Serum Leptin, Adiponectin, Resistin, Visfatin and Inflammatory Cytokines in Normal Weight and Obese Women with Normal Pregnancy and with Preeclampsia

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Abstract: The changes in some adipocytokines were conducted on twenty five Saudi pregnant women complicated with preeclampsia (PE) at their third trimester. For comparison, a group of women with normal pregnancy was included. Serum leptin, adiponectin, resistin, visfatin, TNF-α and IL-6 concentrations were analyzed. In PE group with BMI <30, elevation in resistin was observed in comparison to BMI matched control group. On the other hand, decreased leptin with elevated adiponectin, resistin and TNF-α mean values were noted in PE with BMI ≥ 30 compared to their matched values in normal pregnancy with same BMI. The impact of obesity on maternal adipocytokin in PE showed no significant changes between the two PE groups with different BMI. The obtained changes demonstrated between PE and normotensive pregnancy for leptin, adiponectin, resistin and TNF-α may point out to their role in the development of PE. These changes were more exaggerated in obese subjects.
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1. Introduction

Preeclampsia (PE) is a sever complication in the second half of pregnancy that adversely affects maternal and fetal prognosis by increasing prenatal mortality and morbidity. PE may develop from 20 weeks of gestation up to 6 weeks postpartum and is considered early onset before 34 weeks of gestation. It shares risk factors with the metabolic syndrome including insulin resistance, subclinical inflammation and obesity [1, 2]. PE affects about 2.5 to ~ 3% of all Saudi pregnant women [3, 4]. Several reports have demonstrated that increased body mass index increases the risk of PE, and have suggested that obesity is an important risk factor for PE [5].

Human pregnancy is characterized by a progressive decrease in insulin sensitivity, which parallels the growth of feto-placental unit and facilitates the diversion of glucose to the fetus [6]. Normal gestational insulin resistance is further enhanced in pregnancy complicated with PE.

Insulin resistance in pregnancy and PE is mainly attributed to placental hormones [7] and increased maternal adiposity [8]. Adipose tissue is not only involved in energy storage but also functions as an endocrine organ that secretes various bioactive molecules. Adipokines are involved in a wide range of physiological processes including homeostasis, lipid metabolism, atherosclerosis, blood pressure regulation and insulin sensitivity.

Some adipokines have been shown to play a role in normal and in complicated pregnancies. In this respect, investigators have focused on several potential mediators of insulin resistance including adipokines [9,10]. During pregnancy, adipokines including leptin, adiponectin, resistin, visfatin, TNF-α and IL-6 are secreted by the placenta [11-16]. Besides regulating maternal energy metabolism and insulin sensitivity in normal pregnancy, adipokines have been implicated in PE. Increasing number of studies reported the role of these proteins in the deleterious insulin resistance associated with PE, however these reports are characterized by some inconsistency and contradictions [17].

The target of this study was to find out the changes in the levels of circulating leptin, adiponectin, resistin, visfatin and the infalmatory cytokines (TNF-α and IL-6) in normal weight and obese Saudi pregnant women with PE compared to BMI matched normotensive healthy pregnant women at third trimester of gestation period, to suggest the possible efficient marker(s) that may be involved in the development of PE.

2. Subjects and Methods

Subjects: This study was approved by Directorate of Health Affairs. Samples used for the present study were collected from Maternity and Children's Hospital, Al-Azizya, Jeddah and from Obstetrics & Gynecology Department, King Abdulaziz University Hospital, Jeddah, KSA. Signed informed consent and a questioner were obtained from each subject. All laboratory measurements were carried out at Carcinogenicity and Mutagenicity

Laboratory, King Fahd Medical Research Center, King Abdulaziz University.

The study was conducted on a total number of sixty two Saudi pregnant women. Twenty five of them were complicated with preeclampsia. The body mass index (BMI) at the time of enrollment ranged from 25-40 kg/m^2 (9 with BMI < 30 and 16 with BMI ≥ 30 kg/m^2) with a gestational age range from 29-40 weeks. For comparison, thirty seven normotensive women with normal pregnancy were included. Their pregnancy BMI at the time of sampling ranged from 24-40 kg/m^2 (15 with BMI < 30 and 22 with BMI ≥ 30 kg/m^2) and gestational age range from 28-39 weeks. Fasting blood glucose was measured for all subjects and all women were requested to undergo oral glucose tolerance test (OGTT) using 75g glucose.

PE was defined as two consecutive measurements of diastolic blood pressure ≥ 90 mmHg and systolic blood pressure ≥ 140 mmHg after 20 weeks gestation combined with proteinuria ≥ 2+ by dipstick or > 300 g protein in 24 hours urine collection as recommended by American Congress of Obstetricians and Gynecologists [18].

Exclusion criteria included: multiple gestation, diabetes mellitus, chronic hypertension, active labor. Gestational diabetes mellitus was also excluded since all subjects had normal glucose tolerance and normal fasting blood glucose. The normal pregnant controls had no signs of gestational complications.

Overnight fasting single venous blood sample was obtained from each subject during one of their routine medical examinations. Sera were separated and were subjected to determinations of adipocytokines levels. Specific kits purchased from Assaypro Company, Missouri, USA were used for determination of all adipocytokines except visfatin which was determined using kit provided by Phoenix Pharmaceuticals, INC. Company, California, USA. The sensitivity of leptin, adiponectin, resistin, visfatin, TNF-α and IL-6 kits were ~ 0.12 ng/ml, 0.5 ng/ml, 0.2ng/ml, 1.9 ng/ml, ~ 0.015 ng/ml and about 0.008 ng/ml, respectively.

Statistical analysis: Data analysis was performed using SPSS computer software program. Normality of the data was tested using sample Kolmogorov-Smirnov test. Significance of difference between groups mean values was tested using one way analysis of variance (ANOVA) in case of variables that distributed normally. In case of significant ANOVA test, multiple comparison, to test which group mean value differ from which, was performed using Bonferroni as a posthoc test. In case of abnormal distributed variables, Kruskal-Wallis test was used to find out groups significance. Statistical significance was set at $p \leq 0.05$. All values are expressed as mean value for each parameter ± standard error of the mean (X ± SE).

3. Results

Statistical analysis of the data indicated that all variables except IL-6 were distributed normally. Therefore, ANOVA test followed by multiple comparisons were applied to all variables except IL-6.

To evaluate the differences in adipocytokines levels between pregnant women with PE compared to those with normal pregnancy at third trimester, we studied two groups of PE with either BMI < or ≥ 30 kg/m^2. Another two groups of normal pregnant women with matched BMI were included for comparison.

At BMI < 30 kg/m^2, no significant differences were obtained between women with PE and their matched control for maternal and gestational ages and BMI, while both systolic and diastolic blood pressure were significantly elevated in PE women group (p = 0.005 and 0.0001, respectively), Table 1. Mean values of all studied adipocytokines showed no significant difference between PE and control pregnant women groups except resistin that showed significant elevation in PE (p = 0.0001), Table 2.

Obese pregnant women (BMI ≥ 30) with PE showed no significant differences regarding mean values of maternal age and BMI compared to their BMI matched control group, meanwhile, significant elevation were noted in PE group for gestational age (p = 0.007), systolic (p = 0.005) and diastolic (p = 0.0001) blood pressure ,Table 1. Leptin mean value was significantly lower in PE group (p = 0.029). Opposite trend was observed for adiponectin (p = 0.0001), resistin (p = 0.041) and TNF-α (p = 0.021). On the other hand, visfatin and IL-6 showed no significant differences between obese pregnancy complicated with PE and BMI matched normal pregnancy (Table 2).

To evaluate the impact of obesity on adipocytokines, we compared their levels in normal pregnancy and in pregnancy complicated with PE with different BMI.

For normotensive pregnant women with BMI < 30 and ≥ 30, no significant differences were noted for gestational age and blood pressure (either systolic or diastolic). On the other hand, maternal age was higher in normal pregnant group with BMI ≥ 30 (p = 0.013), Table 1. No significant differences between the two groups mean values for each of resistin, vifatin, TNF-α and IL-6, although leptin showed significant increase (p = 0.018) while adiponectin was decreased (0.0001) with obesity, Table 2.

Testing the impact of obesity on adipocytokines in PE indicated no significant differences between

normal and obese PE groups for all the studied hormonal parameters, (Table 2). It is worth mentioning that almost all the examined characteristics except gestational age, of the two PE groups showed no significant difference (Table 1).

Table 1: Characteristics of normotensive pregnant control and preeclampsia groups (mean ± SE).

Groups / Parameters	BMI < 30		*p* value	BMI ≥ 30		*p* value
	Normal	PE		Normal	PE	
MA (years) Range	27.8 ± 1.421 (18.0-40.0)	30.4 ± 2.539 (19.0-40.0)	NS*	33.9 ± 1.161 (21.0-43.0)	32.3 ± 1.380 (22.0-40.0)	NS* NS** 0.013***
BMI (kg/m^2) Range	26.0 ± 0.664 (24.0-29.9)	27.6 ± 0.826 (25.0-29.9)	NS*	34.1 ± 0.679 (30.4-40.0)	36.0 ± 1.221 (30.8-40.0)	NS* 0.0001** 0.0001***
GA (weeks) Range	31.9 ± 0.822 (28-37)	33.3 ± 0.453 (29-38)	NS*	32.4 ± 0.832 (28-39)	36.1 ± 0.574 (32-40)	0.007* 0.049** NS***
SBP (mmHg) Range	103.1 ± 2.436 (86-116)	145.9 ± 15.945 (140-164)	0.005*	109.8 ± 2.341 (91-128)	150.9 ± 8.651 (145-170)	0.005* NS** NS***
DBP (mmHg) Range	58.7 ± 1.678 (50-73)	93.3 ± 3.287 (95-113)	0.0001*	60.1 ± 2.328 (55-77)	95.2 ± 1.824 (90-110)	0.0001* NS** NS***

**p* value between PE groups and their BMI matched normal pregnancy. ***p* value between PE with BMI < and ≥ 30 kg/m^2.
****p* value between normal pregnancy with BMI < and ≥ 30 kg/m^2.

Table 2: Adipocytokines in normotensive pregnant control and preeclampsia groups (mean ± SE).

Groups / Parameter	BMI < 30		*p* value	BMI ≥ 30		*p* value
	Normal	PE		Normal	PE	
Lep.(ng/L) Range	5.46 ± 1.017 (1.51-15.11)	2.70 ±0.413 (1.01-4.22)	NS*	8.76 ± 1.161 (1.86-19.62)	5.66 ± 0.791 (2.03-12.79)	0.029* NS** 0.018***
Adip.(ng/ml) Range	45.60 ± 3.359 (14.74-60.53)	48.78 ±4.359 (25.00-78.57)	NS*	23.32 ± 1.956 (11.26-43.92)	38.10 ± 4.726 (3.65-48.68)	0.0001* NS** 0.0001***
Res. (ng/L) Range	7.12 ± 1.268 (0.70-17.44)	15.11 ± 1.650 (8.00-22.21)	0.0001*	7.35 ± 1.195 (1.10-22.34)	12.06 ±0.973 (8.21-19.61)	0.041* NS** NS***
Visf. (ng/L) Range	8.81 ± 0.765 (5.08-14.55)	10.01 ± 1.061 (5.05-13.91)	NS*	11.36 ± 1.527 (2.39-30.81)	8.27 ± 0.786 (2.56-13.59)	NS* NS** NS***
TNF-α (ng/L) Range	13.19 ± 0.769 (9.00-18.80)	13.36 ± 0.436 (11.50-15.50)	NS*	12.84 ± 0.348 (11.30-17.00)	15.23 ± 0.674 (11.00-19.90)	0.021* NS** NS***
IL-6 (ng/L) Range	5.36 ± 1.130 (1.0- 16.0)	3.25 ± 0.366 (1.0 – 6.0)	NS*	3.40 ± 0.237 (1.0 – 6.0)	3.51 ± 0.641 (1.0 – 11.0)	NS* NS** NS***

**p, **p and ***p* as indicated in Table 1.

4. Discussion

Insulin resistance in pregnancy and pregnancy complications is mainly attributed to placental hormones [7]. Many investigations have focused on several potential mediators of insulin resistance, including adipose tissue derived hormones, adipocytokines. During pregnancy adipocytokines are also secreted by placenta [19-21]. In the present study we confirmed the existence of important changes in some adipocytokines, namely; leptin, adiponectin, resistin and TNF-α in pregnant women with PE compared to BMI matched normotensive pregnant subjects.

Leptin, the protein product of *ob* gene [22], is mainly synthesized in adipose tissue [23]. The human placenta expresses high amounts of leptin messenger RNA (mRNA) and protein, while leptin receptors are abundant in the placenta, as well as the chorion and amnion [20, 24]. In the present study, maternal leptin concentrations were decreased in pregnant women with PE compared to their BMI matched women with normal pregnancy, being only significant in obese

subjects. Our results are consistent with other report [25] indicated changes in circulating maternal leptin only in obese pregnancies complicated with PE (but not in normal weight PE) compared to matched control healthy pregnancy. Maternal leptin concentrations in PE are characterized by some contradictions and inconsistency. While a group of researchers observed an increased leptin concentrations in PE with respect to normal pregnancies [17, 26-30], others observed reduced maternal leptin in PE [31] or no change [32, 33]. Moreover, in the present study no significant changes in circulating leptin were noted between normal weight and obese women with PE. On the other hand, significant elevation in leptin concentrations were detected in women with normal pregnancy as BMI increased, which may be due to increased mobilization of maternal fat stores to increase availability and to support transplacental transfer of lipid substrates [34]. Previous studies [35, 36] have demonstrated no significant association between BMI and leptin concentrations in PE, in contrast to healthy pregnant women. The authors suggested that other factors than the levels of adiposity may influence serum leptin concentrations in PE. The finding was further supported by Masuyama *et al.* [37] who reported no significant change in maternal leptin between overweight and normal weight pregnancies complicated with PE, which support our findings, this observation led the authors to suggest that leptin may play a role as a placenta- derived factor, as well as in the pathophysiology of PE. In the contrary, similar sera leptin in women with mild, sever and normotensive women were found [33]. In addition, second trimester leptin were found to be increased in PE women who had normal weight but decreased in overweight PE women [38]. All the previous observations and our results might indicate that there is no consensus, although the majority of studies found elevated leptin in PE. The discrepant data could be also due to several factors including different criteria for diagnosing PE, medications that influence energy balance, smoking or differences in GA, ethnic origin of the patients.

Adiponectin is the most abundant adipose tissue specific protein [39]. Adiponectin receptors are abundantly expressed in human placenta [12], whereas, adiponectin expression by the placenta during pregnancy is detectable [12, 17, 40]. In this study, significant elevation in maternal adiponectin concentrations was noticed in obese pregnancies complicated with PE compared to obese normal pregnancies, such significant difference was absent at lower BMI. Ramsay *et al* [41] reported an elevation in maternal adiponectin levels by nearly 50% in PE. This result was further supported by another study [42] indicating more than 50% elevation in maternal adiponectin in women with increased uteroplacental resistance (predicting high risk for PE) regardless of the later course and outcome of pregnancy [43]. It has been postulated that elevated fat secretion of adiponectin might contribute to the increased serum levels found in PE [44-46]. In the present study, no significant differences in adiponectin mean values were noted between normal weight and overweight pregnancies complicated with PE, however, we have demonstrated that overweight normotensive pregnant women showed significantly lower adiponectin levels than do normal weight pregnant women. Our results are in agreement with the study by Hendler *et al*. [25], who observed significant change in adiponectin only in obese subjects with PE, while in normal weight pregnant women with PE adiponectin did not show any significant variation when compared to normal control. Elevated maternal adiponectin in PE was noticed by others [17, 25, 47-49]. However some authors demonstrated reduced [19, 28, 50] while others failed to observe changes [51, 52] in maternal circulating adiponectin in PE relative to controlled pregnancies. Increased adiponectin concentrations in PE may be a feedback response to minimize excess fat accumulation in women. Increased adiponectin concentrations could be part of a physiological feedback mechanism improving insulin sensitivity and vascular function in PE. It may suppress the expression of adhesion molecules in vascular endothelial cells and cytokine production from macrophages [17, 41]. These effects might positively influence the preservation of normal blood pressure and insulin sensitivity.

Resistin is a hormone abundantly expressed in monocytes and macrophages and to a lesser extent by the adipocytes [53]. It is expressed in human placenta [9], up-regulated in the third trimester [19, 40, 54]. We have found higher maternal resistin in PE compared to their matched normal pregnancy with either BMI < 30 or ≥ 30. Our results are consistent with others [17, 55]. In contrast, other researchers reported decreased [19, 54, 56] or unchanged [25, 57] maternal resistin in PE. Increased resistin levels in PE was previously suggested to be due to progressive impairment of renal function and depends on glomerular filteration rates [58] and was not due to up regulation of placental gene expression [17]. In this study, no significant difference was found in circulating maternal resistin between normal weight and obese normal pregnancies, or between normal weight and obese pregnancies complicated with PE. Although some authors ruled out the role of resistin in the pathophysiology of PE and indicated that maternal BMI does not contribute to plasma resistin concentrations in pregnancy [25, 59], however we

suggest that resistin may be a promising marker for the prediction of PE early before its development. Further studies are required to find out changes in maternal resistin early during pregnancy and before the development of PE in order to predict its role in the pathogenesis of PE.

Visfatin, another adipocytokine, is highly expressed in visceral as compared to subcutaneous adipose tissue that promotes adipogenesis [60]. The presence of visfatin transcript in human fetal membrane has been reported [14, 61]. In the current study we failed to find out significant variation between maternal visfatin in PE and BMI matched normal pregnancy. It is worth mentioning that the impact of obesity on maternal visfatin levels in PE or in normotensive pregnancy was not significant. The lack of significance in maternal visfatin between PE and normal pregnancy might rule out its role in the development of PE and it could be due to decreased placental production. This view is supported by the presence of visfatin transcript and protein which was documented in human fetal membranes and the placenta [14, 61]. Maternal visfatin was found to be elevated in PE irrespectively of the severity of the disease [62]. Others reported decreased [63] or similar [64] visfatin in PE relative to normal pregnancy. Differences in the specificity of the visfatin immunoassay utilized might potentially contribute to the inconsistencies observed in patients with PE [65].

In the present study, TNF-α was overproduced in women with PE and BMI $\geq$ 30 as compared to their matched control. On the other hand, maternal IL-6 concentrations did not show significant differences in PE relative to control subjects. Similarly, higher maternal TNF-α has been demonstrated in PE [17, 35], which contributes to the endothelial damage occurred in PE and explain the mechanism underlying leukocyte activation in this disorder [66]. TNF-α is overproduced by the placenta in response to local ischemia or hypoxia, which may explain elevated levels of this inflammatory cytokine in PE [67,68], although others [69] reported that the elevated levels in PE might be a consequence rather than a cause for the disease. Studies carried out using experimental animals have demonstrated that a 2-fold increase of TNF-α concentrations in pregnant animals is sufficient to significantly increase mean arterial pressure [67,68] an effect potentially mediated by induction of endothelin [70]. Peracoli et al. [71] suggested that TNF-α could be a marker for the severity of PE due to the correlation between plasma concentrations and different stages of the disease.

Conclusion

This study confirms the existence of some changes in adipocytokines in PE compared to their matched values in normal pregnancies. Changes in adipocytokines were more pronounced in obese pregnant women with PE than normal weight pregnancy complicated with PE. Adipocytokines that showed significant changes included leptin , adiponectin, resistin and TNF-α. These results might point out to their role in the pathogenesis of PE, and might indicate their importance as non invasive efficient markers for the prediction of PE. We think that differences in studied populations may represent a possible reason for the reported inconsistency and contradictions that characterize the role of adipocytokines in PE. We were not able to observe changes in Visfatin concentrations between PE and normal pregnancy, which ruled out its involvement in the prediction of PE. Further studies are required to evaluate changes in the levels of leptin, adiponectin, resistin and TNF-α early during pregnancy and before the development of PE.

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