ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ADIPONECTIN AND LEPTIN PROFILES IN PREGNANT WOMEN WITH OBESITY AND PREECLAMPSIA COMPARED TO WOMEN WITHOUT PREECLAMPSIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract: Preeclampsia (PE) is a serious public health problem for mothers, as it is estimated that 8-22% of pregnancies worldwide suffer from preeclampsia and 800 maternal deaths are attributed to PE (1.2).
Keywords*:* Adipokine, adiponectin, leptin, obesity, preeclampsia.

INTRODUCTION

Preeclampsia is a specific condition during pregnancy, characterized by placental dysfunction and the mother's reaction to systemic inflammation with endothelia activation and coagulation. The diagnosis of preeclampsia is based on the presence of specific hypertension caused by pregnancy, accompanied by multi-organ disorders after 20 weeks of gestation (1.2).

Preeclampsia was previously defined by the presence of hypertension [systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg on two examinations at least 4 hours apart after 20 weeks of gestation in women with previously normal blood pressure], accompanied by proteinuria (≥300 mg/24 hours or dipstick +1), which developed during pregnancy (newly diagnosed hypertension with proteinuria). Although these two criteria remain common symptoms of preeclampsia, in some women, hypertension is accompanied by other symptoms of multi-organ dysfunction, indicating severe preeclampsia even in the absence of proteinuria. Meanwhile, edema is no longer used as a diagnostic criterion, as it is very common in women with normal pregnancies (1-3).

The exact cause of preeclampsia remains a mystery. Several hypotheses have been proposed regarding the pathophysiology of preeclampsia (4-8). A recent study (9) reports that the pathogenesis of preeclampsia involves changes in lipid metabolism. Due to accelerated fetal growth in the last trimester of pregnancy, a higher rate of lipolysis is often observed in a more pronounced catabolic state (9). According to an in vitro study (10), preeclampsia is associated with a stronger catabolic state than normal pregnancy, leading to hyperlipidemia. This hyperlipidemia results in endothelial dysfunction and increases oxidative stress and inflammation (10,11).

This mechanism leads to a significant decrease in mitochondrial dehydrogenase, which in turn enhances cell apoptosis (12). However, obesity, defined as a condition where body mass index (BMI) is ≥30 kg/m2, is considered a substantial risk factor for PE and affects more than one-third of women of reproductive age (13-18). Although obesity increases the risk of PE by two to three times, only 10% of obese women develop PE (13). These findings indicate that assessing the risk of PE development using BMI data alone is highly limited (19). Therefore, more precise and specific obesity-related biomarkers are needed to provide a clinical risk assessment and offer new insights into the pathophysiology of obesity in relation to PE (13-19).

Fat distribution can vary significantly in obesity. Generally, fat is distributed in adipocytes found in adipose tissue. Total adipose tissue consists of outer subcutaneous adipose tissue and inner visceral adipose tissue (19, 20). Like macrophages, adipocytes express various cytokine-mediated inflammatory cytokines called adipocytokines or adipokines, as they

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

often share structural similarities with cytokines and chemokines (19, 20). Adipokines such as adiponectin and leptin are secreted by total adipose tissue. Adiponectin is an anti-inflammatory adipokine, while leptin is a type of pro-inflammatory adipokine (19-25). The systemic effects of adipokines can be severe due to the enormous amount of white adipose tissue in obese patients (23-27).

The relationship between adipokines secreted by total adipose tissue and PE is not yet clear, as previous studies show ambiguous results (19-21), and the connection between obesity, total adipose tissue, and PE during pregnancy remains unclear. Furthermore, there has never been a meta-analysis specifically assessing the role of adipokines from total adipose tissue in the development of PE during pregnancy, especially in obese women. Therefore, to determine whether there are changes in adipokines from total adipose tissue in women with PE and obesity, a study is needed that will examine obese women with and without PE, comparing clinical profiles and profiles of adipokines considered more specific to total adipose tissue, namely adiponectin and leptin, with a meta-analysis. These adipokines can be considered as obesity-associated biomarkers, which are necessary for clinical assessment of PE risk and the relationship between obesity and PE.

MATERIALS AND METHODS

Forty-eight women in their third trimester of pregnancy admitted to the Republican Perinatal Center in 2024 were studied. The main group comprised 28 women with preeclampsia and obesity. The diagnosis of preeclampsia was established based on the criteria of the national clinical guidelines. The control group consisted of 20 pregnant women with obesity but without preeclampsia or hypertension. Exclusion criteria were multiple pregnancies and emergency obstetric conditions. The mean age of women in the main and control groups was 27.8±4.4 and 28.7±4.9 years, respectively, with no statistically significant difference between them. Plasma adiponectin levels were determined using an enzyme-linked immunosorbent assay (ELISA) with Bio Vendor (Czech Republic) reagents. Body mass index (BMI) was calculated for each patient using the formula: BMI = Weight (kg) / [Height (m)]2. BMI in the main group was 33.8 kg/m2 (31.6-37.8 kg/m2), and in the control group - 33.4 kg/m2 (30.8-39.6 kg/m2).

RESULTS

The study of plasma adiponectin levels showed that the median adiponectin concentration in the main group of pregnant women with preeclampsia and obesity was 12.8 mg/ml (range 5.8 to 22.4 mg/ml), while in the control group of pregnant women with obesity but without hypertension it was 6.7 mg/ml (range 2.6 to 13.9 mg/ml). These differences were statistically significant ($p<0.05$). A negative correlation was observed between plasma adiponectin levels and blood pressure (both systolic and diastolic) in both groups: $r=-0.67$ and $r=-0.75$ ($p<0.02$), $r=-0.82$ and $r=-0.94$ ($p<0.02$), respectively. Insulin resistance, hyperlipidemia, enhanced inflammatory response, and vascular transformation play significant roles in the pathophysiology of preeclampsia. Since low serum adiponectin concentrations are closely associated with these metabolic manifestations, it suggests that adiponectin plays a leading role in the pathogenesis of preeclampsia, particularly when accompanied by obesity. Previous studies have shown that low adiponectin levels correlate with arterial hypertension, insulin resistance, and cardiovascular diseases. Consequently, it was expected that adiponectin levels would decrease in preeclampsia. However, our study demonstrates an increase in plasma adiponectin concentration in preeclampsia with obesity compared to pregnant women with obesity but without hypertensive disorders. The increase in adiponectin levels in preeclampsia may be explained by the intensification of non-specific lipolysis in adipocytes, a physiological response to increased fat utilization and reduced

ISSN: 2692-5206
AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

endothelial damage, possible adiponectin resistance, changes in kidney function, and ongoing adiponectin synthesis in adipose tissues.

KEY FINDINGS

The relationship between adipokines secreted by total adipose tissue and preeclampsia (PE) remains unclear, as previous studies show mixed results, while the relationship between obesity, total adipose tissue and PE during pregnancy
is still not fully elucidated (32-34). According to recent studies (32-35), alterations in lipid metabolism are associated with the pathogenesis of PE. Obesity is one of the main risk factors for PE. However, considering only BMI to predict the risk of PE incidents is quite limited (19). According to previous studies (32-35), in patients with adipose tissue metabolic syndromes and obesity, pro-inflammatory cytokines such as tumor necrosis factor (TNF) -α and interleukin-6 (IL-6) are increased, while plasma adiponectin levels decrease. Insulin resistance and endothelial dysfunction accompany the pro-inflammatory state caused by this process (32-36). Previous studies (32,33) show that mild systemic inflammation, typical for women with preeclampsia, correlates with obesity and resistance to
insulin. This mild inflammatory state is also proposed as the main mechanism influencing the fundamental processes that precede the clinical manifestations of the disease and endothelial function. Adiponectin stimulates the production of endothelial nitric oxide synthase (eNOS), increases the levels of vasodilator NO and, in some cases of preeclampsia, reduces nitrites, a stable metabolite of NO, while leptin has pro-inflammatory properties. Adiponectin has an anti-inflammatory effect, inhibiting the synthesis and release of
pro-inflammatory cytokines. Moreover, adiponectin acts by increasing sensitivity to insulin effects, while leptin increases resistance to them (32-37). In support of this finding, previous studies (32-38) reported that pregnant women with obesity and preeclampsia had elevated leptin levels compared to healthy pregnant women. In addition, it was reported (32,33) that a higher leptin level suppresses the proliferation of cytotrophoblasts.

As mentioned earlier, the first abnormalities associated with preeclampsia are a decrease in cytotrophoblast migration and invasion into the uterus.

Previous studies (32-38) raised the question of the possibility
that hyperleptinemia may contribute to placental ischemia and subsequent onset of preeclampsia. Factors causing preeclampsia include chronic elevation of leptin in pregnant rats, increased blood pressure, and inflammatory factors
released from the placenta. Elevated levels of circulating leptin are associated with higher levels of circulating TNF-α in pregnant
rats with obesity (38). Furthermore, placental macrophages isolated from pregnant women with obesity and peripheral blood mononuclear cells have higher levels of TNF-α mRNA compared to pregnant women without obesity. It is reported that TNF-α increases in response to placental ischemia and hypoxia based on both experimental and clinical reports (38-40).

CONCLUSION

An increase in plasma adiponectin levels was determined in pregnant
women with preeclampsia against the background of obesity, as well as a negative correlation between adiponectin and blood pressure levels. Further research is needed to understand the mechanisms involved in regulating adiponectin levels in preeclampsia against the background of obesity, which will allow for the development of preventive measures to reduce the incidence of preeclampsia and its complications.

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