,26]. Moreover, it is released by chorionic syncytiotrophoblast, stomach epithelial, and fetus tissue in addition to fat tissue and functions in trophoblastic proliferation and food transfer of placenta in pregnancy [4,22,23]. Leptin increases in accordance with the increase in pregnancy age and estrogen and reaches its peak at the second trimester [27].

The theory of the relationship between leptin and nausea and vomiting of pregnancy as the result of increased fat mass during pregnancy and placenta leptin production is suggested to have interaction with factors such as cortisol, thyroid, and insulin through the mechanism of reducing appetite and negative energy balance in nausea and vomiting of pregnancy [4,13,24,28]. Earlier studies reported contradictory results in this regard. Some researchers believe that a sudden increase in leptin concentration, without considering the pregnancy age, can be a predictive marker of nausea and vomiting of pregnancy [11,29]. Others reported that serum leptin in patients with fatal pregnancy vomiting is higher than the one in patients with nausea and vomiting of pregnancy [6]. In contrast, other studies concluded that leptin is lower in patients with hyperemesis [30,31]. A study conducted on 91 mothers in Taiwan showed that fatal vomiting decreases along with the increase in pregnancy age from the first trimester to second [30]. However, Gangor et al. reported that leptin is significantly lower in fatal pregnancy vomiting [31].

Due to the contradiction in previous studies and a high prevalence and importance of this issue among mothers, the present study examines the relationship between leptin and pregnancy nausea and vomiting.

Methods

This nested case-control study was conducted on pregnant women referring to medical centers covered by Shahid Beheshti University of Medical Sciences in 2015. First, 110 mothers were selected using convenient sampling, and their information was controlled by the inclusion criteria. Inclusion criteria encompassed Iranian nationality, age range of 18-40, solo pregnancy, the lack of systemic diseases like lupus, diabetes, thyroid, heart disease, kidney disease, coagulation disease, epilepsies, asthma, hepatitis, and hypertension, the lack of mental problems, family member death, psychotropic and anti-nausea drug use, no addiction to tobacco, drug and alcohol, being at first or second trimester of pregnancy, and an ordinary diet (not following special diets). Exclusion criteria were the incidence of any pregnancy problem like preeclampsia, mole,

ectopic pregnancy, diabetes, and placental abruption and the use of any drug other than pregnancy supplement during the study.

Sample size was calculated via the following formula at 95% confidence level and 0.8 robustness. The sample included 55 members according to the follow up study of initial cohort study.

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 (S_1^2 + S_2^2)}{(\mu_1 - \mu_2)^2}$$

During the initial study, sampling was done in two groups for examining the nested case-control. Finally, mothers were placed in healthy and without pregnancy nausea group (24) and nausea and vomiting of pregnancy group (21). Due to the sample selection from different districts of Tehran, the two groups were homogenous in terms of demographic and intervention factors which were confirmed by the statistical tests. This increased the strength of the study.

After giving full description of the study, its benefits, obtaining consent, and checking the inclusion criteria, the blood samples were taken from mothers. Moreover, mothers were informed of data confidentiality and contact information was given to them for any problem or question.

Pregnancy age was calculated using the first day of last menstruation or first trimester sonogram. At first visit, demographic characteristics, pregnancy description, and medical histories of mothers were collected based on direct interviews using prenatal care standard form of Ministry of Healthcare. Mothers were classified into two groups via Rhodes Questionnaire using codes instead of names.

Rhodes nausea and vomiting index is a tool for assessing nausea, vomiting, and gagging during the last 12 hours. This tool includes 8 questions and is scored based on five-point Likert scale (0-4). Three questions are related to number, amount, and the time of nausea with a score range of 0-12. Two questions are about gagging including the number and amount of gagging within 0-8 score range. The total score of Rhodes nausea and vomiting scale ranges from 0 to 32. Based on this scale, a higher score is related to intense nausea, vomiting, and gagging, and lower score is related to light nausea, vomiting, and gagging. In this

scale, scores 3-8 show light nausea and vomiting, scores 9-16 are indicators of medium nausea and vomiting, and scores 24-32 are intense nausea and vomiting [32] in five-point Likert scale. Score 1 is placed in the group without nausea, and the scores 2-3 are placed in the experiment group. Score 4 is among the inclusion criteria.

Pregnant mothers' diet was planned using the food protocol of Ministry of Health which presents instructions for a suitable diet during pregnancy. At each prenatal visit, weight, height, BMI, blood pressure, fetus heartbeat, etc. were examined to assess the mothers' health. At the end of each visit, next visit was determined based on the pregnancy age about which mothers were informed.

Venous blood samples of mothers were taken in the weeks of 6-12 and 15-20 between 9 and 11 in the morning to discover serum leptin and were examined until the end of pregnancy for exclusion criteria or automatic abortion.

In the laboratory, samples were centrifuged with 3000 rpm for 10 minutes, plasma was separated, and obtained serums were frozen at low temperature (-20 to -70) until the experiment day. Samples were evaluated using ELISA method based on leptin special kit. Leptin special kit for humans was purchased from Sweden with label Mercodia (Intra-assay CV%: 7.1 and with sensitivity of 0.024 ng/ml). According to kit instructions, samples were diluted 11 times, and, finally, the results were multiplied by 11.

The homogeneity of the two groups in terms of background and demographic variables like age, education, occupation, number of family members, infant gender, type of giving birth, productivity condition, income, and BMI was confirmed via the statistical tests, and the raw data

were analyzed using SPSS 16 software. Quantitative variables were reported using mean and standard deviation, and qualitative variables were reported in percentages. The relationships among variables were separately examined using independent t-test, Pearson correlation, and regression tests. A statistic with significance level of $p < 0.05$ was used in order to compare the correlation coefficients of variables in two groups (RA Vs RB).

Results

The mean age of mothers ($n=45$) was found to be 27.47 ± 5.55 within which 19 and 37 were the lowest highest ages, respectively. Most mothers were within the age range of 21-30. The education level of 55.5% of mothers was high school and higher, while 53.3% of their spouses had high school or higher education level. 95.6% of mothers in the experimental group and 91.3% of mothers in the control group were housewives. A majority of the spouses (82.2%) were self-employed. Besides, 6.7% of the spouse had low, 80% middle, and 13.3% good monthly income. 31.1% of the participants were from a 2-member family, 60% from a 3-member family, and 8.9% from a 4-member (or more) family. 44.4% of the infants born during the study were male and 55.6% female. 33.3% of the research units were nulligravida, and 66.7% were multi-gravida, and 17.8% of mothers had abortion history.

The homogeneity of the two groups in terms of background and demographic variables such as age, education, occupation, number of family members, productivity condition, type of giving birth, income, and BMI was confirmed via statistical tests (Table 1).

Table 1: Frequency distribution of homogenous variables in the two groups

Variable	Experiment group	Control group	P value
Age	24.5±5.718	29±5.198	0.6
BMI	Natural	52%	0.9
	High	48%	
Type of giving birth	Natural	52%	0.6
	Cesarean	48%	
Education	Elementary	18.2%	0.6
	Junior high school	22.7%	
	Senior high school	54.5%	
	university	4.5%	
Occupation	employed	100%	0.1
	Housewife	0%	
Number of family members	2	40.9%	0.2
	3	50%	
	4 and more	9.1%	
Income	Less than 600000 Rials	4.5%	0.09
	600000-1000000 Rials	72.7%	
	More than 1000000 Rials	21.7%	
Infant gender	Male	36.4%	0.3
	Female	63.6%	
Productivity condition	Number of pregnancy	2	0.9
	Number of giving birth	1	0.9
	Number of abortion	0	1
	Number of alive children	1	0.7

Finally, the mean of serum leptin in first and second trimester as well as the changes in leptin

during this period were compared in the two groups (Table 2).

Table 2: Comparison of serum leptin (ng/ml) in experimental and control groups

	Experiment group	Control group	P value
First trimester leptin	36.25±0.7	35.15±0.6	0.5
Second trimester leptin	38.09±0.6	40.58±0.8	0.3
Changes of leptin	2.93±0.2	4.33±0.3	0.04

The findings showed that the amount of leptin at first and second trimesters of pregnancy did not have significant correlation with nausea and vomiting of pregnancy ($p=0.5$ and 0.3 , respectively). However, changes of leptin during pregnancy was significantly lower in the experimental group compared to those in the control group ($p=0.04$).

Discussion

Various studies have been conducted on the relationship between nausea and vomiting of

pregnancy and leptin, and results have been contradictory. Some studies found a significant relationship between leptin and pregnancy nausea and vomiting, while some did not report any significant relationship. In case of the former, higher leptin was found both in the control experimental groups. The design of those previous studies was generally case-control assessing first and second trimesters' leptin. Analyzing plasma leptin was done through ELIZA and RIA methods in fasting and non-fasting forms, and most studies have focused on mothers hospitalized for fatal pregnancy

vomiting. However, ordinary pregnancy nausea has rarely been studied

The conducted examinations had similar designs but different target groups. For example, some assessed the incidence of fatal pregnancy nausea and vomiting, while others examined its intensity. Studies that reported higher serum leptin in experimental group include Elbirak et al.'s case-control study on 30 women with fatal pregnancy vomiting, 34 women with ordinary nausea and vomiting of pregnancy (morning sickness), and 22 women in the control group. Ghrelin to leptin ratio was significantly higher in fatal pregnancy vomiting group [33]. Furthermore, Orabi et al.'s study on 20 women with fatal pregnancy vomiting, 20 women with morning sickness, and 10 women in the control group in Egypt showed that the serum leptin was higher in the two experimental groups than those in the control group; however, there was no difference between these two groups [29]. Demir et al. compared serum leptin in 54 women with fatal pregnancy vomiting and 42 women in the control group. Leptin was significantly higher in the experimental group and had positive correlation with mothers' BMI [34]. Aka et al.'s study on 18 pregnant women depicted that leptin was significantly higher in the experimental group, and there was a positive correlation among leptin, serum insulin, and BMI [35]. In the same vein, Cho et al. studied 59 women with solo pregnancy in Taiwan and compared the serum leptin in slight and intense nausea. The relationship between serum leptin and early pregnancy nausea was significantly different in the two groups [36]. A study in 2017 which compared 45 pregnant women reported that serum leptin was significantly higher in the experimental group, and there was a positive correlation between leptin and pregnancy age in this group [13]. A study in 2016 in Ankara compared 30 healthy women with 54 women with fatal pregnancy vomiting in weeks 6-14 of pregnancy in terms of parietal fat tissue and BMI. Fat tissue and BMI had 83% and 67% prediction power in fatal pregnancy vomiting, respectively [37].

In contrast, some studies reported that serum leptin was higher in control groups. For instance, Kou et al.'s study on 91 pregnant mothers showed

that leptin had reverse relationship with fatal pregnancy vomiting. In more specific terms, fatal pregnancy vomiting decreased in accordance with the increase in leptin and pregnancy age from the first trimester of pregnancy to the third [30]. Similarly, Gongor's study in 2013 in Turkey on fasting sample of leptin in two 20-member control and experimental groups showed that leptin was significantly lower in experimental group [31].

Some studies did not find significant relationship between leptin and fatal pregnancy vomiting. For instance, a study in 2004 on 40 women with fatal pregnancy vomiting in the experimental group and 30 women in the control group did not find any relationship between leptin and fatal pregnancy vomiting, despite a positive relationship between BMI and pregnancy vomiting. However, the relationship between leptin and BMI was significant [38]. A study in Korea on 16 women with fatal vomiting and 10 women in the control group at weeks 6-9 of pregnancy did not report any differences in serum leptin of the two groups [39]. Moreover, Arsalan et al.'s study in Turkey did not show any significant relationship between leptin and pregnancy nausea and vomiting, while reporting a positive correlation between leptin and BMI in first trimester of pregnancy [40].

The inconclusive results of the previous studies can be due to the effects of race and food habit as the factors affecting the hormone spectra during pregnancy, particularly leptin. Since the present study controlled the homogeneity of the two groups, this difference can result from the difference in the sample sizes of the studies.

Moreover, leptin has been assessed at various trimesters of pregnancy, and changes of leptin have rarely been studied. Since the increase in leptin starts from the first trimester, and the peak serum leptin occurs at the second trimester of pregnancy [27], it seems that assessing leptin at the second trimester of pregnancy is only correlated with pregnancy age and is not related to pregnancy outcomes due to the peak hormone in mothers. Therefore, further studies are recommended to assess leptin at first trimester of pregnancy and examine the changes of plasma leptin using larger samples and in relation to pregnancy nausea and vomiting.

Due to the increase in leptin in the 28th week of pregnancy, the changes of leptin from first trimester of pregnancy to second can be a better index for examining the relationship between leptin and pregnancy nausea and vomiting. Thus, it would be more reliable to examine the changes of serum leptin from the beginning of placenta hormone activity to the peak of serum leptin in order to decrease the bias of incidence and have a better judgment for comparing the two groups.

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