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Adiponectin and leptin profiles among obese pregnant women with preeclampsia *vs.* non-preeclampsia: a systematic review and meta-analysis

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Abstract. – OBJECTIVE: Preeclampsia (PE) affects only about 10% of women who meet the criteria for obesity based on their body mass index (BMI). Obesity is suggested to play a role in preeclampsia pathophysiology, and in addition to BMI, associated biomarkers with higher sensitivity and specificity, such as with adipokines from adipose tissue, are needed to enable clinical risk assessment. This study aimed to investigate obese pregnant women with and without PE by comparing clinical profiles and adipokine profiles specific to general adipose tissue (adiponectin and leptin).

MATERIALS AND METHODS: This meta-analysis was conducted following the PRISMA and was registered in PROSPERO (CRD42023478706). We utilized Cochrane, Scopus, and PubMed/Medline databases. The Cochrane ROBINS-I instrument was employed to assess the quality of studies. Pooled standard mean difference (SMD) and p-value were analyzed using a random-effects model with the DerSimonian-Laird method, while subgroup analysis with the Chi-square test and the inconsistency index (I^2) were used to assess potential sources of heterogeneity.

RESULTS: Three observational studies included a total of 2,646 obese pregnant women and found that adiponectin was more likely to have a lower level in pregnant women with obesity [SMD=-0.32; 95% CI: -0.34-0.17, p=0.003] and leptin was more likely to be higher in obese pregnant women with PE rather than non-PE [SMD=0.53; 95% CI: -0.19-1.08, p<0.00001].

CONCLUSIONS: Adiponectin levels were more likely to be lower in pregnant women with obesity in the PE group than in the non-PE group, and leptin levels were more likely to be higher.

Key Words:
Adipokine, Adiponectin, Leptin, Obesity, Preeclampsia.

Introduction

Preeclampsia (PE) is a major maternal public health concern because it is estimated that 8-22% of pregnancies worldwide experience preeclampsia and 800 maternal deaths every day are attributed to PE[1,2]. In addition, 99% of all these incidents originate from developing countries, such as Indonesia. In Indonesia, preeclampsia contributes around 30-40% of maternal deaths. This number is expected to continue to increase if appropriate intervention steps are not taken immediately[1-3].

Preeclampsia is a specific condition in pregnancy characterized by placental dysfunction and maternal response to systemic inflammation with endothelial activation and coagulation. The diagnosis of preeclampsia is made based on the presence of specific hypertension caused by pregnancy accompanied by multiorgan disorders above 20 weeks of gestational age[1,2]. Preeclampsia was previously defined by the presence of hypertension [at least systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg on two examinations at least 4 hours apart after 20 weeks of gestation in women with previously normal blood pressure],

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accompanied by proteinuria (≥300 mg/24 hours or dipstick +1) which just occurred in pregnancy (new-onset hypertension with proteinuria). Although these two criteria are still the common symptoms of preeclampsia, several other women show hypertension accompanied by other multisystem disorders, indicating the presence of severe preeclampsia even though the patient does not experience proteinuria. Meanwhile, edema is no longer used as a diagnostic criterion because it is very often found in women with normal pregnancies[1-3].

The exact cause of preeclampsia is still enigmatic. Several theories are hypothesized, such as the pathophysiology of preeclampsia[4-8]. A recent study[9] reports that the pathogenesis of PE involves alterations in lipid metabolism. Due to accelerated fetal growth during the last trimester of pregnancy, there is frequently a higher rate of lipolysis in higher catabolic state[9]. According to an *in vitro* study[10], preeclampsia is associated with a stronger catabolic state than normal pregnancy, which results in hyperlipidemia. This hyperlipidemia results in endothelial dysfunction and raises oxidative stress and inflammation[10,11]. This mechanism causes mitochondrial dehydrogenase to decrease significantly, which in turn enhances cell apoptosis[12].

However, obesity, defined as a state in which one's Body Mass Index (BMI) is ≥30 kg/m^2, is considered to be a significant risk factor for PE and impacts over one-third of American women who are of reproductive age[13-18]. Despite the fact that obesity raises the risk of PE by two to three times, only about 10% of women whose BMI classifies them as obese actually develop PE[13]. This condition suggests that estimating the risk of an incident PE using BMI alone is quite limited[19]. Therefore, more sensitive and specific obesity-related biomarkers are required to enable clinical risk assessment and offer new perspectives on the pathophysiology of obesity and PE association[13-19].

Fat distribution can vary greatly in obesity. In general, fat is distributed in adipocyte cells found in adipose tissue. General adipose tissue consists of external subcutaneous adipose tissue and internal visceral adipose tissue[19,20]. Like macrophages, adipocytes express a variety of cytokine-mediated inflammatory signals called adipocytokines or adipokines because they frequently share structural similarities with cytokines and chemokines[19,20]. Adipokines, such as adiponectin and leptin, are secreted by general 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 quantity of white adipose tissue in obese patients[23-27].

The relationship between adipokines secreted by general adipose tissue and PE is still unclear because previous studies show mixed results[19-21], and the relationship between obesity, generalized adipose tissue, and PE in pregnancy has not yet been clarified. Moreover, there has never been a previous meta-analysis study that specifically assessed the role of adipokines from general adipose tissue in the development of PE in pregnancy, especially in women with obesity.

Therefore, to investigate whether there are changes in adipokines from general adipose tissue in women with PE and obesity, this study will investigate obese women with PE and without PE by comparing clinical profiles and adipokine profiles that are considered more specific to general adipose tissue, namely adipokines, and leptin through this systematic review with meta-analysis. These adipokines could be the candidate biomarkers associated with obesity, which are required to offer clinical risk assessment and new insights into the pathophysiology of the obesity-PE relationship.

Materials and Methods

Study Design

This study was carried out following the referred Reporting Item for Systematic Reviews and Meta-analysis (PRISMA) (**Supplementary File**) guidelines[28]. It was registered with PROSPERO and assigned a CRD number of CRD42023478706.

Research Question and Eligibility Criteria

The research question of this study is "How do the adiponectin and leptin profiles compare between obese pregnant women with preeclampsia (PE) and those without PE?". The inclusion criteria of this study were based on the PECO (Population, Exposure, Comparison, Outcome) framework. Obese pregnant women comprised the study population (P). The exposure (E) was the PE status. The following clinical and sociodemographic risk factors – tobacco use, fetal birth weight, parity status (para 1),

and mother age at diagnosis – were extracted in order to investigate their potential associations with PE. The clinical and adipokine profiles of PE patients were compared to non-PE (C) populations in this study. The main outcome (O) is investigating adipokine profiles, which consist of a composite of adipokine indicators, including adiponectin and leptin.

Studies written in English, with original quantitative data, and published in peer-reviewed journals were all included. Articles that contained only a review or an abstract of grey literature were excluded from this review. Study publication dates were limited to the last ten years (2014-2024). Electronic databases, reference lists, and expert consultation were employed to identify studies.

Search Strategy and Study Selection

Several databases, such as Cochrane, PubMed/Medline, and Scopus, were thoroughly searched in order to locate relevant studies published in the last ten years (2014-2024) PE cases with and without severe features were included in this study. A combination of keywords and Medical Subject Headings (MeSH) terms was used to create the search strategy related to "Adipokine", "Adiponectin", "Leptin", "Preeclampsia" and their synonyms.

Data Analysis and Quality Assessment

Data were independently extracted by three authors (ADN, MAA, and MRAAS) using a standard data extraction form that contains information about clinical profiles associated with risk factors and adipokine profiles of adiponectin and leptin levels. The fourth author (DPJS) mediated disputes between the other two authors. We used the Cochrane Reviews for Nonrandomized Studies of Intervention (ROBINS-I) to assess the quality of the nonrandomized clinical trials, which were assessed by two authors (ADN and MRAAS). The other authors (AP, AS, AYP, SI, and ADA) were responsible for supervising the overall content.

Statistical Analysis

For statistical analysis, RevMan (RevMan International, Inc., New York, NY, USA) was utilized. Pooled effect size estimates are presented as standard mean difference (SMD) with 95% confidence intervals (CI) using the DerSimonan-Laird method formula. If any heterogeneity was discovered, it would be assessed using the subgroup analysis with the Chi-square test and the inconsistency index (I^2). A significant result was defined as a p-value lower than 0.05 and an I^2 of more than 50%. A random-effects model was used to account for all interstudy variability[29-31].

Results

Study Selection

After a preliminary search, sixty relevant articles were found. Following the removal of three duplicate articles, the remaining 57 articles were considered eligible. Of those, 53 articles were excluded due to the non-conformity of the parameters assessed by our study criteria; thus, four were considered suitable for additional examination. One full-text article was excluded from subsequent analysis since it only focused on comparing preeclampsia and severe preeclampsia with normoweight and obese BMI status. In the end, three studies[19-21] made up the analysis (Figure 1).

Characteristics of Included Studies

In terms of study design and country of origin, the included studies in this article widely varied (Table I). The three included studies[19-21] were one cohort study, one cross-sectional study, and one case-control study. These studies, which were carried out in Western nations such as the United States of America (USA)[19], the United Kingdom (UK)[20], and Denmark[21], showed that this type of research is currently rare and still concentrates on populations in developed nations where obesity was defined as having a BMI ≥30 kg/m^2. There were 2,646 obese pregnant women in this study. Based on Table I, maternal age at diagnosis, number of gravidities, and number of parity (first parity/para 1) as clinical aspects were similar between the two groups (PE *vs.* non-PE) among all studies included[19-21]. However, fetal birthweight was lower in the PE group. Based on adipokine profiles aspects in all studies included[19-21], adiponectin was lower (Study 1[19] 17.94±15.10 mg/mL *vs.* 23.90±15.40 mg/mL; Study 2[10] 9.00±4.80 mg/mL *vs.* 9.90±4.50 mg/mL; Study 3[21] 6.63±1.11 mg/mL *vs.* 6.95±1.01 mg/mL) while leptin was higher (Study 1[19] 9.36±7.00 ng/mL *vs.* 5.87±2.80 ng/mL; Study 2[20] 85±42 ng/mL *vs.* 50±23 ng/mL; Study 3[21] 10.35±1.15 ng/mL *vs.* 9.81±1.18 ng/mL) in the PE group.

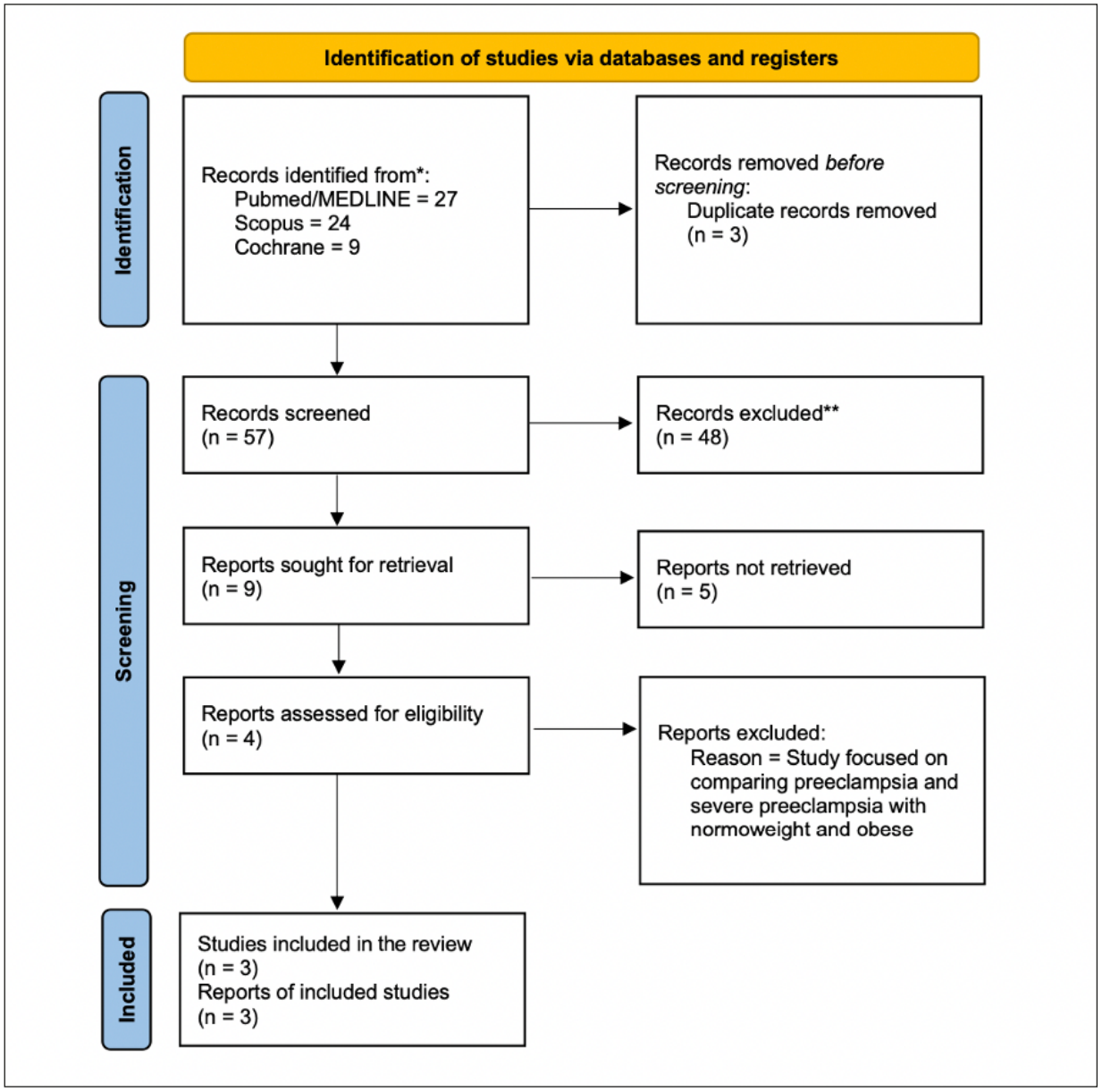

Figure 1. PRISMA flow chart. *In this flowchart, records are tracked only through databases (no registries). **Based on the study's exclusion criteria, articles that contained only a review or an abstract of grey literature were not included.

Clinical Profiles

Maternal Age at Diagnosis

All three studies included the analysis of maternal age at diagnosis. According to Figure 2, the PE group of obese pregnant women had younger mothers than the non-PE group (SMD=-0.12) [95% CI: -0.34-0.09, p=0.26], which may be favorable to the progression of the diseases but was not statistically significant. No significant heterogeneity was found (I^2=0%, $p_{heterogeneity}$=0.26).

Parity (para 1)

Parity status (primiparous or para 1) was only analyzed in two studies[20,21]. Although it was not statistically significant, Figure 3 showed that the para 1 status was higher in the non-PE group than in the PE group (SMD=0.90) [95% CI: 0.28-2.91, p=0.86], which, while not statistically significant, may be favorable to the progression of diseases. The study discovered a high level of heterogeneity (I^2=80%, $p_{heterogeneity}$=0.86).

Table I. Characteristics of the included studies.

Study	Design	Country	Total sample	Maternal age at diagnosis (Mean, SD)		Gravidity at delivery (Mean, SD)		Para 1 (n, %)		Tobacco use (n, %)		Fetal outcome: birth weight in grams (Mean, SD)		Adiponectin levels (mg/mL) (Mean, SD)		Leptin levels (ng/mL) (Mean, SD)	
				PE	Non-PE	PE	Non-PE	PE	Non-PE	PE	Non-PE	PE	Non-PE	PE	Non-PE	PE	Non-PE
Chandrasekaran et al[19] (2019)	Case-Control	USA	117	30.00 (6.10)	29.30 (6.00)	-	-	-	-	-	-	-	-	17.94 (15.10)	23.90 (15.40)	9.36 (7.00)	5.87 (2.80)
Huda et al[20] (2017)	Cross-Sectional	United Kingdom	26	31.10 (6.30)	30.00 (5.90)	35.60 (3.20)	38.90 (1.40)	7 (53.80)	4 (30.80)	2 (15.4)	1 (7.6)	2,330 (926)	3,414 (547)	9.00 (4.8)	9.90 (4.5)	85 (42)	50 (23)
Thagaard et al[21] (2019)	Cohort	Denmark	2,503	28.20 (5.60)	29.30 (5.10)	-	-	13 (20.30)	924 (38.30)	13 (20.30)	438 (18.20)	3,090 (445)	3,580 (350)	6.63* (1.11)	6.95* (1.01)	10.35* (1.15)	9.81* (1.18)

PE=preeclampsia; Non-PE=non-preeclampsia. *After converting to normal data from log-transformed data.

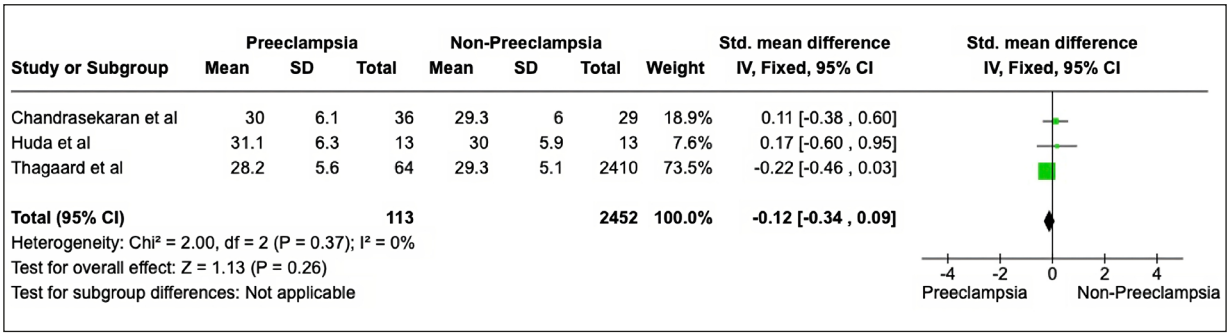

Figure 2. The impact of maternal age at diagnosis on obese pregnant women with PE and non-PE.

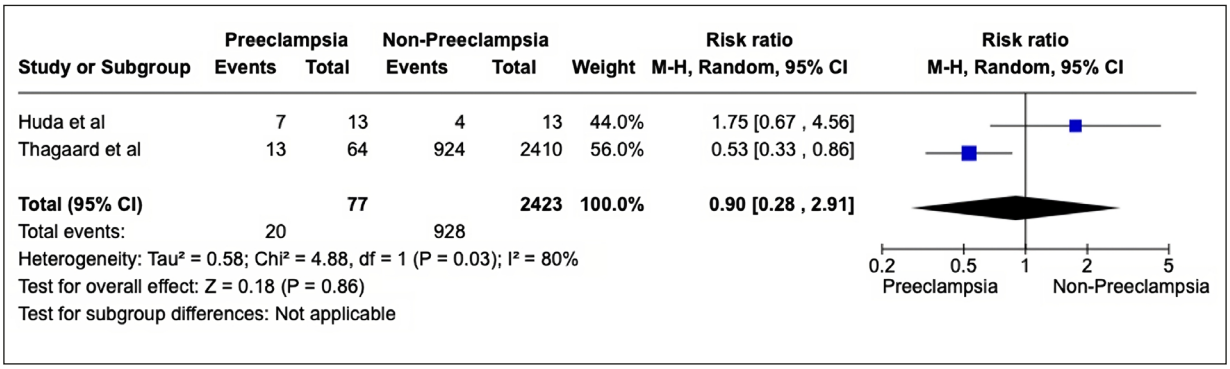

Figure 3. The impact of parity status (para 1) at diagnosis on obese pregnant women with PE and non-PE.

Tobacco use

In the included studies, only Huda et al[20] and Thagaard et al[21] examined tobacco use. Figure 4 showed that, although not statistically significant, tobacco use was associated with a higher risk of preeclampsia in obese pregnant women [RR=1.15 (95% CI: 0.71-1.87, p=0.56)]. This association may be favorable to the progression of the disease. We found no evidence of significant heterogeneity (I^2=0%, $p_{heterogeneity}$=0.56).

Fetal outcome: birth weight in grams

The only studies that included the analysis of fetal outcomes (birth weight) were the ones by Huda et al[20] and Thagaard et al[21]. With an SMD=-1.39 [95% CI: -1.63 – -1.15, p<0.00001], Figure 5 showed that the PE group had a higher likelihood of having lower fetal birth weight than the non-PE group. This finding may significantly favor the course of the diseases. There was no evidence of significant heterogeneity (I^2=0%, $p_{heterogeneity}$<0.00001).

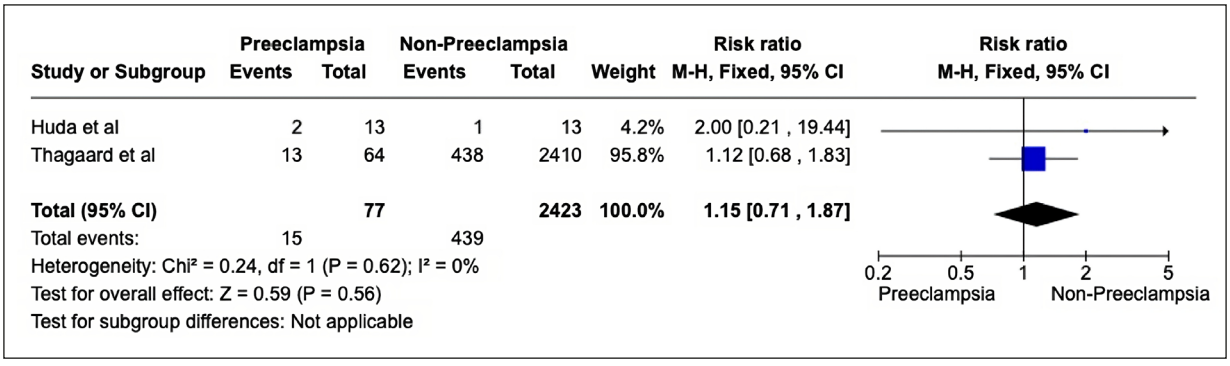

Figure 4. The impact of tobacco use in obese pregnant women with PE and non-PE.

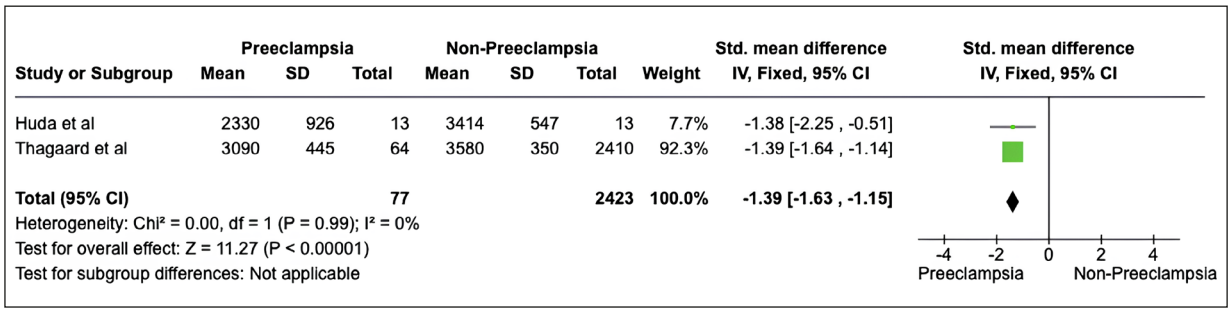

Figure 5. Fetal outcome (birth weight) in PE *vs.* non-PE obese pregnant women.

Adipokine Profiles

Adiponectin levels

All three studies[19-21] included the analysis of adiponectin levels. Figure 6 showed that among pregnant women with obesity, those in the PE group were more likely to have a lower level of adiponectin than those in the non-PE group (SMD=-0.32) [95% CI: -0.34-0.17, p=0.003], which may significantly favor the course of diseases. We found no evidence of significant heterogeneity (I^2=0%, $p_{heterogeneity}$=0.91).

Leptin levels

All three studies included an analysis of leptin levels. Figure 7 revealed that leptin was more likely to be higher in pregnant women with obesity in the PE group rather than the non-PE group (SMD=0.53) [95% CI: -0.19-1.08, p<0.00001], which might favor the course of diseases significantly. No high heterogeneity was identified (I^2=0%, $p_{heterogeneity}$=0.43).

Publication Bias

Based on the ROBINS-I assessment, all the studies were considered to be at moderate risk of

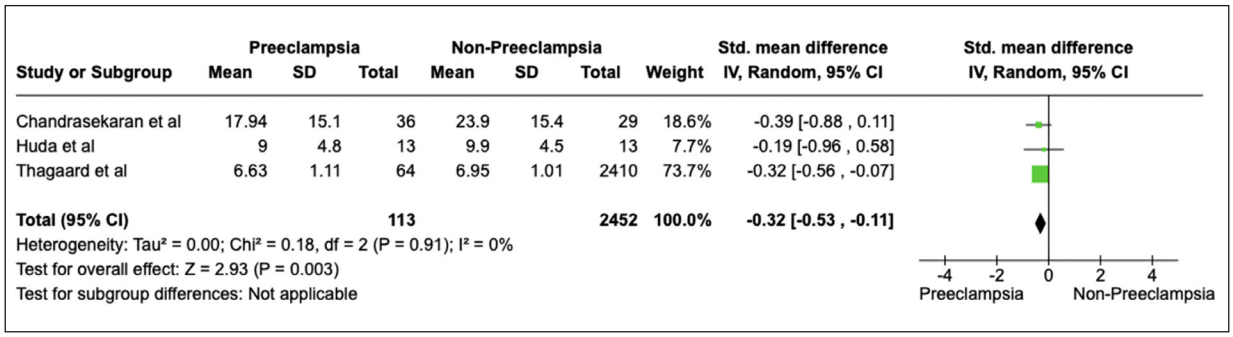

Figure 6. Adiponectin level in PE *vs.* non-PE obese pregnant women.

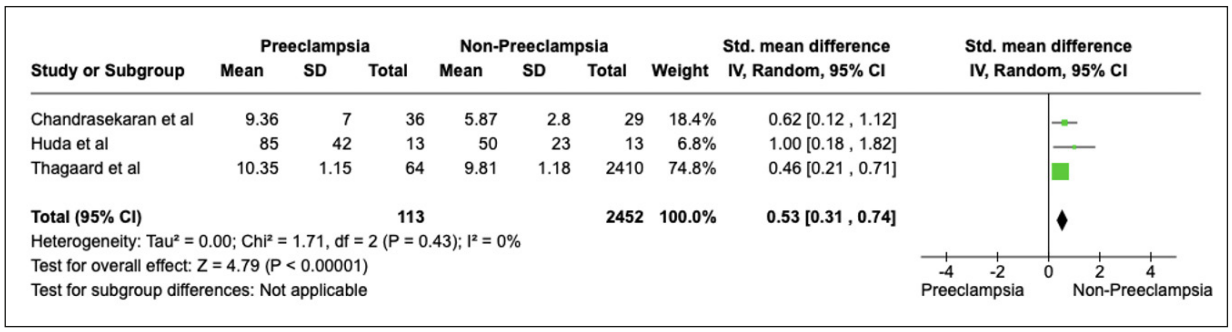

Figure 7. Forest plot of leptin level in PE *vs.* non-PE obese pregnant women.

bias. D1 (bias due to confounding) and D5 (bias due to missing data) dominated the moderate risk of bias domain. The D2 (bias due to selection participants), D3 (bias in interventions classifications), D4 (bias due to deviations from intended interventions), D6 (bias in outcome measurements), and D7 (bias in selection of reported results) bias domains were the low-level risk of bias domains. One[21] of the studies in D4 had a significant risk of bias (Figure 8).

Discussion

Principal Findings

The relationship between adipokines secreted by general adipose tissue and preeclampsia (PE) still remains unclear as previous studies show mixed results, and the relationship between obesity, generalized adipose tissue, and PE in pregnancy has not yet been clarified[32-34]. According to recent studies[32-35], alterations in lipid metabolism have been linked to PE pathogenesis. One major risk factor for PE is obesity. However, considering BMI alone for predicting the risk of PE incidents is quite limited[19]. According to previous studies[32-35], in adipose tissue metabolic syndromes and obesity patients, pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin-6 (IL-6) increase, while adiponectin levels in plasma decrease. Resistance of insulin and endothelial dysfunction accompany a proinflammatory state that is brought on by this process[32-36].

Prior research[32,33] indicates that the low-grade systemic inflammation typical of preeclamptic women is correlated with obesity and resistance to insulin. This low-grade inflammatory state is also proposed as a major mechanism influencing fundamental processes that precede the clinical manifestations of the disease and endothelial function. Adiponectin stimulates the production of endothelial nitric oxide synthase (eNOS), raises vasodilator NO levels, and, in certain preeclamptic cases, lowers nitrite, a stable metabolite of NO, while leptin has pro-inflammatory properties. Adiponectin has anti-inflammatory effects by inhibiting the synthesis and release of pro-inflammatory cytokines. Moreover, adi-

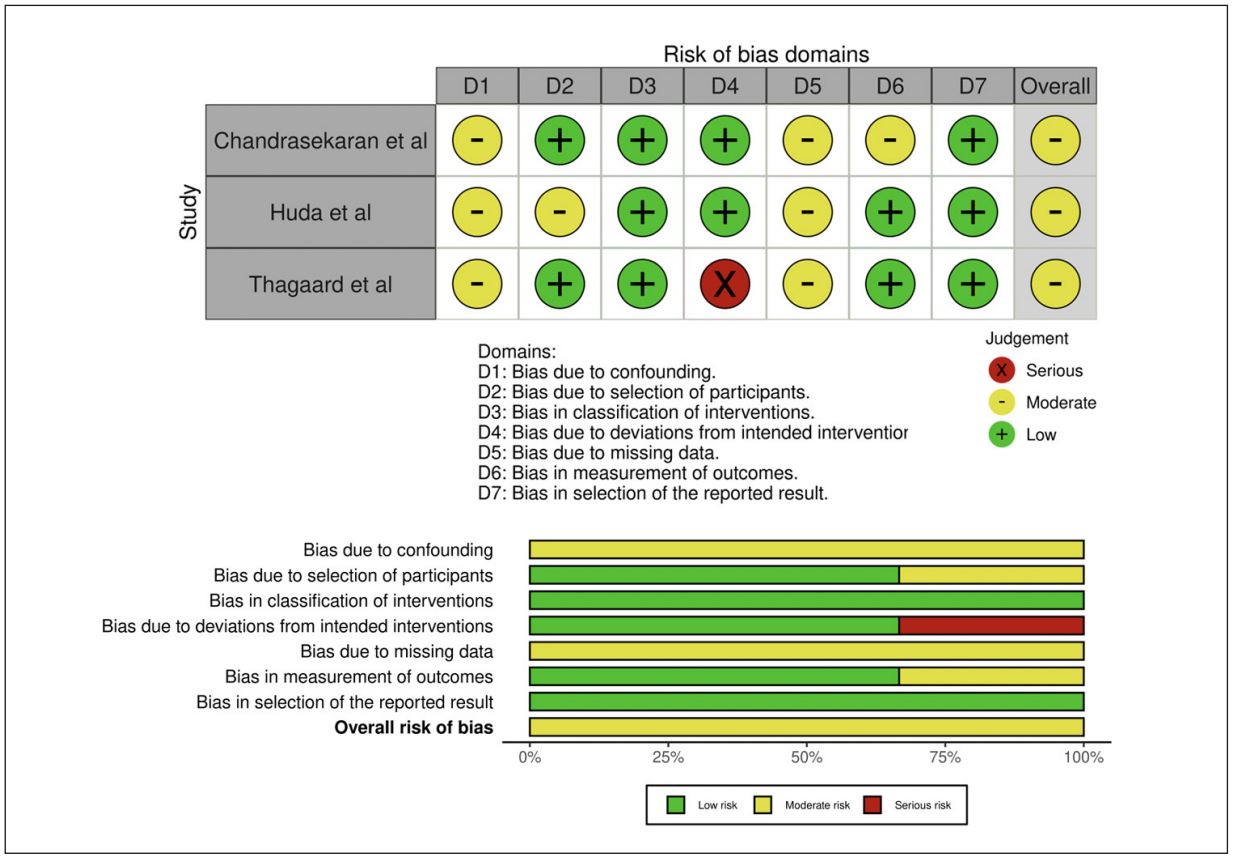

Figure 8. Result of the assessment using ROBINS-I.

ponectin acts to increase sensitivity to the effects of insulin, while leptin increases resistance to them[32-37]. In support of this finding, previous studies[32-38] have reported that obese pregnant women with PE have increased leptin levels compared with healthy pregnant women. Furthermore, it has been reported[32,33] that higher leptin levels inhibit the proliferation of cytotrophoblasts. As was previously mentioned, the first abnormalities linked to PE are decreased cytotrophoblast migration and invasion of the uterus. Previous research[32-38] has raised the possibility that hyperleptinemia may contribute to placental ischemia and the ensuing onset of PE. Preeclampsia-causing factors include chronic elevations in leptin levels in pregnant rats, elevated blood pressure, and inflammatory factors released from the placenta. Increased circulating leptin is linked to higher levels of circulating TNF-α in pregnant rats with obesity.[38] Furthermore, macrophages of the placenta isolated from obese pregnant women and mononuclear cells from peripheral blood have higher TNF-α mRNA levels compared to non-obese pregnant women. TNF-α is reported to increase in response to ischemia and hypoxia of the placenta based on both experimental and clinical reports[38-40].

Moreover, this study found that fetal birth weight was more likely to be lower in the PE group rather than in the non-PE [SMD=-1.39; 95% CI: -1.63 – -1.15, p<0.00001]. During crucial periods of the fetus's prenatal development, the mother's nutrition has a significant impact[41]. Vasospasms, endothelial damage, and placental anomalies are all present in preeclampsia. When trophoblasts invade the spiral arteries in both waves, preeclampsia does not occur. Spiral artery remodeling would not occur, which could lead to a reduction in uteroplacental blood flow and decreased vascular supply to the placenta[42,43]. This theory may explain the findings in this study.

Implications in Clinical Practice

The discovery of biomarkers in preeclamptic women may result in initiatives for care quality improvement. These findings may lead to the early identification of adipokine biomarkers (adiponectin and leptin), which should lessen the likelihood of adverse outcomes linked to late presentation of PE. Additionally, this meta-analysis provides insight into the likelihood that pregnant women with obesity in the PE group have a lower level of adiponectin than in the non-PE group and that pregnant women in the PE group have a higher level of leptin. The results of this study will elaborate on the development of the most recent guidelines for women with preeclampsia, guiding them from early detection through the assessment of adipokines' prognostic role in pregnancy from the first trimester to subsequent management to reduce the possibility of adverse consequences from a delayed PE presentation.

Strength and Limitations

The main advantage of this study is that, to the best of our knowledge, it is the first systematic review and meta-analysis that compares the clinical profiles and adipokine profiles (adiponectin and leptin) of obese women with and without PE. The bias risk associated with each included study was also carefully assessed. There are a few restrictions, though, that must be noted. First, every study had a fairly diverse sample size, and every study design was varied. Second, the study was restricted to developed Western nations, suggesting that, at present, this kind of research is uncommon and still concentrates on white populations where obesity was identified at BMI ≥30 kg/m^2. Third, the number of included studies in this analysis was restricted because not all studies reported the comparison of adipokine levels, especially adiponectin level and leptin levels in obese pregnant women, along with their clinical, sociodemographic, and outcome profiles. Sociodemographic and clinical profiles, including comprehensive parity status, systolic and diastolic blood pressure, medication history, fetal and maternal outcomes, and gestational age at diagnosis and delivery, were not reported in all studies. Only a few studies reported about maternal age at diagnosis, parity status (para 1), tobacco use, and fetal birth weight. Due to this, only a small number of variables could be analyzed using meta-analysis.

Conclusions

This study revealed that adiponectin levels were more likely to be lower in pregnant women with obesity in the PE group than in the non-PE group, and leptin levels were more likely to be significantly higher in pregnant women with obesity in the PE group than in the non-PE group. The small number of studies included and the moderate risk of bias should be taken into account when interpreting the findings. Additional research is required to validate these results.

Conflict of Interest
The authors declare that they have no conflict of interest to disclose.

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Data Availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

AI Disclosure
No artificial intelligence or assisted technologies were used in the study's production.

Informed Consent
Not applicable due to the design of the study.

Ethics Approval
According to the institutional and departmental review boards, there is no need for ethical approval due to the study design (systematic review and meta-analysis).

Authors' Contributions
ADN, MAA, MRAAS, and DPJS did the conception of the study and revised the manuscript critically for important intellectual content. ADN, MRAAS, and DPJS made the acquisition of data, analysis, and interpretation of the data. ADN, MAA, MRAAS, DPJS, and AP drafted and revised the manuscript. AS, AYP, AP, SI, and ADA supervised the study and manuscript critically for important intellectual content. All of the authors (ADN, MAA, MRAAS, DPJS, AS, AYP, SI, AP, and ADA) have read and approved the final manuscript as it has been submitted and agree to be accountable for all aspects of the work.

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