Maternal adiponectin and visfatin concentrations in normal and complicated pregnancies

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Summary

Objective: To evaluate the role of adiponectin and visfatin in the pathophysiology of pre-eclampsia (PE) and how their concentrations correlate with the severity of the disease and neonatal outcomes. *Study Design:* A prospective case-control study was carried out in 52 preeclamptic and 28 healthy pregnant women during the third trimester. The maternal plasma concentrations of adiponectin and visfatin were determined. Neonatal outcomes were also recorded. *Results:* Mean maternal plasma adiponectin concentrations in healthy pregnant women did not differ significantly from those of mild PE and severe PE groups. The plasma adiponectin levels of PE patients with small for gestational age (SGA) and those without SGA did not differ significantly, but the median plasma visfatin concentration of patients with SGA fetus was significantly higher if the patient was preeclamptic ($p = 0.036$). *Conclusion:* The severity of preeclampsia did not change the plasma levels of adiponectin and visfatin, but the median plasma visfatin concentration of patients with SGA fetuses were significantly higher if the patient was preeclamptic. Altered levels of adipocytokines strongly imply that the regulation of adipocytokines in PE is different and more complex compared to that in healthy pregnancy.

Key words: Pregnancy; Preeclampsia; Adiponectin; Visfatin; SGA fetuses.

Introduction

Changes in maternal metabolism occur during pregnancy in order to promote the increasing metabolic needs of the growing fetus and placenta. In normal pregnancy, alterations in the regulation of glucose metabolism lead to increased insulin resistance and changes in endothelial function [1]. The resistance to normal gestational insulin increases and also worsens during pregnancy complications that are associated with disturbed placental function (e.g., gestational diabetes mellitus (GDM), preeclampsia (PE) , and intrauterine growth restriction (IUGR)) [2,3].

PE is a severe complication of pregnancy. It is characterised by endothelial dysfunction (one of the early stages of atherosclerosis) and in part, shares features of the metabolic syndrome including exaggeration of insulin resistance, obesity, low-grade systemic inflammation, and atherosclerosis [4,5]. The insulin resistance and low-grade systemic inflammation may contribute to the pathogenesis of endothelial dysfunction. However, the underlying mechanisms and the molecules involved in PE are not yet certain [3].

One of the facets of pathophysiology of PE is the altered expression of adipocytokines such as leptin, tumor necrosis factor alpha α (TNF-α), interleukin 6 (IL-6), adiponectin, resistin, and visfatin [5,6]. To regulate maternal energy metabolism and insulin sensitivity during normal pregnancy [6], adipocytokines are expressed and secreted by adipocytes and the placenta [7].

Adiponectin, the most abundant adipose-tissue-specific protein, has anti-inflammatory, antiatherogenic, and insulin-sensitizing properties [8]. During normal pregnancy, maternal adiponectin levels were found to be decreased or remained unchanged [9-11]. There is an ongoing debate as to whether the levels of adiponectin in preeclamptic women increase, decrease, or remain the same when compared to gestational age-matched normal pregnancies [11-17].

The adipocytokine visfatin is highly-expressed in visceral adipose tissue which promotes adipogenesis and exerts insulin-mimetic effects [18]. The association of visfatin with both low-grade inflammation and impaired endothelial function has already been studied [19]. In type-2 DM, obesity, GDM patients when compared with control subjects, fluctuations or no change in blood concentration of visfatin is detected [20-22]. Although maternal serum visfatin had been previously demonstrated to be increased in some studies, other studies showed that visfatin levels decreased significantly in PE irrespective of maternal body mass index (BMI) [23-25]. Thus, the relationship between visfatin and PE is not fully apparent.

Growth restriction is more common in infants born to preeclamptic women and is more pronounced with increasing severity [3, 4]. Deterioration of utero-placental perfusion predicts a high-risk for fetal growth restriction (IUGR). Maternal plasma adiponectin levels were studied in growth-restricted fetuses and were lower than normal fetuses, possibly reflecting the state of inflammation and chronic stress in IUGR mothers [26]. In contrast to this, other studies demonstrated no significant alterations in maternal plasma adiponectin concentrations in IUGR pregnancies [27]. In third-trimester patients with IUGR, visfatin was found to be increased nearly two-fold in comparison to healthy pregnant women, but this was not verified by other studies [28, 29].

The levels of adipocytokines are altered in pregnancies

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complicated with PE and growth-restricted fetuses. In the current study, the plasma concentrations of two adipocytokines, visfatin, and adiponectin are measured in normal and preeclamptic pregnancies. In addition, the effects of maternal plasma adiponectin and visfatin concentrations in neonatal outcomes, such as growth restriction and APGAR scores, are investigated.

Materials and Methods

For this prospective case control study, 80 third-trimester pregnant women were recruited among patients managed at the antenatal clinic. The study protocol was approved by the Research Ethics Committee of the Uludag University School of Medicine. All participants gave written informed consent before taking part in the study. The study population consisted of 52 preeclamptic and 28 BMI-matched healthy pregnant women (Group 1; the control group). The preeclamptic patients were divided into subgroups according to the severity of preeclampsia: mild preeclamptic group (Group 2; 23 patients) and severe preeclamptic group (Group 3; 29 patients). In the study, previously normotensive women after 20th gestational weeks of pregnancy were classified as having mild PE if on at least two different occasions that were more than six hours apart, the systolic blood pressure measurement was above 140 mm Hg and diastolic blood pressure reading was above 90 mm Hg, and in a 24-hour urine collection, the proteinuria was more than 300 mg/l. Patients were classified as having severe PE if any of the following conditions observed: 1) on two occasions that were at least six hours apart, the systolic blood pressure measurement was above 160 mmHg or diastolic blood pressure measurement was above 110 mmHg; 2) in 24 hours, urinary protein excretion was more than five grams [9]); 3) 3+ and greater random urine dipstick testing; 4) in 24 hours, urinary discharge was less than 500 ml; and 5) cerebral or visual disturbances, pulmonary edema or cyanosis, or epigastric or right upper quadrant pain was observed. Gestational age was calculated by menstrual history and by ultrasound data obtained during the first or second trimester of pregnancy in case of presence of irregular cycles. Gestational age was calculated by the number of weeks. The BMI was calculated by dividing the weight by squared height (kg/m^2). Women with chronic hypertension, diabetes, preexisting vascular and chronic renal diseases, and present or prior GDM were excluded from the study. Similarly, those women who had multiple gestations and were in active labor were excluded from the study. The diagnosis of SGA was based on ultrasonographic estimated fetal weight and confirmed by a birth weight below the 10th percentile of gestational age [29, 30]. The diagnosis of intrauterine growth restriction used for fetuses who were SGA and who showed other evidence of chronic hypoxia was based on Doppler assessment [31]. All patients with a fetus whose fetal weight was below 10th percentile underwent Doppler velocimetry measurements of the umbilical arteries. Umbilical artery doppler velocimetry was considered abnormal if either the pulsatility index (PI) was above the 95th percentile for gestational age or abnormal waveforms were present (i.e., absent or reversed end-diastolic velocities) [32]. The fetus of preeclamptic patient which was growth-restricted and showed abnormal Doppler values, was considered as intrauterine growth-restricted and such patients were classified into the severe preeclamptic group. If the fetus of preeclamptic women was SGA but had normal Doppler values, then these fetuses were grouped in SGA of mild PE group. The birth weight of all neonates was recorded and those below 10th percentile were considered as SGA. Moreover, APGAR scores at one and five minutes after birth and delta APGAR scores (the difference between the APGAR score of five minutes and that of one minute) of all neonates were recorded.

The blood samples, obtained from the antecubital area, were collected between 8 a.m. and 9 a.m. after a fasting period of 12 hours. A three ml venous blood sample from each patient was drawn into serum tubes. At the time of sampling, none of them was in labour. Serum was separated by centrifugation at 4,000 cycles/min for ten minutes and stored at –80ºC until further analysis. Plasma adiponectin concentrations were measured by BOSTER Immunoleader Human ELISA Kit *(BOSTER Biological Technology Co.)* with standard sandwich enzyme-linked immunesorbent method and visfatin levels were *(RayBiotech, Inc Norcross GA, USA)* measured by competitive enzyme immunoassay method.

Statistical analyses were performed with SPSS, version 13 (SPSS, Chicago, IL). Normality of the data was tested by using the Shapiro-Wilk test. Maternal age was compared among groups by ANOVA test. Post hoc comparisions were performed with Bonferroni test. For non-normality distributed data, Kruskal Wallis and Mann Whitney tests were performed for the comparisons of the groups, where appropriate. Maternal age was represented with mean value and standard deviations, while discrete and non-normality distributed variables were represented as median (minimum-maximum). Categorical variables between groups were compared by Pearson Chi square test with Yates correction. A p value smaller than 0.05 was considered statistically significant.

Results

The demographic and clinical characteristics of the study groups are presented in Table 1. The median gestational age at blood sampling was not different between the control group and the mild PE group, but differed significantly between the mild PE and severe PE groups (p = 0.005). The preeclamptic patients were younger than normal control patients (p = 0.003). The BMI values of patients did not differ between the preeclamptic groups and the control group (p = 0.442). When compared with control patients, the systolic and diastolic blood pressures were significantly higher in preeclamptic patients (p < 0.001). The creatinine and blood urea nitrogen (BUN) levels were higher in the severe PE group compared to the control group (p < 0.001, both groups). The babies of preeclamptic patients had a lower neonatal weight compared to the babies of normotensive pregnant group (p < 0.001). In mild preeclamptic patients, the incidence of SGA was 43.5% and it was not significantly different from the incidence of SGA in normal pregnancies (21.4%, p = 0.212). In severe preeclamptic group, 11 of 29 women had intrauterine growth-restricted neonate (37.9%). This was not significantly different between the mild and severe PE groups. The cesarean rate of the severe PE group was higher than those of the other two groups. This difference reached a statistically significance for control group (p = 0.002) (Table 2). However, that difference between the mild PE group and the control group was not statistically significant (p = 0.260). The APGAR score in one minute and the delta APGAR score of the control group were statistically significantly higher

Table 1. — *The clinical characteristics of control, mild, and severe preeclampsia groups*.

	Group 1 (n = 28)	Group 2 (n = 23)	Group 3 (n = 29)	*p* value
Maternal age (years)	30.25 ± 4.25	25.74 ± 4.33	27.41 ± 5.09	0.003
BMI (kg/m^2)	28.71 (21.83-45.17)	28.84 (16.65-44.44)	28.76 (22.76-41.45)	0.442
Gravidy	2.00 (1.00-5.00)	1.00 (1.00-4.00)	1.00 (1.00-5.00)	0.033
Parity	0.50 (0.00-2.00)	0.00 (0.00-3.00)	0.00 (0.00-4.00)	0.032
Gestational age at sampling (wks)	33.00 (28.00-39.00)	34.00 (28.00-38.00)	30.00 (28.00-39.00)	0.009
Gestational age at delivery (wks)	39.00 (36.00-41.00)	36.00 (28.00-38.00)	31.00 (28.00-40.00)	< 0.001
Systolic blood pressure (mmHg)	110.00 (85.00-130.00)	150.00 (130.00-190.00)	170.00 (140.00-200.00)	< 0.001
Diastolic blood pressure (mmHg)	70.00 (60.00-90.00)	100.00 (90.00-120.00)	100.00 (90.00-120.00)	< 0.001
Mean arterial pressure (mmHg)	97.00 (77.00-113.00)	133.00 (120.00-166.00)	146.00 (123.00-166.00)	< 0.001
BUN	15.50 (9.50-31.00)	23.00 (12.50-36.00)	27.00 (13.00-102.60)	< 0.001
Creatinine	0.60 (0.44-0.90)	0.70 (0.55-1.10)	0.78 (0.60-3.21)	< 0.001
	Pairwise Comparisons			
	Group 1 - Group 2	Group 1 - Group 3	Group 2 - Group 3	
Maternal age (years)	0.001	0.027	0.206	
Gravidy	0.111	0.012	0.367	
Parity	0.263	0.009	0.154	
Gestational age at sampling (wks)	0.361	0.025	0.005	
Gestational age at delivery (wks)	< 0.001	< 0.001	0.001	
Systolic blood pressure (mmHg)	< 0.001	< 0.001	0.004	
Diastolic blood pressure (mmHg)	< 0.001	< 0.001	0.013	
Mean arterial pressure (mmHg)	< 0.001	< 0.001	0.002	
BUN	0.008	< 0.001	0.016	
Creatinine	0.019	< 0.001	0.061	

Group 1: normotensive pregnant, Group 2: mild preeclampsia, Group 3: severe preeclampsia.
Cell values were representes as *mean ± standart deviation* and *median (minimum-maximum)*.

Table 2. — *The neonatal characteristics of control, mild, and severe preeclampsia groups*.

	Group 1 (n = 28)	Group 2 (n = 23)	Group 3 (n = 29)	*p* value
Birth weight (g)	3300 (1920-4400)	2150 (780-3950)	1280 (670-4850)	< 0.001
Apgar Score (one minute)	10.00 (7.00-10.00)	8.00 (3.00-10.00)	4.00 (0.00-10.00)	< 0.001
Delta APGAR score*	0.00 (0.00-2.00)	1.00 (0.00-4.00)	2.00 (-1.00-6.00)	< 0.001
SGA	6 (21.40)	10 (43.50)	11 (37.90)	0.212
Cesarean delivery	14.00 (50.00)	16 (69.60)	26 (89.70)	0.005
Fetal complication	1 (3.60)	9 (39.10)	25 (86.20)	< 0.001
	Pairwise Comparisons			
	Group 1 - Group 2	Group 1 - Group 3	Group 2 - Group 3	
Birth weight (g)	< 0.001	< 0.001	0.004	
Apgar Score (one minute)	< 0.001	< 0.001	0.002	
Delta APGAR score*	< 0.001	< 0.001	0.179	
Cesarean delivery	0.260	0.002	0.087	
Fetal complication	< 0.001	0.003	0.001	

Group 1: normotensive pregnant, Group 2: mild preeclampsia, Group 3: severe preeclampsia.
Cell values represented as *median (minimum-maximum)* and *n (%)*.
*Delta APGAR Score: APGAR of five minute – APGAR of one minute.

Table 3. — *Visfatin and adiponectin levels in control, mild, and severe preeclampsia groups*.

	Group 1 (n = 28)	Group 2 (n = 23)	Group 3 (n = 29)	*p* value
Plasma adiponectin	34.66 (4.95-49.81)	29.66 (3.04-44.96)	25.70 (3.04-49.94)	0.140
Plasma visfatin	37.11 (5.59-119.94)	47.49 (1.20-107.18)	57.38 (3.76-119.94)	0.168

Group 1: normotensive pregnant, Group 2: mild preeclampsia, Group 3: severe preeclampsia.
Cell values represented as *median (minimum-maximum)* and *n (%)*.

than those of both preeclamptic groups ($p < 0.001$, both groups). Fetal complication rates (e.g., admission to the neonatal intensive care unit, need for neonatal resuscitation, etc.) were higher ($p < 0.001$) and the APGAR scores of neonates were significantly lower than those of the other groups ($p < 0.001$) in the severe PE group (Table 2).

Plasma adiponectin concentrations in normal pregnancies (median 34.66 ng/ml [4.95-49.81 ng/ml]) did not differ significantly from those of mild PE (median 29.66 ng/ml [3.04-44.9 ng/ml]) and severe PE groups (median 25.70 ng/ml [3.04- 49.94 ng/ml]) ($p = 0.140$) (Table 3). When compared with the normotensive group (37.11

Table 4. — *Correlations of visfatin and adiponectin levels.*

	Normotensive pregnant		*Mild preeclampsia*		*Severe preeclampsia*	
	Visfatin *p* value	Adiponectin *p* value	Visfatin *p* value	Adiponectin *p* value	Visfatin *p* value	Adiponectin *p* value
Gestational age at delivery	0.711	0.906	0.936	0.697	0.153	0.585
Birth Weight	0.626	0.278	0.782	0.371	0.815	0.916
BMI	0.878	0.106	0.802	0.78	0.061	0.202

Table 5. — *The maternal visfatin and adiponectin levels and association with SGA.*

		Visfatin	Adiponektin
SGA no	Normotensive group n = 22	46.37 (7.59-119.94)	35.65 (5.75-49.81)
	Preeclampsia group n = 31	45.57 (1.20-119.94)	28.83 (3.41-41.87)
	p value	0.957	0.085
SGA yes	Normotensive group n = 6	27.22 (5.59-78.77)	32.45 (4.95-38.22)
	Preeclampsia group n = 21	72.38 (12.06-119.94)	25.94 (3.04-29.94)
	p value	0.036	0.512

ng/ml), the median plasma visfatin levels were not significantly different ($p = 0.168$) in the mild PE (47.49 ng/ml) and the severe PE (57.38 ng/ml) (Table 3). There were no significant differences among the preeclamptic patients in terms of the median maternal plasma adiponectin concentration and the median visfatin concentration between the mild and severe PE groups ($p = 0.140$). The authors were not able to demonstrate any significant correlation between adiponectin and visfatin levels and the BMI values of patients, birth weight, and gestational age at birth (Table 4). The plasma adiponectin levels of PE patients with SGA and those without SGA did not differ significantly ($p = 0.978$) (not shown). The median plasma visfatin concentration of PE patients with SGA fetuses (21 patients) (45.57 ng/ml) was lower than that of PE patients without SGA fetuses (72.38 ng/ml); but this difference was not statistically significant ($p = 0.091$) (not shown). The median plasma visfatin concentration of patients with SGA fetus was significantly higher if the patient was preeclamptic (72.38 ng/ml in PE patients vs 27.22 ng/ml in control patients, $p = 0.036$) (Table 5).

Discussion

The results of the current investigation revealed no difference in plasma concentrations of adiponectin and visfatin between preeclamptic and healthy pregnant women. In addition, the severity of PE did not affect the values of plasma adiponectin and visfatin. Between the preeclamptic patients with and without a SGA neonate, no significant difference was observed in both the median maternal plasma adiponectin concentration and the median visfatin concentration level, but the plasma visfatin levels were higher in patients with SGA who had PE concomitantly than normotensive group.

It was found that circulating adiponectin concentrations, in contrast to other adipocytokines, were decreased in insulin-resistant states and obesity-related metabolic disorders including type 2 DM and coronary vascular disease [6]. Previous studies concerning adiponectin plasma levels in pregnant women revealed incompatible results. During normal pregnancy, maternal adiponectin levels were decreased [9] or remained unchanged [10, 11]. Although insulin resistance was shown to be increased dramatically during gestation [10], no significant alteration in adiponectin levels was observed throughout pregnancy.

Some studies showed that adiponectin plasma levels were lower in preeclamptic women than normotensive women [11, 12]. The study by Fasshauer [23] reported an association between hypoadiponectinema in early pregnancy and subsequent development of preeclampsia. The decrease in plasma adiponectin levels was associated with the inhibition of adiponectin synthesis by an increase in glucocorticoids, sympathetic activity, and proinflammatory cytokines phenomena. These three characteristics of normal pregnancy were shown to be further increased in PE [12]. The increase in serum levels of adiponectin in preeclamptic women in the third trimester was first shown by Ramsay [16]. However the increased adiponectin levels in plasma of PE women could not be verified in adipose tissue mRNA levels of adiponectin [13]. Ramsay argued that adiponectin released during pregnancy could be a physiologic response representing a regulatory feedback to minimize fat accumulation in tissues of PE women, and inhibiting inflammatory processes that lead to endothelial damage and dysfunction in PE [13, 16].

Adiponectin resistance [15], alteration of renal functions in PE women [13], a difference in the rate of high- to low-molecular-weight oligomers of adiponectin in PE women [9] may possibly explain the increased levels of adiponectin in PE women. Those different findings might be due to the differences between study populations in terms of body fat, insulin sensitivity, and gestational weeks in which the blood sample was withdrawn. The results of previous studies suggested that fat tissue and obesity-related insulin resistance may play a role in the development of PE in obese pregnant women and probably mask the effects of compensatory raise in adiponectin levels at established PE [17].

On the other hand, some studies found no change in maternal adiponectin levels in PE [14, 17]. Even during early weeks of pregnancy, adiponectin levels did not change before the onset of clinical signs of PE [17]. In the presented study, the authors did not find any difference in plasma adiponectin levels of PE patients compared to normal controls. It was shown that adiponectin expression and secretion tend to the regulation of numerous factors. Whether or not placental adiponectin production contributes to maternal or fetal adiponectin levels

remains to be determined. Adiponectin receptors were found to be abundantly expressed in human placenta [7]. However, adiponectin expression by the placenta during pregnancy is debatable and the production of placental adiponectin may not be strong enough to influence maternal adiponectin levels [6]. During pregnancy, adiponectin gene expression has been proved to be regulated in specific tissues [30]. No significant difference of adiponectin mRNA expression was observed in adipose tissue between PE women and normal controls [13], but placental adiponectin expression has been recently found to be decreased in severe PE [33].

Adiponectin is known to have a number of isoforms. These include low-, middle- and high-molecular-weight (HMW) forms [34]. The HMW form of adiponectin is the most active in mediating insulin sensitivity and glucose tolerance [35, 36]. Since most studies of clinical material use ELISA or RIA kits, none of them adequately distinguishes between various complexes of adiponectin. Thus, future research should focus on the role of different forms of adiponectin in PE.

In non-pregnant state, plasma adiponectin concentrations, unlike other adipocytokines, are inversely correlated with adiposity [9]. There is no consensus about the BMI effect on adiponectin levels in pregnant women. Although there exists studies reporting no correlation between adiponectin levels and gestational BMI [10], Hendler [14] stated that PE women with normal BMI had higher adiponectin levels than normotensive women and that adiponectin levels were decreased in women with a BMI greater than 25 kg/m^2. Because BMI correlation with adiponectin concentration is debatable, the groups in the present study were well-matched with respect to this variable ($p = 0.442$).

PE increases the fetal risk of being born SGA particularly in cases of early and recurrent disease [3, 4], but only one-third of fetuses of preeclamptic women are growth-restricted despite low placental perfusion [4]. Adiponectin can be assumed to play a regulatory role in fetal growth considering its importance in insulin metabolism and the fact that fetal growth is controlled by glucose and insulin to a great extent [37]. A positive correlation between cord blood adiponectin levels and birth weight has been shown in many studies [37, 38]. Therefore, it was reasonably speculated that augmented insulin sensitivity by adiponectin might be the cause of positive association of birth weight and adiponectin concentrations [39]. Contrarily, some studies demonstrated the lack of significant differences in fetal adiponectin concentrations between SGA cases and AGA controls. This is probably due to the lack of insulin resistance present in early life [20, 23, 40]. A previous study showed lower maternal adiponectin levels in the growth restricted state. This might be explained by the fact that the state of inflammation and chronic stress in IUGR mothers predisposes them to develop insulin resistance [23]. In this presented study, no significant correlations between maternal plasma adiponectin levels of women and neonatal birthweights or gestational ages were observed. In addition, the authors did not find any significant difference in adiponectin plasma levels of PE patients with or without SGA. In the SGA group, plasma adiponectin levels remained unchanged even in the presence of PE. Maternal serum adiponectin levels seem to be only a marker for maternal fat mass but do not play a major role in fetal growth [37].

Hyperinsulinemia, glucose intolerance, and lipid abnormalities are characteristics of physiological insulin resistance in the second half of pregnancies [1, 2]. Visfatin may play a role in PE since it promotes adipogenesis and exerts insulin-mimetic effects. In PE women, plasma visfatin levels were found to be markedly increased compared to normal pregnant women [23, 24]. However, in contrast to those studies, some studies showed decreased plasma visfatin levels in PE patients with comparable BMI [25]. Although increased synthesis or decreased degradation of visfatin in pregnancies was speculated to contribute in the pathogenesis of PE, this however has not yet been verified [24]. In contrast to these findings, the authors found no significant differences in maternal circulating visfatin concentrations between pregnant women with and without PE. In agreement with these findings, a study on third-trimester women demonstrated that the median maternal plasma visfatin concentration did not differ significantly between patients with PE and those with normal pregnancy [28]. Hu argued that a down-regulation of visfatin expression in adipose tissue may be responsible for decreased visfatin levels and pointed out the involvement of visfatin in excessive insulin resistance in the clinical state of PE [25], but in this study, circulating visfatin in the severe PE group was not significantly different from that in the moderate PE group. These apparent discrepancies between studies might be due to the differences in study population, sample size, or research design.

Fasshauer *et al*. reported higher visfatin concentrations in IUGR neonates compared to AGA counterparts in third-trimester pregnancies and suggested visfatin as a novel marker up-regulated in women with IUGR [27]. This is in agreement with another study where circulating maternal visfatin levels were found to be higher in IUGR women than those in the AGA group [29]. In that study, altered maternal endocrine environment in pregnancies that are complicated with IUGR were argued to be the reason for higher visfatin levels, and higher visfatin concentrations were hypothesized to serve as an early marker with prognostic value for later development of the metabolic syndrome in growth-restricted fetuses [29]. The population of the aforementioned study included patients with GDM and extreme obesity which might have affected the results. In the present study group, plasma concentrations of visfatin with SGA fetuses who were preeclamptic were higher than those of normotensive patients. Altered fetal development of adipose tissue in SGA fetuses may interfere with plasma visfatin concentrations. In a study where plasma visfatin concentrations of preeclamptic women with and without SGA were compared, it was reported that the presence of

a SGA neonate in PE patients was not accompanied by significant alterations in maternal circulating visfatin concentrations. This suggested that PE overwhelmed the effects of the presence of a SGA neonate on maternal plasma visfatin concentration [28]. This was compatible with the results in the present study where similar plasma visfatin levels were observed in preeclamptic women with and without a SGA neonate.

The mechanisms leading to increased visfatin levels in women with IUGR are yet unclear. In a previous study, visfatin was speculated to play a role in the glucose transfer from maternal to fetal circulation based on histological examination of the placenta [41]. In a recent study, visfatin mRNA expression has been shown to be significantly related to TNF-α and IL-6 mRNA expression in placental tissues [42]. Since TNF-α and IL-6, negative regulators of visfatin expression in fat [43], increase in pregnancy-related disease, they unlikely intervene up-regulation of visfatin plasma levels by induction in fat. However, in addition to fat, a wide range of other tissues can produce visfatin. Thus, the modulation of visfatin expression by insulin, TNF-α, and IL-6 might be tissue-specific [44]. The presence of PE in SGA patients is known to increase the levels of plasma visfatin concentrations and this might be related to placental functional deterioration in PE.

Altered levels of adipocytokines strongly imply that the regulation of adipocytokines in PE is different and more complex compared to that in normal pregnancy. Despite paradoxical and controversial reports of adiponectin levels in PE, adiponectin is attracting considerable interest as a potential biochemical indicator.

The reported study has several limitations. The cross-sectional nature of the study and relatively small number of participants included did not enable the authors to come up with a line of reasoning for the association between pregnancy and regulation of adiponectin levels during pregnancy. In order to overcome the inherent limitations of the study, the authors carefully examined the participants for possible maternal parameters that may affect adiponectin levels (i.e., BMI, GDM, age, and more). In conclusion, the authors recognized that further research is necessary to elucidate the pathophysiological role of adipocytokines in normal and complicated pregnancies, particularly defining the risk of future development of maternal insulin resistance.

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