ORIGINAL ARTICLE

The relation of visfatin with nausea and vomiting in the pregnancy

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Background: The etiology of nausea and vomiting during pregnancy (NVP) is unclear and appears multifactorial. It has been shown that the physiological changes associated with NVP include changes in the levels of adipocytokines. Therefore, we investigated the association of nausea and vomiting during pregnancy with visfatin, β-human chorionic gonadotropin (βHCG), and perceived stress. **Materials and Methods:** In this cross-sectional study, 100 nulliparous pregnant women aged 18–45 years were evaluated. Participants completed two questionnaires including the Index of Nausea, Vomiting, and Retching (INVR) and Perceived Stress Scale (PSS) in the three trimesters of pregnancy. They also referred to the laboratory to conduct the biochemical examinations including serum visfatin and βHCG levels in three trimesters. The obtained data were analyzed by SPSS 16 using statistical repeated-measures analysis of variance, Friedman, Bonferroni, and Wilcoxon p*ost hoc* tests. Marginal model (method generalized estimating equation [GEE]) was performed to assess the predictors of the INVR in the participants. **Results:** INVR, PSS, visfatin, and βHCG levels significantly decreased from the first trimester to the third trimester of pregnancy ($P \leq 0.001$). As a result of simple marginal model (GEE method), visfatin was predicted log βHCG ($P = 0.035$). Furthermore, the multiple marginal model revealed that the two predictors of βHCG ($P = 0.01$) and PSS ($P \leq 0.001$) were positively correlated with the INVR. Furthermore, visfatin had an indirect positive effect on INVR. **Conclusion:** The present study showed that visfatin can be indirectly related with nausea and vomiting throughout pregnancy. Furthermore, it seems that fluctuations in visfatin levels are independent of weight gain during pregnancy.

Key words: Human chorionic gonadotropin-beta, nausea, pregnancy, visfatin, vomiting

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INTRODUCTION

Pregnancy as one of the most normal of physiological process influences the quality of life and daily activities of pregnant women including sleep disturbances, fatigue, anxiety, malnutrition, irritability, decreased social activity, stress, and anxiety in mothers.[1] Adaptation to pregnancy is essential for the development of a good relationship between mothers and newborn.[2] Nausea and vomiting during pregnancy (NVP) in 50%–90% of pregnant women typically begin by the 4th week after the last menstrual period and often limited by the 20th week of pregnancy[3] which its severity and emergence time varies in individuals. In its most extreme form, hyperemesis gravidarum (HG) is characterized by severe nausea and excessive vomiting leading to dehydration, electrolyte, and nutritional disturbances, which often necessitates hospitalization that affects 0.5%–2% of pregnancies.[4,5]

Pregnant women often gain weight during the gestation, and maternal obesity is a common consequence of pregnancy. Adipose tissue secrete a variety of bioactive peptides, known as adipokines including visfatin, leptin,

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adiponectin, resistin, and others with diverse functions at both local (autocrine/paracrine) and systemic (endocrine) levels.[6] A variety of adipokines including visfatin secreted from adipocyte may play a crucial role in the development of obesity, insulin resistance, and gestational diabetes in pregnancy.[7]

It is known that adipose tissue and adipokines involved in various processes of normal human gestation, physiological changes associated with nausea and vomiting during pregnancy, and common complications of pregnancy. Visfatin as an adipokine has insulinomimetic activity that is mainly expressed in visceral adipose tissue besides in other tissues including placenta and fetal membrane.[7,8] Thus, the physiological changes associated with nausea and vomiting of pregnancy may include changes in the levels of cytokines and adipocytokine.[9]

The results of the previous study by Kuo *et al*. on 91 primigravida and multigravida pregnant women indicated the average Index of Nausea, Vomiting, and Retching (INVR) score and human chorionic gonadotropin level decreased from the first to the third trimesters, and the average leptin and cortisol levels increased from the first to third trimesters. However, they did not find a relationship between nausea vomiting and leptin.[10]

As there is no study on the evaluation of another adipokine, visfatin, on nausea and vomiting during pregnancy, and because of the important role of adipokines in NVP, we investigated the relation of visfatin with nausea and vomiting during pregnancy in nulliparous women considering two standard questionnaires of INVR and Perceived Stress Scale (PSS).

MATERIALS AND METHODS

Design and samples

Nulliparous pregnant women were enrolled in this longitudinal/cross-sectional study from the private prenatal care clinics in the urban areas of Birjand, South Khorasan, Iran, in 2017–2018. The sample size was determined according to the Kuo *et al*. study,[10] and the following formula with S1 = 6.58, S2 = 3.57, d = 2.6, β = 0.1, and α = 0.05 estimated 87 people which with 15% loss rate increased to 100 people by considering the fall. The sample size formula is as follows:

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)\left(S_1^2 + S_2^2\right)}{d^2}$$

The sampling method was convenience sampling, and the samples were selected among pregnant women referring to gynecologists who had criteria for entering the study. The inclusion criteria were: 18–45 years old and nulliparity. Women with pregnancy complications (bleeding during pregnancy, HG, abortion, etc.), a history of chronic and infectious diseases (mental disease, diabetes, kidney disease, and gastrointestinal disease), and having been treated for nausea and vomiting (NV) with medications, or having used medications, except for supplements and multivitamins, were excluded. After obtaining the approval of the Deputy of Vice President for Research and Technology of Birjand University of Medical Sciences and the ethical approval registration number IR.bums.REC.1394.345, the participants were informed that all identifying information would be kept confidential. Consent was provided by all participants, according to the criteria of the Ethics Committee of the Faculty of Medicine of Birjand University of Medical Sciences. Then, the researcher asked the participants to fill out the questionnaire in the all three trimesters. They were also referred to the laboratory to have five-milliliter blood samples taken to conduct the biochemical examinations of their visfatin and β-human chorionic gonadotropin (βHCG) levels in the 6th week of pregnancy until the 10th week, the 18th week of pregnancy until the 20th week, and the 28th week of pregnancy until the 32nd week. The gestational age was determined by a first-trimester ultrasound for all participants.

Data collection tools

To measure the severity of pregnancy-related nausea and vomiting, the INVR questionnaire was used.[11] The INVR has eight items rated on a five-point Likert scale and consists of three subscales: nausea (3 items with score range: 0–12), vomiting (3 items with score range: 0–12), and retching (2 items with score range: 0–8). The range of scores on the complete INVR is 0–32. The severity of the pregnancy-related nausea and vomiting was divided into three groups based on the scores on the INVR: mild or less (scores 0–8), moderate (scores 9–16), and severe (scores 17–32).[12] To determine the content and face validity, the content validity index (CVI) and content validity ratio (CVR) were used. To this end, the questionnaire was evaluated by 10 experts in the fields of gynecology, midwifery, health education, and epidemiology. The mean CVI was 90%, and the mean CVR equaled 87%. The reliability assessed by internal consistency with Cronbach's alpha for nausea, vomiting, and retching was 0.88, 0.94, and 0.86, respectively, and the total scale was obtained 0. 83.

Besides, additional data were collected using the PSS, concerned with the responder's feelings and thoughts during the previous month. There were10 items in this scale that were rated on a five-point Likert scale ranging from 0 (never) to 4 (very often), with minimum and maximum possible scores of 0 and 40, respectively. Score

0–13 represents low levels of perceived stress, score 14–26, moderate levels, and score 27–40, high levels, respectively.[13] In this study, the English version was translated into Persian by two professional translators. Then, a panel of Iranian experts reviewed the instrument to determine the face and content validity of the duplicate Persian version. The panel experts were consisted of two gynecologists, two midwives, three health education professors, two nursing professors, and one epidemiologist. Then, the revised questionnaire was completed for 25 participants. The CVI and CVR of PSS estimated as 80% and 92%, respectively. As both in acceptable ranges, thus, the validity of the questionnaire was confirmed. In our study, the Cronbach's alpha of PSS was obtained at 0.64. For elimination of recall bias, corroborated medical documents such as sonography and medical records were used.

In addition, commercially available enzyme-linked immunosorbent assay kits were used to measure visfatin (Zellbio GmbH, Germany, ZB-10025-H9648) according to the manufacturer's instructions and the maternal serum level of βHCG measured with (Liaison Diasorin, Germany, type 2229). Then, the samples were read within the linear range of the assay, and the accuracy of the analysis was confirmed by the controls provided in each assay kit. The minimum sensitivity of visfatin assays was 0.2 ng/ml and analytical sensitivity of Liaison Diasorin, 0.3 mIU/ml.

Statistical analysis

The data were analyzed by the Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive analyses were used to summarize the data on the variables. The Kolmogorov–Smirnov test was used to determine the normality of data distribution. This test showed that the distribution of the data on the PSS was normal, but the distribution of the data on the βHCG, INVR, and visfatin was not normal. The Box-Cox transformation was applied for normalized βHCG, INVR, and visfatin. The Box-Cox transformation shows a power transformation that incorporates the optimal normalizing transformation for each variable.[14] Therefore, we applied log transformation for βHCG, second root transformation for INVR, and fourth root transformation for visfatin. Thus, we used repeated-measures analysis of variance to compare the mean scores on the log βHCG, the PSS, $\sqrt{INVR}$ and $\sqrt[4]{Visfatin}$ among the three trimesters of pregnancy, and the Bonferroni *post hoc* test to compare the mean scores of the trimesters.

We used the marginal model with generalized estimating equation (GEE) approach to analyze the INVR score in relation to predictors and confounders (PSS score, visfatin, βHCG, time, and age). In all of the tests, the level of significance was considered at $P < 0.05$.

RESULTS

Of the 100 eligible pregnant women, 82 women participated over the three trimesters of pregnancy (18% loss rate due to abortion of fetus, immigration to other cities, complete bed rest, and unwilling to continue of participants in the study) [Figure 1].

The demographic characteristics of the study participants are presented in Table 1.

Repeated-measures analysis of variance showed a significant decrease in the mean $\sqrt{INVR}$ level in the third trimester compared to the first trimester ($P < 0.001$). The Bonferroni *post hoc* test showed that the $\sqrt[4]{Visfatin}$ levels in the second and third trimesters were significantly lower than the first trimester ($P < 0.001$) [Figure 2a].

Repeated-measures analysis of variance showed a significant decrease in the mean $\sqrt[4]{INVR}$ level in the third trimester compared to the first trimester ($P < 0.001$). The Bonferroni *post hoc* test showed that the $\sqrt[4]{Visfatin}$ levels in the second and third trimesters were significantly lower than the first trimester ($P < 0.001$), and there was a significant difference between the second and third trimesters [Figure 2b].

Furthermore, there was a significant decrease in the mean log βHCG level in the third trimester compared to the first trimester ($P < 0.001$). The Bonferroni *post hoc* test showed that the log βHCG levels in the second and third trimesters were significantly lower than the first trimester ($P < 0.001$) [Figure 2c].

There was a significant decrease in the mean PSS level in the third trimester compared to the first trimester ($P < 0.001$). The Bonferroni *post hoc* test showed that the PSS levels in the third trimester were significantly lower than the first trimester ($P < 0.001$) [Figure 2d].

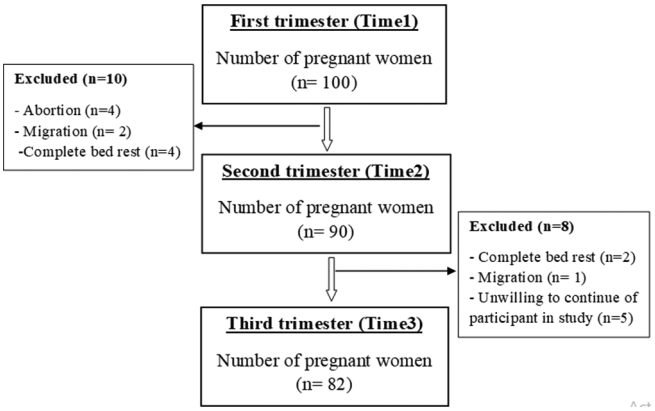

Figure 1: Flowchart of study participants

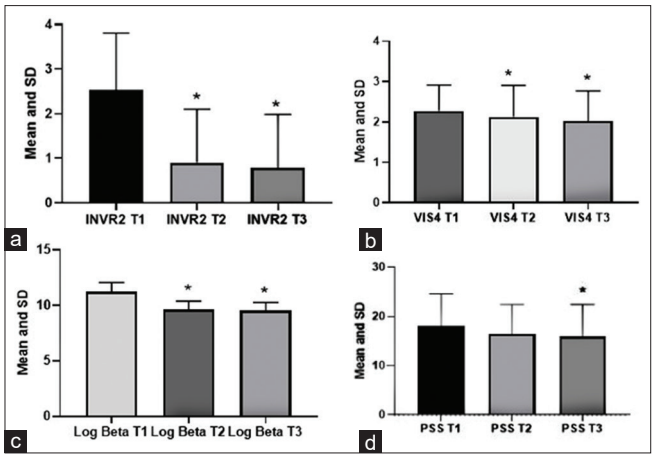

Figure 2: Comparison of mean of $\sqrt{INVR}$ (a), $\sqrt[4]{Visfatin}$ (b), log βHCG (c), and PSS score (d) at three trimesters of pregnancy in evaluated patients. INVR = Index of Nausea, Vomiting, and Retching, BHCG = β-human chorionic gonadotropin, PSS = Perceived Stress Scale, *: *P*-value<0.05 is significant

Table 1: Demographic characteristics of participants (*n*=82)

Variable	*n* (%)
Education	
Elementary	18 (22)
High school	39 (47.6)
University	25 (30.4)
Job	
Employed	12 (14.6)
Housekeeper	70 (85.4)
Pregnancy status	
Planned pregnancy	79 (96.3)
Unplanned pregnancy	3 (3.7)
BMI (kg/m^2), mean (SD)	22.00 (4.40)
Age (year), mean (SD)	24.94 (4.61)

BMI=Body mass index; SD=Standard deviation

Table 2 shows pair relation between $\sqrt{INVR}$ (as outcome variable) age, $\sqrt[4]{Visfatin}$ log βHCG, and PSS score (as predictor) by marginal models. There was a significant positive relation between age ($P=0.015$), $\sqrt[4]{Visfatin}$ ($P=0.04$), log βHCG ($P<0.001$), and PSS score ($P<0.001$) with, $\sqrt{INVR}$ and there was a significant relation between log βHCG and $\sqrt[4]{Visfatin}$ ($P=0.35$).

We carried out marginal models to assess the predictors and potential confounders of the $\sqrt{INVR}$ in the participants. PSS, $\sqrt[4]{Visfatin}$ log βHCG as predictor, and age as confounder were included in the final model simultaneously. The final model indicated that βHCG (β = 0.32, confidence interval [CI] [0.15–0.49], $P < 0.001$), PSS (β = 0.047, CI [0.023–0.071] $P<0.001$), and age (β = 0.037, CI [0.002–0.072], $P=0.045$) were significantly correlated with the $\sqrt{INVR}$ ($P<0.05$) [Table 3]. Moreover, time variable was negatively correlated with

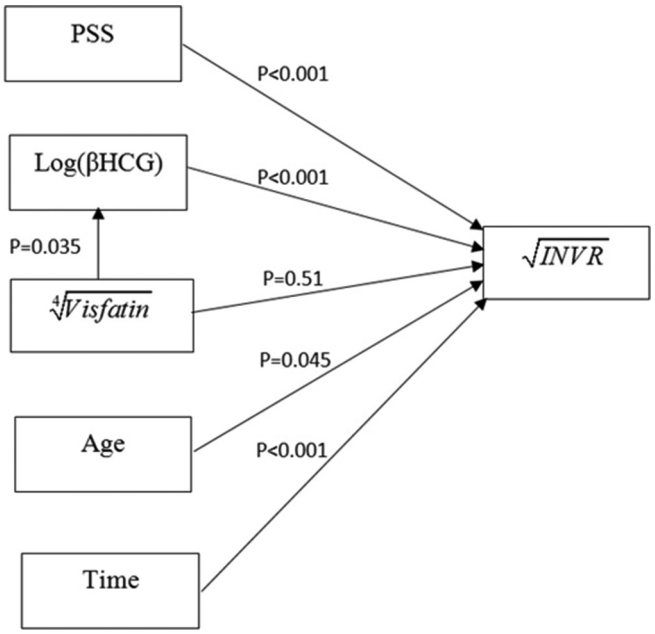

Figure 3: The summarized predictors that can predict INVR. INVR = Index of Nausea, Vomiting, and Retching, BHCG = β-human chorionic gonadotropin, PSS = Perceived Stress Scale

INVR (β = −0.56, CI [−0.78–−0.34], $P \leq 0.001$). However, there was no significant relation between $\sqrt[4]{Visfatin}$ and $\sqrt{INVR}$ (β = 0.074, CI [−0.14–0.29], $P = 0.51$).

Figure 3 summarizes the final model extracted from Tables 2 and 3. This figure shows that $\sqrt[4]{Visfatin}$ had an indirect effect of $\sqrt{INVR}$. In other words, $\sqrt[4]{Visfatin}$ has a modifier effect on relation between log βHCG $\sqrt{INVR}$ and with controlling age and time and adjusting PSS.

DISCUSSION

In this study, the final model in marginal model indicated that the two predictors of βHCG, which were PSS and age, significantly correlated with the $\sqrt{INVR}$.

Although the etiology of nausea and vomiting in pregnancy is multifactorial, several studies have shown that various metabolic and endocrine factors, the most implicated factor, HCG, closely correlate with nausea and vomiting of pregnancy. Symptoms typically begin in the first trimester, and the peak occurs between 12- and 14-week gestation[15] that is in accordance with our results.

The available data on the relationship between NVP and psychosocial health are controversial, and research is inconsistent on the factors predisposing women to pregnancy-related nausea and vomiting.

Table 2: Parameter estimation of marginal models (generalized estimating equation method) for each response and predictor separately (*n*=82)

Outcome	Predictors	β	SD	CI		*P*	Effect size
				0.025	0.975		
$\sqrt{INVR}$	Age	0.046	0.019	0.009	0.083	0.015	0.02
$\sqrt{INVR}$	Time	−0.86	0.082	−1.021	−0.699	<0.001	0.30
$\sqrt{INVR}$	PSS	0.076	0.015	0.047	0.105	<0.001	0.11
$\sqrt{INVR}$	$\sqrt[4]{Visfatin}$ (ng/ml)	0.29	0.14	0.016	0.564	0.04	0.02
$\sqrt[4]{Visfatin}$	Log βHCG (mIU/ml)	0.71	0.071	0.571	0.849	<0.001	0.29
$\sqrt[4]{Visfatin}$	Log βHCG (mIU/ml)	0.085	0.036	0.014	0.156	0.019	0.02
$\sqrt[4]{Visfatin}$ (ng/ml)	PSS	0.007	0.013	−0.018	0.032	0.602	0.003
Log βHCG (mIU/ml)	$\sqrt[4]{Visfatin}$ (ng/ml)	0.20	0.09	0.024	0.376	0.035	0.02

INVR=Index of Nausea, Vomiting, and Retching; BHCG=β-human chorionic gonadotropin; PSS=Perceived Stress Scale; CI=Confidence interval; SD=Standard deviation

Table 3: Parameter estimation of multiple longitudinal marginal models (generalized estimating equation method) of age, time, Perceived Stress Scale, $\sqrt[4]{Visfatin}$ false, and Log β-human chorionic gonadotropin on Index of Nausea, Vomiting, and Retching (*n*=82)

Outcome	Predictors	β	SD	Confidence interval		*P*	Effect size
				0.025	0.975		
INVR	Age	0.037	0.018	0.002	0.072	0.045	0.02
	Time	−0.56	0.11	0.776	0.344	<0.001	0.08
	PSS	0.047	0.012	0.023	0.071	<0.001	0.04
	$\sqrt[4]{Visfatin}$ (ng/ml)	0.074	0.11	0.142	0.290	0.51	0.03
	Log βHCG (mIU/ml)	0.32	0.087	0.149	0.491	<0.001	0.001

INVR=Index of Nausea, Vomiting, and Retching; BHCG=β-human chorionic gonadotropin; PSS=Perceived Stress Scale; CI=Confidence interval; SD=Standard deviation

Since pregnant women are a sensitive group who are responsible for the next generation, their mental health is very important. Pregnant women may face stressors such as physical changes, hormonal changes (often accompanied by mood swings), and pregnancy-related anxiety such as fear of neonate's health and labor pain; hence, the stress induced by the birth of the first child (particularly delaying pregnancy which is increasingly common and the increase of age at the first birth) is classified as severe stress, and NVP is positively associated with stress.[16]

Furthermore, the psychosocial adaptation to pregnancy is considered a key component of the transition to motherhood that occurs gradually during pregnancy. Basharpoor[17] found that perceived stress and social support were the two significant predictors of maternal psychosocial adaptation during pregnancy and poor maternal psychosocial adaption can lead to NVP. Social support is defined as support received from family, friends, and others that lead to social adaptation, stress reduction, and psychological health.[18]

There was a significant positive relation between age and $\sqrt{INVR}$.

Delaying pregnancy is increasingly common, and it creates new challenges for obstetric care and is associated with the increased risk of complications in pregnancy.[19] Our findings supported the findings of Klemetti *et al*.[20] but are in conflict with Chortatos *et al*.[21]

One possible explanation is that older women may use less antenatal maternity service with exceptions screening for the Down syndrome and ultrasound scans and are less likely to seek help.[22]

Furthermore, age increasing is associated with enhanced brain inflammation and production of pro-inflammatory cytokines and a decreased production of anti-inflammatory cytokine that can be involved in the positive relation between age and INVR.[23]

Our study showed that the $\sqrt[4]{Visfatin}$ levels in the second and third trimesters were significantly lower than the first trimester.

Our findings are in conflict with Skvarca *et al*.[24] and Rezvan *et al*.[25] that demonstrated higher plasma levels of visfatin in the second and third trimesters than those in the first trimester. Agreement article was not found with our result.

One possible explanation can be that fluctuations in visfatin levels are independent of weight gain *per se* and are dependent on the rate of maternal weight gain during pregnancy.[25]

Furthermore, there was a significant positive relation between $\sqrt[4]{Visfatin}$ and $\sqrt{INVR}$ as an indirect effect, and there was a significant relation between log βHCG and $\sqrt[4]{Visfatin}$.

To our knowledge, there are scant studies about the positive relation between visfatin and INVR. In this regard, one study that investigated ovulation in mammalians that is associated with inflammatory reaction found that HCG and prostaglandin E2 treatment could increase the expression of visfatin mRNA in human granulosa-luteal cells.[26]

Furthermore, several previous studies highlighted the role of visfatin in the inflammatory response and associated with pathogenesis of various metabolic disorders including obesity, metabolic syndrome, and insulin resistance.[27,28] In this regard, one study showed that intracerebroventricular (ICV) administration of visfatin induced hypothalamic inflammation and increased proinflammatory cytokines of tumor necrosis factor-alpha (TNF-α) and interleukin-1beta (IL-1β) expression in the rat hypothalamus via regulation of cyclooxygenase (COX) and the melanocortin pathways. On the other hand, sickness response is related to inflammatory condition and inflammation in central nervous system(CNS) can cause to sickness symptoms.[29]

In our study, changes of both $\sqrt[4]{Visfatin}$ levels and log βHCG were parallel. $\sqrt[4]{Visfatin}$ levels and log βHCG levels in the second and third trimesters were significantly lower than the first trimester.

Furthermore, according to magnitude effect size, we can find some predictors of INVR; therefore, we suggest that further studies be done with a larger sample size.

A limitation of this study was that approximately one-fifth (18%) of the women enrolled in the study did not complete their participation because of abortion of fetus, immigration to other cities, and failure to participate in the study; thus, our findings may not show the experiences of the entire sample size. In addition, we could not measure the concentration of cortisol, which is considered a biomarker of stress reactions in humans.

CONCLUSION

Our study indicated that visfatin besides current factors including βHCG, age, and PSS can be associated with INVR indirectly through βHCG. However, further studies in large scale needed to identify of various mechanisms and related factors.

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Conflicts of interest

There are no conflicts of interest.

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