Serum Adiponectin, Visfatin, and Omentin Compared between Non-pregnant and Pregnant Women in Overall, Non-obese, and Obese subjects

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ABSTRACT

Objective: This study aimed to compare serum adiponectin, visfatin, and omentin between non-pregnant and pregnant women in overall, non-obese, and obese subjects.

Methods: There were 40 pregnant and 33 non-pregnant women classified by body mass index (BMI) into non-obese or obese subjects. Fasting blood samples were collected in the morning for the non-pregnant group and before delivery for the pregnant group.

Results: Plasma glucose levels were significantly lower, but plasma insulin levels were significantly higher in pregnant when compared to non-pregnant women in overall, non-obese, and obese women ($p<0.05$ all). The homeostasis model assessment of insulin resistance (HOMA-IR) was significantly higher, but the quantitative insulin sensitivity check index (QUICKI) was significantly lower only in obese pregnant when compared to obese non-pregnant women ($p<0.01$ all). However, in non-obese women, HOMA-IR and QUICKI were comparable between pregnant and non-pregnant women. Serum adiponectin, visfatin, and omentin were significantly lower in pregnant compared to non-pregnant women in overall, non-obese, and obese groups ($p<0.05$ all). In pregnant women, serum adiponectin and omentin levels were significantly lower in obese compared to non-obese pregnant women while serum visfatin levels were comparable in both groups. Serum adiponectin levels were highest followed by omentin and visfatin, respectively in both non-obese and obese pregnant groups. These results indicated that lower serum adiponectin, visfatin, and omentin in pregnant women might contribute to higher insulin resistance in pregnancy. Furthermore, serum adiponectin and omentin were reduced in increasing adiposity similarly to non-pregnant women.

Conclusion: Lower serum adiponectin, visfatin, and omentin in pregnant women might lead to decreased insulin sensitivity in these women.

Keywords: Adiponectin; insulin resistance; omentin; pregnancy; visfatin (Siriraj Med J 2018;70: 219-226)

INTRODUCTION

Pregnancy is a physiological condition that increases insulin secretion to provide sufficient carbohydrates for the growing fetus leading to insulin resistance.[1] In maternal insulin resistance, fat is used more for maternal energy than carbohydrates[1] with a decreased response of target tissues such as liver, adipose tissue, and muscle to insulin.[2] Furthermore, pregnancy is considered as a state of increasing adiposity.[3] Adipose tissue, a powerful endocrine organ, secretes various adipokines which contribute to the regulation of glucose hemostasis and insulin sensitivity including adiponectin, visfatin, and omentin.[4,5]

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Adiponectin, a collagen-like protein, is mainly synthesized by adipocytes and the most abundant adipose-specific protein.[6] It controls the action of insulin by activating AMP-activated protein kinase in the muscle and the liver[7] leading to increased insulin sensitivity.[8] Adiponectin was found to be decreased in type 2 diabetes mellitus patients[9] and was inversely related to insulin levels and the homeostasis model assessment of insulin resistance (HOMA-IR).[5,9] Furthermore, adiponectin levels were decreased in obese compared to non-obese humans[5,10] and were negatively correlated with body mass index (BMI).[11] A previous study found that serum adiponectin levels were significantly lower in pregnant compared to non-pregnant women[12], although another study found no significant difference between pregnant and non-pregnant women when normal and overweight pregnant women were pooled together.[13]

Visfatin, an adipocytokine, was found to be expressed in visceral fat.[14] However, a previous study reported that visfatin expression was found to be comparably expressed in both subcutaneous and visceral adipose tissues in obese subjects, but had a trend to be more expressed in subcutaneous adipose tissue in non-obese subjects.[5] It induces insulin secretion and activates insulin receptor, insulin receptor phosphorylation, and intracellular signaling revealing its insulin-mimetic properties.[15] Administration of glucose to humans caused an increase in circulating visfatin concentrations.[16] Circulating visfatin concentrations were increased in type 1[17] and 2 diabetes mellitus.[17,18] Concentrations of visfatin were found to be lower[10,19], comparable[5], or even higher[20] in obese compared to non-obese subjects. A previous study reported that visfatin concentrations were decreased in non-pregnant women compared to pregnant women even though their pre-pregnancy BMI was matched with non-pregnant women.[21] However, another study reported comparable serum visfatin levels between non-pregnant and pregnant women in the third trimester even though their pre-pregnancy BMI was matched with non-pregnant women.[22] Therefore, the changes of visfatin concentrations were inconclusive regarding obesity or pregnancy.

Omentin is an adipokine mainly secreted from visceral adipose tissue. It increases insulin-stimulated glucose uptake by adipocytes[23] and triggers signaling cascades of an intracellular second messenger, Akt, for multiple cellular functions including glucose metabolism.[24] Levels of serum omentin were lower in impaired glucose tolerance, type 2 diabetes, and obese subjects and were negatively correlated with insulin, HOMA-IR, and BMI.[5,25-27] However, another study found comparable serum omentin between obese and lean subjects.[10] Omentin was found to be lower in normal pregnant women compared to non-pregnant controls without BMI matching.[28]

Collectively, adiponectin, visfatin, and omentin are 3 interesting adipokines that are associated with insulin resistance and obesity. However, comparisons of their serum levels between non-pregnant and pregnant women between groups of their current BMI have not been determined. As BMI/obesity status could affect adiponectin, visfatin and omentin serum levels, and comparisons of their levels within the same BMI group might help to avoid this confounding factor. This study aimed to compare serum adiponectin, visfatin, and omentin levels between pregnant and non-pregnant women categorized into non-obese and obese groups according to their current BMI. Furthermore, the present study also aimed to compare serum adiponectin, visfatin, and omentin between non-obese and obese pregnant women. Comparisons of these adipokines differentiated between non-pregnant and pregnant women classified by BMI could reveal the changes of these peptides without the confounding effect of obesity.

MATERIALS AND METHODS

Subjects

The study protocol was approved by the Siriraj Institutional Review Board (Si.423/2013 for non-pregnant and Si.545/2015 for pregnant subjects) of the Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. Informed consent was collected from pregnant and non-pregnant females prior to the study. Sample size calculation for the comparison between the mean of 2 independent groups was obtained as follows: $n = 2 (Z_{\alpha/2} + Z_{\beta})^2/((\mu_1-\mu_2)/\sigma)2$, where $\alpha = 0.05$, 2 sided test, $Z_{\alpha/2} = 1.96$, $\beta = 0.2$, $Z_{\beta} = 0.842$, σ = common SD, $\mu_1-\mu_2$ = difference in mean, and n = sample size per group. Sample size was obtained from previously published papers as 36 per group for adiponectin[12] and 18 per group for visfatin.[22] In this study, there were 40 pregnant and 33 non-pregnant subjects. For non-pregnant women, subjects were recruited from female patients who underwent open abdominal surgery excluding those undergoing endocrine therapy (e.g., steroids, hormone replacement therapy, and thyroxine therapy) and having pregnancy, lactation, traumatic operation, malignancy diseases, operations related to endocrine diseases, severe abdominal inflammation, and menopause. In non-pregnant women, 23 subjects had myoma uteri, 4 subjects had ovarian tumor, 3 subjects had adenomyosis, and 3 subjects had endometriosis. For pregnant patients, subjects who underwent either cesarean or normal labor, had antenatal care and were

in labor at Faculty of Medicine Siriraj Hospital, were aged at least 18 years old, gestational age of at least 34 weeks, and singleton, were recruited. Subjects who had human immunodeficiency virus (HIV) infection, type 1 or type 2 diabetes mellitus, metabolic syndrome, hypertension, other endocrine disorders, previous history of chronic diseases, smoking habits, malignancies, pre-term membranes rupture, fetuses with malformations, and fetal distress during delivery, used drugs that might affect blood glucose and insulin levels, and/or received drugs for pre-term delivery risk, were excluded.

Demographic data of subjects

Age of subjects, gestational age of the pregnant group, and BMI of the non-pregnant group were obtained from questionnaires and medical records. For the pregnant group, their current BMI was calculated from pre-delivery body weight obtained from medical records subtracted by neonatal weight, placental weight, and estimated amniotic fluid weight. The estimated amniotic fluid weight was calculated as 6% of the gestational weight gain obtained from medical record as a previous study reported that amniotic fluid accounted for 6% of the gestational weight gain.[29] BMI classifications for Asians were applied[30] for both pregnant and non-pregnant women into either non-obese (BMI < 23 kg/m^2) or obese (BMI ≥ 25 kg/m^2) groups. In the non-pregnant and pregnant groups, there were 13 and 9 non-obese subjects, respectively and 20 and 31 obese subjects, respectively.

Blood collection

Fasting blood samples were collected in the morning for the non-pregnant group and before delivery for the pregnant group. Blood for glucose and insulin assay was sent to the central laboratory at the Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. Some of the samples were stored in clot activator tubes which were immediately kept in an ice bucket and transferred to the laboratory at the Department of Physiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. Blood sample was weight balanced and separated by centrifugation at 3000 round per minute (rpm), and stored at 4°C for 15 minutes. Serum sample was stored at -70°C until analysis of adiponectin, visfatin, and omentin.

Glucose and insulin assays

Plasma glucose and insulin were collected during the fasting state and were measured by the central laboratory at the Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. An enzymatic reference method with hexokinase (cobas integra® 800 analyzer) (Roche Diagnostics, Tokyo, Japan) was used for determination of plasma glucose and a sandwich electrochemiluminescent immunoassay (cobas® 8000 modular analyzer series module e602) (Roche Diagnostics, Tokyo, Japan) was used for determination of plasma insulin. Fasting plasma glucose and insulin levels were calculated to determine the levels of insulin resistance using the homeostasis model assessment of insulin resistance (HOMA-IR) which is calculated by multiplication of fasting glucose (mg/dl) and fasting insulin (μU/ml) divided by 405 and the quantitative insulin sensitivity check index (QUICKI) which is calculated by the inverse of the sum of the logarithms of the fasting insulin (μU/ml) and fasting glucose (mg/dl).

Analysis of serum adiponectin, visfatin, and omentin-1 levels

Serum adiponectin levels were analyzed by commercial enzyme linked immunosorbent assay (ELISA) kits (Phoenix Pharmaceuticals Inc., Burlingame, CA, USA). The range of adiponectin detection was 0.15-10 ng/ml with a minimum detectable level of 0.15 ng/ml, with 100% cross reactivity to adiponectin (human). Intra-assay variation was 4.73% for pregnant subjects and 2.55% for non-pregnant subjects. Inter-assay variation was 0.92%.

Serum visfatin levels were analyzed using enzyme immune assay (EIA) kits (Phoenix Pharmaceuticals Inc.). The detection range was 0.1–1,000 ng/ml and the minimum detectable level was 1.9 ng/ml with 100% cross reactivity to visfatin C-terminal peptide (human). Intra-assay variation was 4.65% for pregnant subjects and 6.85% for non-pregnant subjects. Inter-assay variation was 6.17%.

Serum omentin-1 levels were evaluated using ELISA kits (Elabscience Biotechnology Co. Ltd., Wuhan, People's Republic of China) with a detection range of 0.63-40 ng/ml, a minimum detectable level of 0.38 ng/ml, cross-reactivity to natural and recombinant HumanITLN1. Intra-assay variation was 3.00% for pregnant subjects and 6.19% for non-pregnant subjects. Inter-assay variation was 2.97%. The absorbance was read at 450 nm using a Synergy HT Multi-Detection Microplate Reader (BioTek Instruments, Inc., Winooski, VT, USA).

Statistics

Values are presented as mean ± standard error of mean (SEM) using SPSS 18.0 software. The Kolmogorov-Smirnov test was performed for normality test. For normally distributed data, comparisons between the

pregnant and non-pregnant groups or between the non-obese and obese groups were performed by student's unpaired t-test. For non-normally distributed data, the Mann-Whitney U test was performed. Comparisons between serum levels of adiponectin, visfatin, and omentin in non-obese and obese pregnant women were done using two-way repeated-measures analysis of variance (ANOVA) followed by the post-hoc least significant difference test. Statistical significance for all tests was set at $p < 0.05$.

RESULTS

Demographic and clinical parameters

Clinical parameters of the subjects including age, BMI, plasma levels of glucose and insulin, HOMA-IR, and QUICKI of pregnant women and controls, and gestational age of pregnant women categorized by BMI are shown as mean ± S.E.M in Table 1.

Serum levels of adiponectin, visfatin, and omentin in pregnant and non-pregnant subjects

Serum levels of adiponectin, visfatin, and omentin compared between pregnant and non-pregnant subjects are shown in Fig 1. Serum levels of adiponectin ($p<0.05$ all) (Fig 1A), visfatin ($p<0.01$ all) (Fig 1B), and omentin ($p<0.001$ all) (Fig 1C) were significantly lower in pregnant subjects when compared to non-pregnant subjects in overall, non-obese, and obese groups.

Serum levels of adiponectin, visfatin, and omentin in obese and non-obese pregnant subjects

Serum levels of adiponectin, visfatin, and omentin compared between obese and non-obese pregnant subjects are shown in Table 2. When compared obese to non-obese pregnant women, serum adiponectin and omentin were significantly lower ($p<0.001$), but serum visfatin was unchanged. When compared among serum levels of adiponectin, visfatin, and omentin in non-obese and obese pregnant women, levels of serum adiponectin were highest followed by serum omentin and serum visfatin, respectively in both obese and non-obese subjects ($p<0.001$ all).

TABLE 1. Clinical parameters including age, gestational age, BMI, plasma levels of glucose and insulin, HOMA-IR, and QUICKI of pregnant women and controls categorized by BMI. Values are expressed as mean ± S.E.M. *p<0.05, **p<0.01, ***p<0.001 compared between non-pregnant and pregnant subjects. †p<0.05, ††p<0.01 †††p<0.001 compared with the non-obese pregnant group. Note: For the pregnant group, their current BMI, calculated from pre-delivery body weight obtained from medical record subtracted by neonatal weight, placental weight, and estimated amniotic fluid weight, was used.

Parameters	Overall (n= 73)		Non-obese (n = 22)		Obese (n = 51)	
	Non-pregnant (n = 33)	Pregnant (n = 40)	Non-pregnant (n = 13)	Pregnant (n = 9)	Non-pregnant (n = 20)	Pregnant (n = 31)
Age (year)	44.9±1.3	29.1±0.9***	42.1±2.0	28.4±2.0***	46.8±1.5	29.2±1.0***
Gestational age (week)	-	38.1±0.2	-	37.6±0.2	-	38.3±0.2
BMI (kg/m^2)	25.7±1.2	27.3±0.7	20.5±0.6	21.0±0.5	30.26±1.1	29.2±0.6†††
Glucose (mg/dl)	88.6±3.1	75.3±1.4***	84.9±3.4	70.9±1.4**	91.1±4.7	76.6±1.7**,†
Insulin (μU/ml)	6.4±0.8	12.9±1.2***	4.6±0.9	7.8±1.2*	7.6±1.2	14.5±1.4***,†
HOMA-IR	1.5±0.2	2.5±0.3***	1.0±0.2	1.4±0.2	1.8±0.3	2.8±0.3**,†
QUICKI	0.39±0.01	0.35±0.01**	0.41±0.02	0.37±0.01	0.37±0.01	0.34±0.01**,††

TABLE 2. Serum adiponectin, visfatin, and omentin levels in non-obese and obese pregnant women. Values are expressed as mean ± S.E.M. ***p<0.001 compared between non-obese pregnant and obese pregnant women. †††p<0.001 compared with adiponectin within groups. ‡‡‡p<0.001 compared with visfatin within groups.

Adiponectin (ng/ml)		Visfatin (ng/ml)		Omentin (ng/ml)	
Non-obese	Obese	Non-obese	Obese	Non-obese	Obese
3211.3±396.6	2113.3±199.8***	5.3±1.1†††	4.7±0.6†††	22.5±3.3†††,‡‡‡	12.8±0.9***, †††,‡‡‡

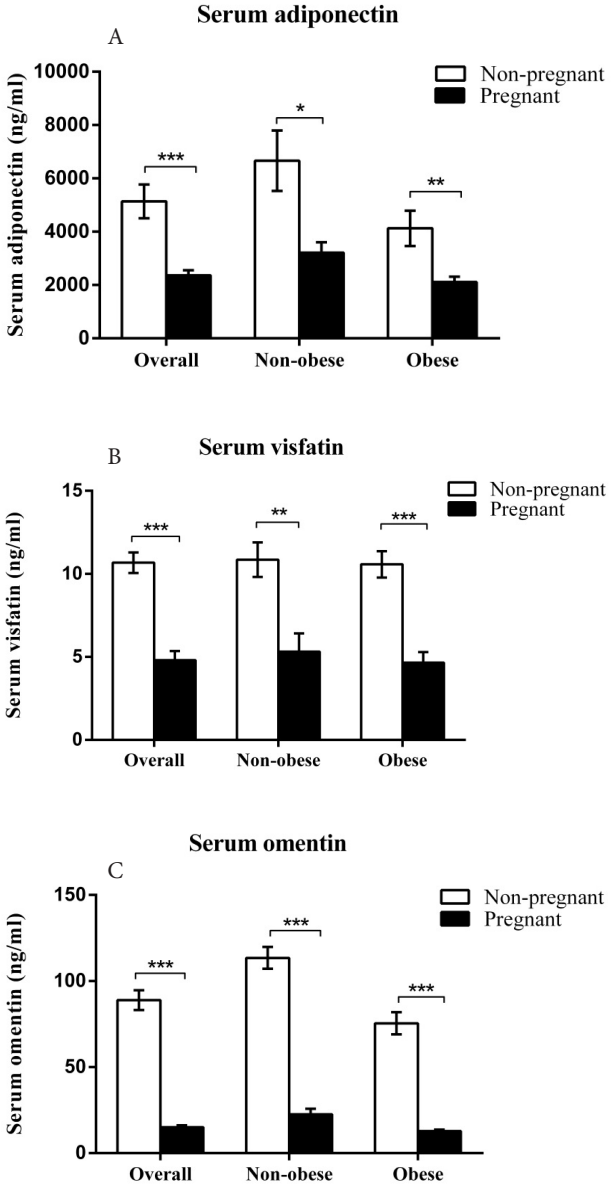

Fig 1. Serum adiponectin, visfatin, and omentin levels compared between pregnant and non-pregnant women in overall, non-obese, and obese subjects. Panels A, B, and C show serum adiponectin, visfatin, and omentin levels, respectively. Values are expressed as mean ± S.E.M. *p<0.05, **p<0.01, ***p<0.001 compared between non-pregnant and pregnant women.

DISCUSSION

This study focused on comparing serum levels of adipokines that are involved in increased insulin sensitivity including adiponectin, visfatin, and omentin in pregnant and non-pregnant women. In pregnancy, there are several physiological changes including increased maternal adiposity and insulin resistance which might lead to changes of these adipokines levels. As a result, in this study, subgroup analysis by BMI classification was performed to decrease confounding effects of obesity from pregnancy.

In this study, plasma glucose levels were significantly lower, but plasma insulin levels were significantly higher in pregnant when compared to non-pregnant women in overall, non-obese, and obese subjects. Blood samples of pregnant women were collected in the latent phase of labor with no strong uterine contraction. As labor is considered as a psychophysiological stress leading to increased corticotrophin releasing hormone and cortisol levels[31], this might interfere with glucose metabolism and/or adipokine levels. Normally, there is a rise of blood glucose levels throughout the labor process[32]; although in this study, blood was drawn during the latent phase of labor which might not lead to a significant increase in glucose levels. Furthermore, glucose levels of pregnant women were lower than non-pregnant women suggesting more nutrients were utilized by neonates that affected the mothers' fasting glucose levels.[33] In pregnancy, insulin-mediated glucose disposal declines by 40–60 %[34] which can lead to insulin resistance.[35] Furthermore, HOMA-IR was higher and QUICKI was lower in pregnancy compared to non-pregnancy, although statistical difference was found only in the obese group. When compared obese pregnant to non-obese pregnant subjects, glucose levels and QUICKI were significantly lower, but insulin levels and HOMA-IR were significantly higher suggestive of marked insulin resistance found in the obese subjects. In obese pregnant women, insulin resistance is amplified by excess lipolysis and release of free fatty acids from expanded

adipose tissue and increased secretion of inflammatory factors (such as IL-6 and TNF-α) and adipokines.[36]

In this study, serum levels of adiponectin, visfatin, and omentin decreased significantly in pregnancy compared to non-pregnancy in the overall, non-obese, and obese groups. For adiponectin, our result had a same trend to a previous study showing that serum adiponectin levels were significantly lower in pregnant (pre-pregnancy BMI <25, gestational age (GA) 10-40 weeks) compared to non-pregnant (BMI <25) women.[12] However, another study found no significant difference between pregnant and non-pregnant women when normal and overweight pregnant women were pooled together.[13] This inconsistency could be explained by the fact that the previous study pooled all weight together, unlike in this study where BMI was classified into obese and non-obese. Obesity status could affect serum adiponectin levels as they were found to be decreased in obese compared to non-obese humans due to the inhibition of adiponectin secretion from high levels of inflammatory cytokines including IL-6 and TNF-α in obese condition.[5] Therefore, lower adiponectin found in pregnant women in both non-obese and obese groups explicitly revealed its low levels in pregnancy regardless of obesity status.

For visfatin, our result was inconsistent with previous studies showing unchanged[22] or even higher[21] visfatin levels in pregnant women even though their pre-pregnancy BMI was matched with non-pregnant controls. These inconsistencies might be because previous studies[21,22] used pre-pregnancy BMI in the pregnant group to match BMI in the non-pregnant group, therefore confounding effects from weight gain in pregnancy, partly from increased adiposity, might affect the levels of visfatin. In this study, BMI of subjects was calculated from their current body weight subtracted by neonatal weight, placental weight, and estimated amniotic fluid weight. Since a previous study found that serum visfatin levels were correlated negatively with weight gain[5], the confounding effect of weight gain in the current study was dissected out. This approach could pinpoint that serum visfatin levels were in fact decreased in pregnancy status.

For omentin, our result was consistent with a previous study showing that omentin levels were lower in normal pregnant women (GA 24-28 weeks) compared to non-pregnant controls without BMI matching.[28] Pregnancy is considered as a state of increased visceral adiposity[37] which is known to decrease omentin levels[5,25] as visceral adipose tissue accretion can cause hepatic toxicity that might inhibit omentin secretion.[38] Collectively, as these adipokines have an effect to increase insulin sensitivity, the decrease in adiponectin, visfatin, and omentin levels in pregnancy might contribute to the cause of insulin resistance to increase blood glucose for the fetus regardless of the obesity status of the mother.

Our study limitation was that age was lower in pregnant women in both obese and non-obese groups. Previous studies reported that adiponectin levels rose with increasing age when male and female subjects were pooled together.[39,40] However, previous studies found that plasma adiponectin concentrations did not change significantly with age in females[40-42] while serum adiponectin levels increased with age in male subjects only.[40] Hence, age does not seem to affect adiponectin levels in women. For visfatin, a previous study revealed no association with age, gender, or BMI.[43] For omentin, previous studies showed either a significant negative correlation[44] or a weak positive correlation[45] between age and omentin levels in newly diagnosed female type 2 diabetic patients and age-matched controls. However, another study found no correlation between serum omentin and age in patients with polycystic ovary syndrome.[46] As a result, the association between omentin levels and age is still inconclusive.

When compared between obese and non-obese pregnant women, serum adiponectin and omentin levels were significantly lower in the obese group while serum visfatin levels were comparable in both groups. These results were consistent with a previous study in non-pregnant women showing low adiponectin and omentin levels, but unchanged visfatin levels in obese compared to non-obese subjects.[5] The decrease in adiponectin and omentin levels in pregnancy indicates that these peptides were reduced in increasing adiposity regardless of pregnancy. Obesity, a state of chronic inflammation with increased levels of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1ß[47], causes the release of free fatty acids and high levels of inflammatory cytokines resulting in inhibition of adiponectin and omentin secretion.[5] For the comparable levels of visfatin between obese and non-obese pregnant women, this result supports the previous study in non-pregnant women that visfatin levels were not affected by the body weight nor BMI.[5,43]

To compare serum adiponectin, visfatin, and omentin in pregnant women, serum adiponectin showed the highest levels in the circulation, followed by omentin and then visfatin, respectively suggesting that adiponectin might have the highest contribution to insulin sensitivity among these three adipokines. These results were in accordance with a previous study in the circulation of non-pregnant women[5] suggestive of similar level patterns of these hormones between pregnant and non-pregnant women.

In conclusion, serum adiponectin, visfatin, and omentin were significantly lower in pregnant compared to non-pregnant women in the overall, non-obese, and obese groups which might contribute to higher insulin resistance in pregnancy. Another study limitation was that the exact amniotic fluid weight could not be obtained. However, the estimated body weight in the pregnancy group in this study is a better representation of current BMI than pre-pregnancy BMI.

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