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## Maternal Serum Level of Adiponectin and Macroscopic Changes of Placentae in Preeclampsia

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### Abstract

The objective of the present study was to measure the serum level of adiponectin in preeclamptic Egyptian pregnant women and find the possible correlations of maternal adiponectin level to measured insulin resistance in such case and to macroscopic features of placentae included in this study.

The study population consisted of 30 preeclamptic patients and 30 matched healthy pregnant women during the third trimester.

The results revealed that preeclamptic women were more insulin resistant with a significant decrease in adiponectin level compared with healthy controls. Correlation analysis presented a significant negative correlation between adiponectin levels and measured insulin resistance among preeclamptic women. Pregnant women with preeclampsia had lower placental weight and decreased number of cotyledons with marginal insertion of umbilical cord. The present study did not show any correlations between adiponectin levels versus macroscopic features of placentae among preeclamptic mothers.

It can be concluded that preeclamptic mothers are more insulin resistant, which was reflected through increased HOMA-IR value; this relationship postulates that insulin resistance may be one of the casual pathways of preeclampsia. Hypoadiponectinemia may be one of the possible etiologies of preeclampsia. Preeclamptic placentae exhibited definite morphological changes which may be attributed to the vascular insufficiency of placenta.

**Keywords:** Adiponectin, Preeclampsia, Insulin resistance, Placenta

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## 1. Background

Preeclampsia (PE) is a multi-system disorder of pregnancy, which is characterized by new onset hypertension (systolic and diastolic blood pressure of  $\geq 140$  and  $90$  mm Hg, respectively, on two occasions, at least 6 hours apart) and proteinuria (protein excretion of  $\geq 300$  mg in a 24 h urine collection, or a dipstick of  $\geq 2+$ ), that develop after 20 weeks of gestation in previously normotensive women [1].

Insulin Resistance (IR) syndrome is comprised of a cluster of metabolic abnormalities that confer increased risk of diabetes, hypertension and cardiovascular disease [2]. Several features of the insulin resistance syndrome, such as obesity, hypertension, dyslipidemia, systemic inflammation and impaired fibrinolysis, are also associated with preeclampsia. In addition, women with polycystic ovary syndrome or gestational diabetes, two disorders characterized by insulin resistance, are at increased risk of preeclampsia. Collectively, these data suggest that insulin resistance may contribute to the pathogenesis of preeclampsia [3].

Adipose tissue represents an active endocrine organ that releases a large number of bioactive mediators (adipokines) that signal to organs of metabolic importance including brain, liver, skeletal muscles and the immune system thereby modulating hemostasis, blood pressure, lipid and glucose metabolism and inflammation. These adipokines include adiponectin, leptin and others [4].

Adiponectin is an abundant protein hormone which belongs to a family of so-called adipokines. Adiponectin is expressed mostly by adipocytes and is important regulator of lipid and glucose metabolism. It is established that adiponectin is an insulin-sensitizing hormone with anti-diabetic, anti-inflammatory and anti-atherogenic properties [5].

Plasma levels of adiponectin, which is derived mainly from adipose tissue and possibly from placenta, is inversely correlated with insulin resistance and is consequently reduced in obesity and Type 2 diabetes, but it is paradoxically irregular in preeclampsia [6-8].

The aim of this present study was to measure the plasma levels of adiponectin in normotensive and preeclamptic Egyptian pregnant women and the

possible correlations of adiponectin levels to the measured insulin resistance in such cases and to the macroscopic features of the placentae included in this study.

## 2. Patients and Methods

### 2.1 Patients

This study was conducted in the departments of Obstetrics and Gynecology in Benha, Mansoura Universities Hospitals and Biochemistry Department Medical Research Institute, Alexandria University. It included sixty pregnant women, recruited from the attendants of the outpatient clinic of Obstetrics Gynecology Department during their third trimester of pregnancy. A written and verbal consent has been obtained from all participants in the study according to the Instructions and Guidelines of the Ethics Committee of the Medical Research Institute, Alexandria University. They were divided into two groups: -

Group I: Consists of thirty pregnant women with no obstetric or medical complications of pregnancy, no medications were given during pregnancy apart from tonics and iron.

Group II: Consists of thirty preeclamptic women with blood pressure  $140$  mmHg or higher systolic or  $90$  mmHg diastolic after 20 weeks of gestation in women with previously normal blood pressure and proteinuria  $+1$  or greater on urine dipstick test.

Exclusion criteria were patients with combined chronic diseases e.g., diabetes mellitus, autoimmune disease, thyroid, heart, chest, kidney, liver diseases and patients with preexisting chronic hypertension or taking hormonal therapy.

### 2.2 Methods

All subjects included in this study were asked for complete history and subjected to clinical and obstetrical examination. During fasting condition, urine and blood samples were collected from each case.  $5$  mL blood from each case was taken and allowed to clot for 30 minutes before centrifugation for 15 minutes at  $1000 \times g$ . Serum collected and stored in three aliquots at  $-20^{\circ}$  C.

Biochemical studies:

1-Creatinine levels [9]: Quantitative determination of urinary creatinine was performed

according to the manufacturer's instructions (Diamond Diagnostics) with detection limit 0.09 mg/dL.

2-Albumin levels [10]: Quantitative determination of urinary albumin was measured turbidimetry as to manufacturer's instructions (Biosystems S.A. Costa Brava 30, Barcelona, Spain).

Calculation of urinary albumin creatinine ratio (UACR): Usually expressed as milligram of albumin excreted per gram of urinary creatinine [11].

3-Fasting glucose levels [12]: It was measured using enzymatic colorimetric glucose oxidase method (kit purchased from spin react, Spain) with detection limit from 1 mg/dL to linearity limit 500 g/dL.

4-Insulin levels [13]: Concentration of insulin was measured using ELISA method according to the manufacturer's instructions (DRG International Inc., USA, (EIA-2935)).

Calculation of Insulin resistance: It was calculated by using homeostasis model assessment of insulin resistance (HOMA-IR) [14].

$$\text{HOMA-IR} = \frac{\text{fasting insulin } (\mu\text{IU/mL}) \times \text{fasting glucose (mmol/L)}}{22.5}$$

4- Adiponectin levels [15]: Adiponectin levels were measured using ELISA method according to the manufacturer's instructions (RayBiotech Inc, USA, Cat#: ELI-ADIPONECTIN-001).

Pathological studies:

The placentae were collected after delivery. The shape, weight, number of cotyledons, and site of insertion of umbilical cord of placentae was noted.

Statistical analysis:

Quantitative variables were expressed as the mean, standard deviation and range and analyzed using unpaired t-test in parametric data (SD (standard deviation) <50% mean) where Mann Whitney Willcoxon U test was used instead of unpaired t-test in non-parametric data (SD >50% mean). Qualitative variables were expressed as number and percentage and analyzed using Chi-square test. Fisher exact test was used instead of chi-square when one or more expected cell  $\leq 5$  and all hypothesis tests were two-tailed with statistical significance assessed at the p-value  $\leq 0.05$ .

### 3. Results

The present study results showing a significant decrease in gestational age at delivery in preeclamptic group than control group, in addition to a significant increase in body mass index, systolic blood pressure and diastolic blood pressure in preeclamptic group than control group but results did not show any significant difference between preeclamptic and control groups in maternal age and parity (Table 1).

**Table 1: Clinical characteristics in control and preeclamptic groups**

variables	Controls (n=30)	Preeclamptic group(n=30)	p-value
Age (years)			
Range	22-36	20-35	P= 0.787
Mean±SD	27.27±3.57	27.50±3.09	
Gestational age at delivery (weeks)			
Range	37- 41	34-39	P <0.0001*
Mean±SD	38.80±1	37.07±1.26	
Parity			
Primiparous	11 (36.66%)	17 (56.67%)	P= 0.121
Multiparous	19 (63.33%)	13 (43.33%)	
Body mass index (kg/m <sup>2</sup> )			
Range	22.6-33	24.6-34	P<0.0001*
Mean±SD	26.38±1.99	28.70±2.29	
Systolic blood pressure (mmHg)			
Range	90-130	140-210	P <0.0001*
Mean±SD	113.33±9.94	162.33±18.79	
Diastolic blood pressure (mmHg)			
Range	60-85	90-120	P <0.0001*
Mean±SD	76.17±5.68	103.33±10.61	

\*: Statistically significant at p  $\leq 0.05$ .

The present study results show also a significant increase in urinary albumin creatinine ratio and insulin resistance value in preeclamptic mothers than healthy controls in addition to a

significant decrease in adiponectin levels in pregnant women with preeclampsia compared with healthy controls (Table 2).

**Table 2: Biochemical measurements in control and preeclamptic groups**

variables	Controls (n=30)	Preeclamptic group(n=30)	p-value
Albumin creatinine ratio (mg/g)			
Range	6.9-62.1	157.3-398.9	P <0.0001*
Mean±SD	22.47±12.52	302.30±67.59	
HOMA-IR			
Range	0.97-3.82	1.22-4.07	P <0.0001*
Mean±SD	2.06±0.68	3.23±0.72	
Adiponectin (pg/ml)			
Range	212.5-991.7	119.4-789.1	P= 0.003*
Mean±SD	620.6±176.4	489.82±155.1	

\*: Statistically significant at  $p \leq 0.05$

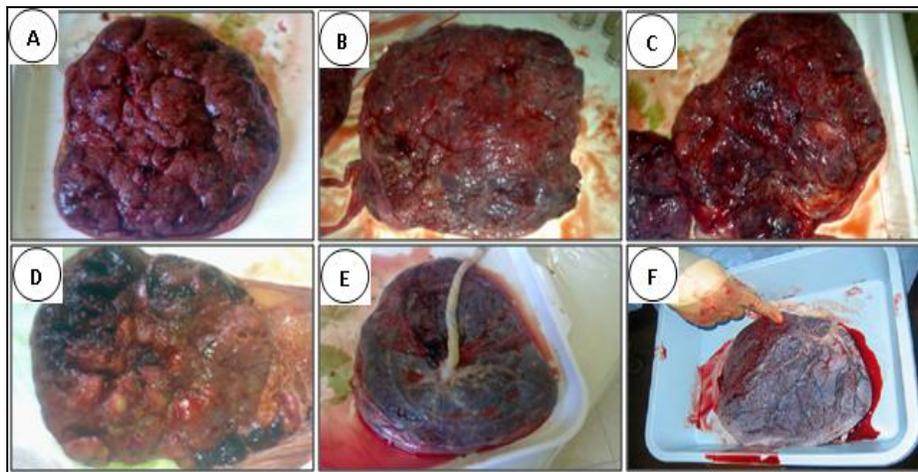
Results showed that preeclamptic mothers had lower placental weight and decreased number of cotyledons with marginal insertion of cord

compared with control group but results did not show any difference between preeclamptic and control groups in placental shape (Table 3, Fig 1).

**Table 3: Macroscopic examination of placenta in control and preeclamptic groups**

variables	Control group(n=30)	Preeclamptic group(n=30)	p-value
Placental Shape			
Circular	16(53.33%)	13(43.33%)	P = 0.685
Irregular	4(13.33%)	6(20%)	
Oval	10(33.33%)	11(36.66%)	
Marginal insertion of cord			
Yes	1(3.33%)	8 (26.67%)	P = 0.026*
No	29(96.67%)	22(73.33%)	
Placental weight (grams)			
Range	391-612	328-512	P < 0.0001*
Mean±SD	500.53±46.28	413.80±47.94	
Cotyledon number per placenta			
Range	17-23	14-22	P = 0.002*
Mean±SD	19±1.53	17.63±1.77	

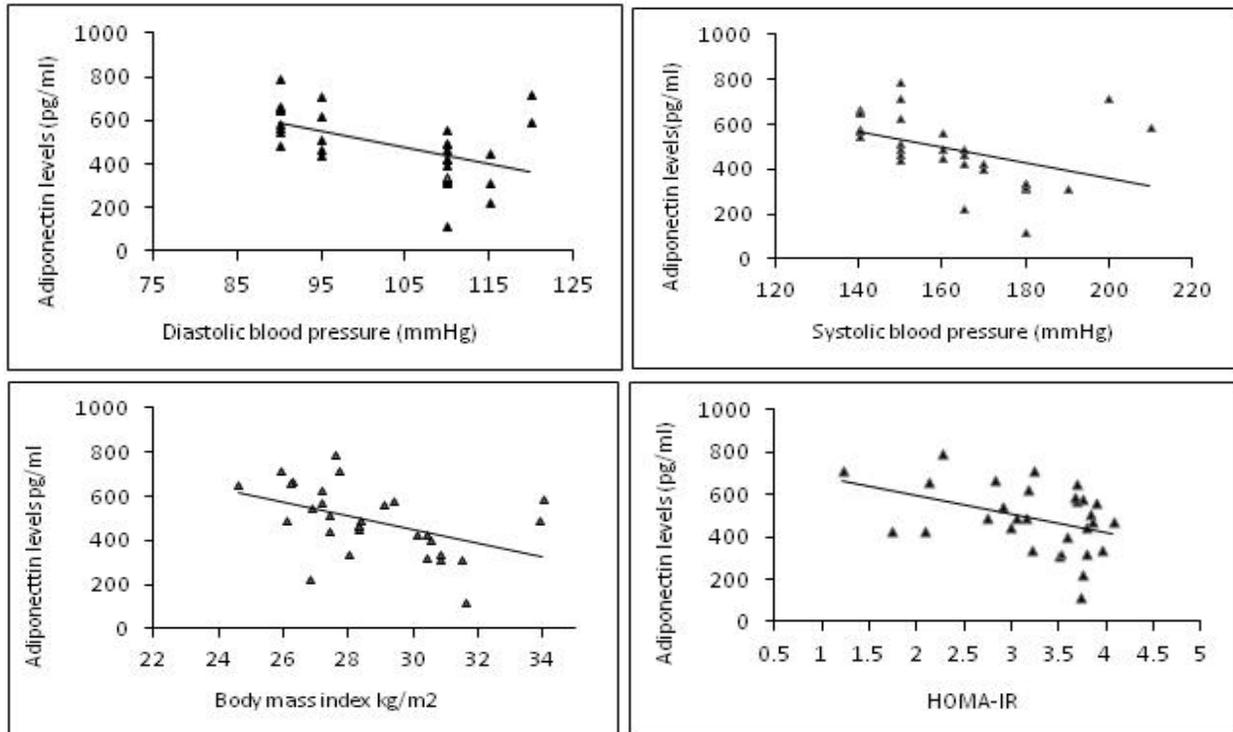
\*: Statistically significant at  $p \leq 0.05$



**Figure 1: Different shapes of placentae and insertion of the cord: A (Normal), B, C, D (shapes of preeclamptic placentae), E (normal insertion of cord) and F (marginal insertion of cord).**

Correlation analysis found that there was a significant negative correlation between maternal serum levels of adiponectin versus body mass index ( $r = -0.456$ ,  $p = 0.011$ ), systolic blood pressure ( $r = -0.425$ ,  $p = 0.019$ ), diastolic blood pressure ( $r = -$

$0.514$ ,  $p = 0.004$ ) and insulin resistance value ( $r = -0.397$ ,  $p = 0.030$ ) (Fig 2), but study results did not find any correlations between adiponectin levels versus macroscopic features of placentae among preeclamptic mothers.



**Figure 2: Correlation between adiponectin level versus body mass index, systolic blood pressure, diastolic blood pressure and HOMA-IR among preeclamptic women**

#### 4. Discussion

Zhang H. and Zhang C. [16] in their review stated that the general concept has emerged that chronic low-grade inflammation is the condition linking excessive development of adipose tissue and obesity-associated pathologies such as type 2 diabetes and cardiovascular diseases. Obesity and type 2 diabetes are characterized by a diminished production of protective factors such as adiponectin and increased detrimental adipocytokines such as leptin, resistin, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF), and monocyte chemoattractant protein-1 (MCP-1) by adipose tissue. Moreover, the evidence that the growth of the fat mass is associated with an accumulation of adipose tissue macrophages and T-lymphocytes has raised the hypothesis that the development of an inflammatory process within the growing fat mass is a primary

event involved in the genesis of systemic metabolic and vascular alterations [16]

Insulin resistance in pregnancy and pregnancy complications is mainly attributed to placental hormones [17]. 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 [18-20]. In the present study we confirmed the existence of important changes in some adipocytokines, namely; adiponectin in pregnant women with preeclampsia compared with healthy pregnant women. The present study found a significant increase of insulin resistance value in preeclamptic group than control group. These results partially in agreement with those of Masuyama et al. [21] who found HOMA-IR in overweight patients with late-onset preeclampsia was significantly high. Placental oxidative stress is regarded as an intermediate event in the

pathogenesis of preeclampsia [22]. Several studies have addressed the molecular mechanisms by which oxidative stress might lead to insulin resistance. In vitro, Reactive oxygen species (ROS) and oxidative stress lead to activation of multiple serine/threonine kinases signaling cascades, these activated kinases can act on a number of potential targets in the insulin signaling pathway [23].

Adiponectin is the most abundant adipose tissue specific protein [24]. Adiponectin receptors are abundantly expressed in human placenta [25], whereas, adiponectin expression by placenta during pregnancy is detectable [25, 26]. Our results showed a significant decrease in adiponectin levels in preeclamptic women than normal pregnant women and these results were in agreement with that reported by Khosrowbeygi et al [27] and Mori et al [8]. Masuyama et al [28] did not support these results; they found a significant increase in adiponectin level in late-onset preeclamptic group. Hemoconcentration is a main characteristic of preeclampsia. However, it was shown that significant difference in levels of adipocytokines between preeclamptic and normal pregnant women is not affected by correcting adipocytokines levels for hematocrit [29]. Hyperleptinemia might contribute to the decreased levels of adiponectin and this assumption were in a line with results of Khosrowbeygi et al. [27]. They found a significant negative correlation between leptin and adiponectin that might confirm our hypothesis. As well D'Anna et al. [30] also reported that there was a strong association between hypoadiponectinemia and preeclampsia and that plasma adiponectin could be predictive of pregnancy induced hypertensive disorders. Unlike our results, Ramsay et al. [7] suggested that elevation of plasma adiponectin may be result of compensatory mechanism for decreased expression of adiponectin receptors in muscles and adipose tissue or due to an exaggerated adipocyte release or a physiological response to increased use of fat. However, he believed that possibility of a clear renal dysfunction in preeclampsia lead to increase circulating adiponectin could not be excluded, although no correlation between adiponectin and urine protein or urate was found by Lu et al. [31].

Concerning macroscopic examination of placentae, there was no statistically significant

difference in placental shape between preeclamptic and control groups but it was found a significant decrease in cotyledon numbers per placenta in preeclamptic group than control group and these results were in agreement with those of Kishwara et al. [32]. The present study results demonstrated that preeclamptic group had a significant increase in marginal insertion of the cord with a significant decrease in placental weight compared with control group and these findings were in agreement with those of Majumdar et al. [33]. Vasospasm, apoptosis and compensatory hyperplasia causing loss and fibrosis of parenchymal tissue results in lowered weight, diameter and central thickness of placentae in hypertensive pregnant women [34].

Correlation analysis presented a significant negative correlation between maternal serum adiponectin levels with both systolic and diastolic blood pressure in preeclamptic group and these finding was in line with that of Abd-Alaleem et al. [35]. Moreover, Ouchi et al. [36] concluded that this effect may be mediated via inflammatory pathway or lipid metabolism. Moreover, hypoadiponectinemia was associated with impaired endothelium-dependent vasodilatation and reduced blood flow [37] and was an independent risk factor for hypertension [36]. Analysis of mutations in the human adiponectin gene provides further information about the link between adiponectin and hypertension. Among several single-nucleotide polymorphisms of adiponectin gene, single-nucleotide polymorphism at position 164 has been associated with hypoadiponectinemia and high blood pressure [38]. Further, Tanida et al. [39] reported that adiponectin dose-dependently decreases renal sympathetic nerve activity and blood pressure in rats and that its action may be mediated through the hypothalamic suprachiasmatic nucleus.

On the other side, the present study showed a significant negative correlation between serum adiponectin levels and HOMA-insulin resistance index (HOMA-IR) among preeclamptic women. Plasma adiponectin levels decreased in parallel with the progression of insulin resistance, suggesting that a reduction in circulating adiponectin may be related to the development of insulin resistance [40] and these findings may be coupled with Combs et al. [41]. who reported that administration of recombinant adiponectin can lead to enhance insulin action.

Consequently, it appeared that this peptide could play a physiological role in maintaining insulin sensitivity and glucose homeostasis. This suggestion could not exclude the possibility that insulin may also have an effect to modulate adiponectin production from adipocytes [42], so giving adiponectin as a drug in high risk women before and during early pregnancy may reduce risk of preeclampsia by increasing insulin sensitivity.

Regarding correlation between maternal adiponectin levels and body mass index (BMI), the present study showed a significant negative correlation between maternal serum levels of adiponectin and body mass index among preeclamptic women. Hendeler et al. [43] concluded that pregnant women complicated with severe preeclampsia and had body mass index greater than 25 kg/m<sup>2</sup> have decreased serum adiponectin levels, while normal weight preeclamptic women have increased serum adiponectin levels. It was suggested that increased adiponectin levels in normal weight preeclamptic women may represent normal feedback response, but this mechanism might not function properly in overweight and obese preeclamptic woman because of increased adiponectin levels and insulin resistance, suggesting that decreased adiponectin level may play a role in pathophysiology of preeclampsia [43]. In a contrast to study results about correlation between adiponectin levels and BMI, Herse et al. [44] reported that adiponectin levels did not correlate with BMI. This can be explained that BMI in pregnancy doesn't accurately reflect fat stores because maternal weight is influenced by weight of the fetus, placenta and amnions and by plasma volume [45].

Briefly, in case of preeclampsia in the present study, it has been observed that there is a significant increase in body mass index and insulin resistance index, and a significant decrease in plasma adiponectin. The increase in body mass index may be due to an increase in body fat mass which may be involved in systemic metabolic and vascular alterations [16] this is evidenced by the correlation analysis which exhibited a significant negative correlation between adiponectin and body mass index, adiponectin and each of systolic blood pressure and diastolic blood pressure as vascular

parameters, and adiponectin and HOMA-IR as a metabolic parameter.

## 5. Conclusions

Preeclamptic women are more insulin resistant, which was reflected through increased HOMA-IR value.

Insulin resistance may be one of the casual pathways of preeclampsia.

Improving insulin sensitivity in high risk women before and during early pregnancy may reduce risk of preeclampsia.

Preeclamptic women in third trimester of pregnancy had low adiponectin levels than normal pregnant women.

Hypoadiponectinemia may be one of the possible etiologies of preeclampsia, so measuring of this adipokine may be useful for prognosis of preeclampsia.

Preeclamptic mothers had lower placental weight and decreased number of cotyledons per placenta with marginal insertion of umbilical cord compared with normal placentae

Preeclamptic placentae underwent definite morphological changes seemed to be the result of insufficiency of placenta in preeclampsia.

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