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Elevated IL-6 Levels in Severe Preeclampsia: A Comparative Analysis of Obese and Non-Obese Pregnant Women

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KEYWORDS

interleukin-6; obesity; severe preeclampsia

ABSTRACT:

Introduction: Obesity is a factor that can increase the risk of preeclampsia, which is characterized by metabolic inflammation. Obesity before pregnancy can increase interleukin 6 (IL-6) levels due to increased adipose tissue. Although differences in IL-6 levels between obese and non-obese pregnant women have been widely reported, evidence in cases of severe preeclampsia remains limited.

Objectives: This study examines the association between obesity and IL-6 levels in pregnant women with severe preeclampsia.

Methods: This cross-sectional analysis compared women with severe preeclampsia based on obesity status prior to pregnancy or in early gestation. Obesity was classified using the WHO Asia–Pacific criteria. Serum IL-6 concentrations were assessed by ELISA, and group differences were evaluated using independent t tests and chi-square analyses.

Results: The study included 88 women with severe preeclampsia, evenly divided into obese and non-obese groups. Obese participants showed significantly higher IL-6 concentrations than non-obese participants ($p < 0.05$). However, IL-6 levels were not significantly related to obesity severity, maternal age, educational level, parity, or gestational age ($p > 0.05$).

Conclusions: IL-6 levels can be a marker of inflammation in cases of severe preeclampsia exacerbated by comorbid obesity. Regular evaluation of IL-6 levels could be considered for obese women prior to pregnancy, potentially helping to mitigate systemic inflammation and the risk of developing severe preeclampsia.

1. Introduction

Preeclampsia is a hypertensive disorder occurring during pregnancy [1]. Severe preeclampsia, characterized by significant hypertension and proteinuria after 20 weeks of gestation, poses serious risks to maternal and fetal health, contributing to an estimated 50,000–100,000 maternal deaths globally each year, alongside serious fetal and neonatal mortality [2].

Obesity increases the risk of preeclampsia. This risk doubles with every 5–7 kg/m² increase in body mass index (BMI), a association linked to obesity-related hypertension [3]. Obesity can impair placental function and perfusion through associated metabolic alterations such as hyperlipidemia, hyperinsulinemia, and hyperleptinemia [4]. Notably, hyperinsulinemia and insulin resistance are key obesity-related features that often precede the clinical onset of preeclampsia [4].

Obesity is associated with persistent low-grade metabolic inflammation, characterized by monocyte infiltration into enlarged adipose tissue and their differentiation into adipose tissue macrophages. These macrophages release proinflammatory cytokines, including interleukin-6 (IL-6), which has been widely implicated in adverse pregnancy outcomes [5]. As a proinflammatory adipokine, IL-6 levels rise with increasing obesity and are closely linked to glucose intolerance and insulin resistance [6]. Chronically elevated IL-6 disrupts energy metabolism in tissues like the liver and white adipose tissue. The infiltration and polarization of macrophages within adipose tissue toward a pro-inflammatory M1 phenotype further amplifies this inflammation, increasing the release of cytokines such as TNF-α, IL-1β, and IL-6 [7].

Previous research has demonstrated a significant increase in IL-6 in the fetal circulation and placentas of

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obese pregnant mice compared to normal-weight controls [8]. Other studies report significantly elevated IL-6 levels in preeclampsia compared to normotensive pregnancies [9]. Research on the role of IL-6 in obesity-associated preeclampsia has indicated that IL-6 is elevated in preeclampsia and that a link exists between preeclampsia and obesity [10]. Furthermore, pre-pregnancy BMI has been correlated with IL-6 levels during pregnancy [11].

A review of the existing literature confirms that while IL-6 levels have been compared between preeclamptic and healthy pregnancies, and the association between obesity and preeclampsia incidence has been studied, a direct comparison of IL-6 levels between obese and non-obese individuals specifically within a cohort of severe preeclampsia patients—classified by pre-pregnancy or first-trimester obesity—has not been conducted. This constitutes the novelty of the present study. Therefore, this study aims to analyze the relationship between obesity and IL-6 levels in pregnant women with severe preeclampsia.

2. Methods

This study was reported in accordance with the STROBE 2007 guidelines for observational research [12]. A cross-sectional design was implemented across the primary hospital and its network from January 2025 to August 2025.

This study included pregnant women with severe preeclampsia who attended antenatal care and delivered at the study site. Participants were enrolled using consecutive sampling. Eligible subjects were those with singleton pregnancies beyond 20 weeks of gestation who provided informed consent. Women with chronic conditions, such as hypertension, diabetes, renal or cardiac disorders, or active infections were excluded. Samples were considered dropouts if they were damaged or rendered uninterpretable.

Obesity served as the main independent variable, while serum IL-6 concentration was the primary outcome. Obesity was classified based on pre-pregnancy or first-trimester BMI using the WHO Asia–Pacific criteria (≥25 kg/m²), calculated from measured height and weight with calibrated instruments. Participants were grouped as non-obese (BMI <25 kg/m²), obesity class I (25–29.9 kg/m²), or obesity class II (≥30 kg/m²). Serum IL-6 was quantified from venous blood samples using a sandwich enzyme immunoassay and reported in pg/mL.

Other assessed variables included baseline characteristics: maternal age, parity, gestational age, and education level. Age was categorized as <20, 20–35, or >35 years. Parity was defined by the total number of previous deliveries and classified as nulliparous (0), primiparous (1), multiparous (2–4), or grand multiparous (>4). Gestational age was determined from the last menstrual period and grouped into preterm (<37 weeks), term (37–41 weeks), or post-term (≥42 weeks). Education was dichotomized as <9 years (no school to junior high school) or ≥9 years (high school to university).

Participants were categorized into obese and non-obese groups, all diagnosed with severe preeclampsia. Severe preeclampsia was diagnosed by the treating physician based on blood pressure ≥160/110 mmHg accompanied by at least one severe feature, including proteinuria (>1+), headache, visual symptoms, epigastric pain, oliguria (<400 mL/24 h), elevated serum creatinine (>1.2 mg/dL), increased AST or ALT levels, foetal growth restriction, or pulmonary oedema. Eligible women were enrolled after providing written informed consent. Data were collected via structured interviews and recorded in a case report form. A 3 mL peripheral venous blood sample was drawn into an EDTA tube and transported to the laboratory for IL-6 analysis using a commercial ELISA kit.

Sample size estimation was based on a two-group mean comparison formula [13], assuming a 5% significance level (α), 10% type II error (β), a standard deviation of 7, and an expected intergroup IL-6 difference of 5.29. These parameters yielded a minimum requirement of 37 participants per group, for a total of 74 subjects.

Statistical analyses were performed with SPSS v26.0. Data are presented as mean ± SD. Group differences in IL-6 were assessed using independent t tests after normality confirmation by the Shapiro–Wilk test, while categorical variables were analyzed with chi-square tests; $p < 0.05$ indicated statistical significance.

3. Results

This study enrolled 88 pregnant women with severe preeclampsia, comprising 44 with obesity and 44 without obesity. Table 1 summarizes baseline characteristics of

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both groups. The majority of participants were 20–35 years old, had more than nine years of formal education, and delivered preterm. In the obese group, 45% were nulliparous and 36.4% were multiparous. No significant differences were observed between groups in age, education, parity, or gestational age ($p > 0.05$), indicating comparable baseline profiles.

Table 1. The baseline characteristics of samples

Characteristics	Obesity (n= 44)	Non-obesity (n= 44)	p-value
	n (%)	n (%)	
Age (years)			
< 20	2 (4.5)	3 (6.8)	
20-35	31 (70.5)	26 (59.1)	0.534
> 35	11 (25.0)	15 (34.1)	
Education			
≤ 9 years	7 (15.9)	9 (20.5)	0.580
> 9 years	37 (84.1)	35 (79.5)	
Parity			
Nulliparous	20 (45.5)	15 (34.1)	
Primiparous	11 (25.0)	13 (29.5)	0.551
Multiparous	13 (29.5)	16 (36.4)	
Gestational age			
Preterm	23 (52.3)	31 (70.5)	0.080
Aterm	21 (47.7)	13 (29.5)	

Chi square test

The comparison of IL-6 levels between the obese and non-obese groups is presented in Table 2. IL-6 levels were significantly higher in obese pregnant women compared to the non-obese group. A further comparison between obesity class 1 and class 2 is shown in Table 3. Although mean IL-6 levels were higher in the class 2 obesity group, this difference was not statistically significant ($p > 0.05$).

Table 2. Comparison of IL-6 levels between obese and non-obese groups

	Obesity (n= 44)	Non-obesity (n= 44)	p-value
	Mean ± SD	Mean ± SD	
IL-6 value (pg/mL)	8.11 ± 4.25	6.03 ± 2.82	0.009

Independent sample t test

Table 3. Comparison of IL-6 levels between obese 1 and obese 2 groups in severe preeclampsia

	Obese 1 (n= 26)	Obese 2 (n= 18)	p-value
	Mean ± SD	Mean ± SD	
IL-6 value (pg/mL)	7.98 ± 4.03	8.29 ± 4.67	0.823

Independent sample t test

Table 4 shows the analysis of variables related to IL-6 levels. Maternal age, education, parity, and gestational age were not significantly associated with IL-6 concentrations ($p > 0.05$), suggesting that these factors did not confound the association between obesity and IL-6 in this cohort.

Table 4. Subgroup analysis of factors associated with IL-6 levels

Characteristics	IL-6 value (ng/mL)	p-value
Age (years)		
< 20	3.72 (1.90-12.85)	0.215

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20-35	6.38 (1.84-16.43)	
> 35	7.56 (1.90-12.39)	
Parity		
Nulliparous	6.01 (1.84-16.23)	0.264
Primiparous	7.28 (2.00-15.21)	
Multiparous	6.46 (1.84-16.43)	
Gestational age		
Preterm	6.76 (1.90-16.23)	0.990
Aterm	6.81 (1.84-16.43)	

Chi square test

4. Discussion

This study demonstrates that serum IL-6 levels are significantly higher in pregnant women with severe preeclampsia and obesity, compared to their non-obese counterparts. BMI was assessed based on pre-pregnancy or first-trimester measurements. The observed IL-6 levels exceeded those reported in healthy second- and third-trimester pregnancies (<4.40 pg/ml) [14].

Our findings indicate that pre-pregnancy or early-pregnancy obesity influences IL-6 levels during gestation in the context of severe preeclampsia. To our knowledge, this is the first study to specifically compare IL-6 levels between obese and non-obese women within a severe preeclampsia cohort. However, similar trends have been reported in other populations. In normotensive pregnancies, MacGregor et al. reported analogous results, with the highest IL-6 levels at 12-20 and 32-35 weeks found in obese, followed by overweight, and then normal/underweight groups [15]. IL-6 levels increased across all BMI groups from early to late pregnancy. Similarly, Sominsky et al. found that pre-pregnancy obesity (BMI ≥30 kg/m²) was associated with higher maternal serum IL-6 at 28 weeks gestation compared to normal-weight controls [16]. Thus, our results align with existing evidence of elevated IL-6 during pregnancy in women with pre-pregnancy or early-pregnancy obesity and provide novel data confirming this relationship specifically in severe preeclampsia.

This phenomenon can be attributed to heightened systemic inflammation during pregnancy, which is further amplified in women with pre-existing obesity due to increased adipose tissue mass. Early-pregnancy BMI reflects pre-gravid adiposity, which is a significant source of IL-6 secretion [17]. Furthermore, adipose tissue present at the start of pregnancy persists throughout gestation [5]. The direct relationship between adiposity and pro-inflammatory IL-6 during pregnancy underscores the impact of BMI on cytokine levels [17], although the longitudinal pattern of IL-6 change warrants further investigation.

Longitudinal studies report increasing IL-6 levels from early to late pregnancy in women with obesity. One comparative longitudinal study in women with a BMI ≥25 kg/m² at 9-12 weeks found that IL-6 levels increased by week 36. Maintaining constant diet and physical activity from early pregnancy was shown to prevent abnormal increases in certain cytokines in this group [18]. Similarly, Ross et al. reported a gradual increase in IL-6 from 8-16 weeks gestation until delivery, with higher pre-pregnancy BMI correlating with higher IL-6 levels, linking pre-gravid adiposity to inflammatory outcomes during pregnancy [11]. This is consistent with previous research indicating that pre-pregnancy BMI has the strongest positive effect on IL-6 levels and is negatively associated with insulin sensitivity during gestation [5,17].

The elevated IL-6 in early-pregnancy obesity is mechanistically linked to adipose tissue mass. IL-6 is secreted from adipose tissue into circulation, and its expression correlates positively with BMI and total fat mass [10]. While normal pregnancy involves a balanced inflammatory response crucial for implantation and placentation, obesity exacerbates this state through adipose tissue inflammation. Adipose tissue hosts immune cells like macrophages and T-lymphocytes. Inflamed adipocytes and immune cells, particularly macrophages polarized toward a pro-inflammatory M1 phenotype, secrete cytokines, including IL-6 [19]. Increased IL-6 levels in obesity are largely driven by visceral fat accumulation, as IL-6 expression is elevated in the visceral adipose tissue of obese individuals compared with those of normal weight [20].

In severe preeclampsia with comorbid obesity, high IL-6 levels may also be linked to impaired placentation.

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Obesity-induced increases in maternal plasma IL-6 can elevate placental IL-6, potentially altering placental function [21]. In normal pregnancy, IL-6 regulates key processes at the fetal-maternal interface, stimulating trophoblast invasion and migration, and activating endothelial cells to recruit immune cells for spiral artery remodeling [22,23]. In maternal obesity, interaction between adipose tissue and the maternal–fetal interface may impair placental vascular development through elevated circulating proinflammatory cells and cytokines. IL-6 and other anti-angiogenic mediators released from ischemic adipose and placental tissues are thought to contribute to preeclampsia pathogenesis [22]. Obesity-related increases in IL-6 within decidual and placental cells may disrupt extra villous trophoblast invasion and spiral artery remodeling by promoting macrophage polarization toward the proinflammatory M1 phenotype. In addition, excess IL-6 skews $CD4^+$ T-cell differentiation toward Th17 and cytotoxic lineages while suppressing Th2 and regulatory T cells, resulting in immune dysregulation and systemic inflammation characteristic of preeclampsia [23].

Our study found no significant association between IL-6 levels and the severity of obesity (class 1 vs. class 2) within the severe preeclampsia cohort. This aligns with a previous report in obese patients where BMI class was not associated with IL-6 levels [24]. This suggests that the presence of pre-pregnancy or early-pregnancy obesity, rather than its degree, is associated with elevated IL-6 in severe preeclampsia. The non-significant result may be due to the uneven sample distribution, with more participants in obesity class 1, or could reflect IL-6 resistance, a condition sometimes observed in obesity where circulating IL-6 is elevated but its signaling is impaired [25].

In summary, elevated inflammation and cytokines like IL-6 likely disrupt spiral artery remodeling and exacerbate severe preeclampsia. Therefore, IL-6 may serve as an inflammatory marker in severe preeclampsia complicated by pre-pregnancy or early-pregnancy obesity. A key clinical implication is the importance of pre-conception weight management. Women planning pregnancy should strive to achieve and maintain a normal weight and nutritional status.

While prior research has compared IL-6 levels between obese and non-obese individuals in various disease states, this is the first study to do so specifically in pregnant women with severe preeclampsia, which is its primary strength. A main limitation is the single time-point measurement of IL-6; levels were not assessed prior to pregnancy or at multiple points during gestation. Furthermore, the study lacked a control group of normotensive pregnancies with or without obesity for comparison, which presents an opportunity for future research.

5. Conclusion

Pregnant women with severe preeclampsia and obesity exhibit significantly higher IL-6 levels than their non-obese counterparts. This indicates that obesity present before or during early pregnancy is a risk factor for a heightened inflammatory state in severe preeclampsia. These findings suggest that regular evaluation of IL-6 levels could be considered for obese women prior to pregnancy, potentially helping to mitigate systemic inflammation and the risk of developing severe preeclampsia. Future research should involve comprehensive, longitudinal monitoring of IL-6 at multiple time points before and during pregnancy to better elucidate its dynamic profile in obese versus non-obese women with severe preeclampsia.

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