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Review article

What Do We Know About Adiponectin in Preeclampsia? A Comprehensive Review

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Abstract

Preeclampsia is a pregnancy-specific condition with an unknown etiology. It has a significant risk of prenatal and mother morbidity and mortality; the only known treatment is pregnancy termination. Screening for high-risk populations destined to have preeclampsia will effectively guide obstetricians in providing preventative measures, assessing the severity of cases, and scanning for related complications. Adipokines are hormones released by adipose tissue that regulate energy balance, lipid metabolism, and insulin sensitivity. Adiponectin is an adipokine with anti-inflammatory and antiatherogenic characteristics. Adiponectin is believed to have a role in preeclampsia pathogenesis by controlling placental angiogenesis endothelial dysfunction and reducing systemic inflammation. The use of novel markers to identify preeclampsia offers more effective preventive and therapeutic avenues. This review aims to discuss the existing data in the field and determine if serum adiponectin can be used to predict preeclampsia, assess its severity, and scan-related complications.

Keywords: *Adiponectin, Preeclampsia, Prediction, Severity, Fetal Growth Restriction.*

Introduction

Preeclampsia (PE) is a pregnancy-specific illness that occurs after the twentieth week of pregnancy and complicates between 5% -10% of pregnancies worldwide.[1] Although the exact method by which this disease develops is unknown, it has been hypothesized that Preeclampsia is a two-stage disease. The first stage is abnormal placentation caused by poor spiral arteries invasion, and the second stage is when the condition manifests clinically in the mother, mainly Hypertension (140/90 mmHg), severe proteinuria (300 mg/day) [2].
The criteria were recently updated to include severe symptoms, such as reduced platelets or increased liver enzymes, in addition to hypertension [3]. Endothelial dysfunction and inflammation are prominent among these clinical features. PE can be early or late in its onset based on 34 weeks as a divider [4]. Ealy onset PE results from faulty placentation of the early placenta, the early onset is more severe with fetomaternal complications than late-onset PE [5]. The latter is more likely caused by a growing mismatch involving normal maternal perfusion and the metabolic needs of the placenta and fetus, along with a maternal vulnerability to inflammation [6]. Increased vulnerability can be attributed to a high body mass index, a co-existence of Diabetes Mellitus, and high arterial pressure. Proper risk classification is vital in PE prevention to prompt therapies in high-risk pregnant women, including aspirin delivery [7].
To date, termination of pregnancy is the only known treatment. Many theories have been proposed to explain why PE develops. Some suggested inflammation theory; others postulated imbalance between oxidative and anti-oxidative stress, while others suggested a synergism of multiple factors [8]. The giant leap in the mid-1990s that adipose tissue is a big endocrine organ that secretes a variety of physiologically active adipokines into circulation marked a significant advancement in our knowledge of human metabolic systems [9].
Adiponectin (AD) is a cytokine generated in adipose tissue and may be categorized as a hormone since it works on peripheral target tissues via particular receptors.AD is released in response to various stimuli, including gut-derived chemicals, adipocyte cells hypoxia, or death. Serum AD levels are influenced by many factors, including gender, age, and lifestyle. Moreover, AD gene expression is suppressed by β-adrenergic stimulation and glucocorticoid. Oxidative stress was proposed to inhibit AD expression [10]. A low AD serum levels were linked to typed two diabetes mellitus, insulin insensitivity, obesity, and increased

arterial pressure. It is found in normal adult plasma at concentrations ranging from 3 to 30 g/mL and accounts for around 0.01 percent of total plasma proteins [11].
Adiponectin has become a cytokine of interest in metabolic illnesses due to its regulatory roles in various processes, particularly in the pathogenesis of cardiovascular disorders. AD has anti-inflammatory, antiatherogenic, and insulin-sensitizing properties, making it sensible that its deficiency raises cardiovascular disease chances [12]. The available evidence indicates that adiponectin levels decrease as pregnancy progresses. In addition, it regulates placentation and protects against preeclampsia symptoms. Elevated levels of AD are present in normal-weight preeclamptic women; conversely, reduced levels are present in obese and overweight preeclamptic women [13].
Adiponectin protects against pregnancy hypertension as it prevents endothelial dysfunction, systemic inflammation, and proteinuria, all of which are related to Preeclampsia. Lower levels of AD were linked to endothelial dysfunction, a key element in Preeclampsia. Adiponectin functions by inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells signaling; it decreases CRP and increases nitric oxide via activating endothelial nitric oxide synthase [14]. Additionally, Adiponectin facilitated trophoblast invasion via modulating the matrix metalloproteinase to tissue inhibitor of metalloproteinase ratio. As a result, clinical use of Adiponectin as a biomarker, therapeutic target, or therapeutic agent is promising and should be studied [15]. This review of the current data on Adiponectin and Preeclampsia will aid in our knowledge of the etiology, pathophysiology, prediction, and categorizing of the severity of the disease.

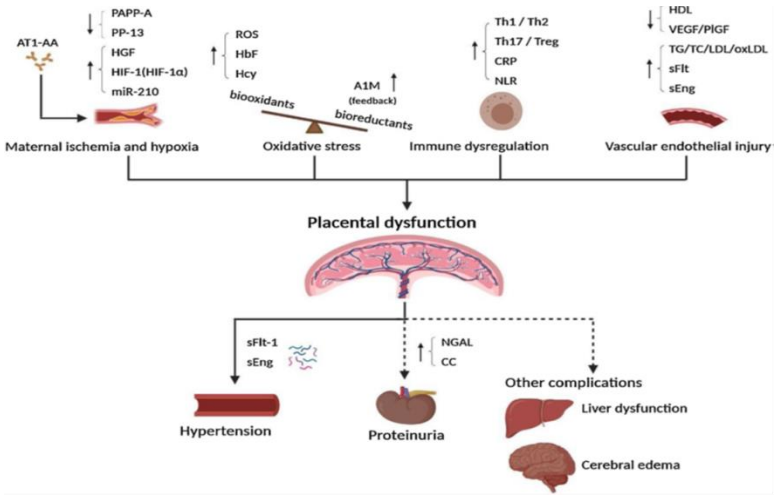

Fig 1. Biomarker's interaction in PE pathogenesis. Different biomarkers are linked to PE onset and pathogenesis. The spotted lines imply that PE signs do not always occur, Liu N et al. [3].

Adiponectin as a Predictor in Preeclampsia

Globally, PE is the second leading cause of materno-fetal deaths. It is complex multi-step pathophysiology makes its prediction challenging to address. Many researchers have sought prediction modalities to reduce its morbidities; however, no method was proved to be superior to others. Prediction and screening for pregnant women deemed to develop PE are critical since no definitive treatment exists to date but to terminate the pregnancy [16]. AD was one of the markers used to screen for PE due to its correlation to early implantation and placentation. Furthermore, serum AD levels are inversely associated with obesity, insulin resistance, and hypertension. All are recognized risk factors for PE. Preeclampsia [17,18].
AD serum levels were high in the first trimester and decreased till the third trimester; however, the difference was statistically meaningless; This negative correlation with pregnancy progression is attributed to fat accumulation in the pregnant body as pregnancy advances [19-21] however, in PE deemed pregnancy, that was not the case. Although AD was significantly low among women who subsequently developed PE [22], AD level was even more reduced among obese PE women than normal weight PE women [23]. Furthermore, D'Anna et al. declared that reduced AD among PE women was negatively related to insulin insensitivity during the first trimester [24].
Another study examined the value of serum AD among early and late-onset PE. They confirmed significantly reduced AD levels among late rather than early-onset PE. In line with these results, another study confirmed that first-trimester serum Adiponectin was meaningfully lower in obese PE pregnant women who developed late-onset PE [25,26].

Adiponectin level in the third trimester showed contradicting behavior; some researchers confirmed that its levels were low among obese preeclamptic women [27]; conversely, its value was higher among average weight preeclamptic women than healthy controls [28]. This diversity in AD level based on the patient body mass index present an exciting avenue for prediction and possible therapeutic option for a syndrome of ambiguous etiology [29].
Adu-Gyamfi et al. recommended a longitudinal study with good analysis power with strict criteria among the full range of body mass index [normal, overweight, and obese women] among each pregnancy trimester to define the exact role of this extraordinary adipokine in Preeclampsia [30].

Adiponectin In Categorizing Preeclampsia Severity

We discussed earlier that PE is a leading cause of maternal mortality, one of the critical issues in managing pregnant women is maintaining a balance between women's welfare and achieving mature infants. From that, we can comprehend the importance of categorizing Preeclampsia's severity and how it affects the clinical decision. AD was one of the biomarkers tested to define PE severity due to its remarkable correlation with the metabolic derangements liked to PE. Nien et al. conducted a cross-sectional study, testing AD's performance in defining PE severity [31]. Furthermore, they liked serum levels of AD with doppler indices that categorize PE severity. Their results showed significantly higher AD levels among severe PE cases versus healthy pregnancy, $P<0.001$. Interestingly, sub-group analysis based on BMI among severe PE cases showed that serum AD failed to score statistical significance, $P<0.7$. likewise, serum AD scores no meaningful difference in patient with abnormal and without Doppler study parameters [32]. Hyperadeponectemia was attributed to many factors; some suggested a contract mechanism to the hyperinflammatory state underlies severe PE. Others proposed that it was caused by AD insensitivity which triggers more AD release by the adipose tissues. Further, others accredited this to a compensatory defense mechanism to the metabolic dysregulation and pro-atherogenic state of severe PE [33,34].
Khosrowbeygi et al. [35] introduce a serum leptin ratio over serum AD to define PE severity. They tested the performance of this ratio in a case-control study for a better and more precise performance than either of these cytokines alone. They declared that the ratio increased significantly with PE severity among affected women and was significantly high among pooled PE cases (severe and mild PE) compared to healthy controls. The author recommended this ratio to evaluate therapeutic intervention and to follow PE progression since it did not differ on adjustment of BMI [36].

Prediction of Fetal growth restriction in PE:

Fetal growth restriction (FGR) is defined as a statistical deviation in fetal size from a community-based scale. GRF will not reach their genetic potential owing to nutritional deficiency caused by faulty placentation, and they will face higher morbidity and mortality risks than normal-weight babies. FGR may be classified into two types: symmetrical (constitutional) and non-symmetrical. In comparison to constitutional FGR s, the former has greater morbidity rates [37]. Imaging methods or biochemical markers were used to screen for growth limitation.
As a causative pathology, PE and FGR share a faulty invasion of the maternal spiral arteries, in which the sick placenta will seek to compensate for diminished blood flow by releasing a variety of hormones and cytokines into the maternal bloodstream, AD was one of those heavily investigated cytokines [2,7]. Adiponectin possesses anti-inflammatory, angiogenic, atherosclerotic, and insulin-sensitizing effects. Low adiponectin levels decrease trophoblastic invasion, increase endothelial damage, and escalate atherosclerosis in PE women.
Barş Büke study examined AD levels in 3 groups, IUGR, PE-IUGR, and healthy controls. Their result demonstrated higher serum AD in the IUGR group, but no significant differences were identified between the IUGR-PE and healthy controls, and their findings were consistent with previous studies [38-40]. This elevation in serum AD in FGR was attributed to endothelial damage, which is one of the predominant features in PE pregnancies resulting in reduced placental blood flow and increased resistance to blood flow and reduced flow, which eventually reduces fetal growth and manifests as FGR [41].
Savvidou et al. [42] found no relationships between serum maternal AD levels in the middle trimester in women who were destined to have IUGR. Kyriakakou, and Street et.al studies looked at AD in umbilical cords from mothers with IUGR and found a decreased level of AD [43]. Some attributed this to the oxidative stress theory that IUGR infants suffer from. Others proposed that the chronic inflammatory state in PE will inhibited AD secretion [44].
Some research looked at the efficacy of first-trimester serum AD in predicting the

development of IUGR, though they found that IUGR cases had greater levels of AD yet AD was unreliable for predicting IUGR [45].
Unlike pregnancy complicated with PE; neonatal levels of AD in normal pregnancy directly correlate with many anthropometric adiposity parameters [46,47]. Higher concentrations of cord blood AD are associated with elevated birth weight [48]. These findings imply that maternal and fetal AD have diverging roles in orchestrating fetal growth. At birth, cord blood AD is 4–7 fold higher than maternal levels [49]. later on, a progressive decline in AD concentration in the first neonate life. keeping in mind that maternal AD does not pass the placenta [50], the correlation between cord blood AD and fetal adiposity parameters mirrors an independent action of fetal AD [51,52].

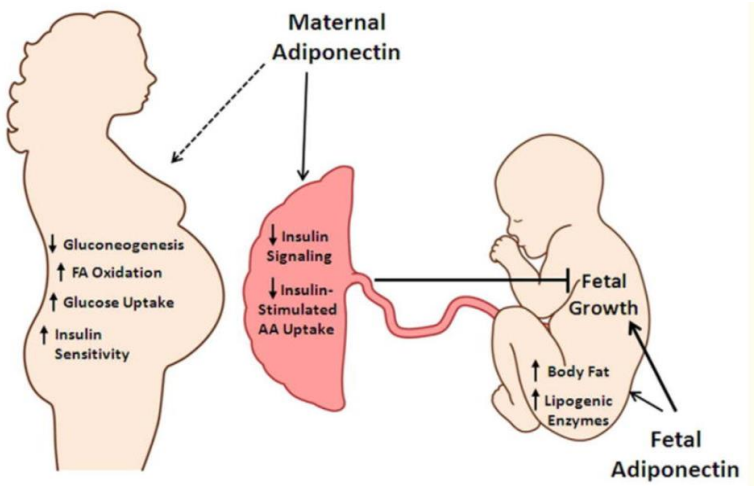

Fig 2. Adiponectin role in regulating fetal growth and adiposity markers, Evangelion et al [50].

Conclusion

Adiponectin had been associated with preeclampsia in more than a way; it predicted PE onset, especially for late-onset and during the second half of pregnancy. It predicted PE severity by correlation with metabolic marker and serum leptin over AD ratio. However, inconsistency among reported studies exists, most likely due to the confounding effect of obesity on adiponectin level. Finally, screening for FGR showed promising results even outside the context of preeclampsia. We recommend more studies to unravel the hidden aspects of this extraordinary adiponectin.

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