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Obesity Marks Higher Circulating Endothelin-1 in Severe Preeclampsia: A Multicenter Cross-Sectional Analysis

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ABSTRACT: **Background**: Obesity and severe preeclampsia share inflammatory, oxidative, and endothelial pathways, but it is uncertain whether obesity is accompanied by additional endothelin-1 (ET-1) elevation once severe preeclampsia is already present.

Objective: To examine circulating ET-1 according to pre-pregnancy obesity status and obesity class among women with severe preeclampsia.

Methods: A multicenter cross-sectional analysis was conducted in 88 women with severe preeclampsia recruited consecutively from four hospitals in South Sulawesi, Indonesia, between May 2025 and March 2026. Pre-pregnancy BMI was classified using the prespecified Asia-Pacific cutoffs (non-obesity, <25.0 kg/m²; class I obesity, 25.0–29.9 kg/m²; class II obesity, ≥30.0 kg/m²). ET-1 was quantified by ELISA, and non-parametric tests were used because ET-1 was not normally distributed.

Results: Women with obesity had higher ET-1 than women without obesity (median [IQR] 3.38 [0.65–27.11] pg/mL vs 0.76 [0.49–2.70] pg/mL, p=0.019). Within the obesity group, class I and class II obesity showed similar ET-1 distributions (3.77 [0.70–22.40] pg/mL vs 3.28 [0.51–37.01] pg/mL, p=0.567). No statistically significant ET-1 differences were detected across age, parity, or gestational-age categories.

Conclusion: Pre-pregnancy obesity was associated with higher circulating ET-1 among women with severe preeclampsia, whereas class I and class II obesity did not differ. These findings support endothelial heterogeneity associated with maternal adiposity but do not establish causality or clinical predictive value.

1. INTRODUCTION

Severe preeclampsia is a systemic vascular disorder of pregnancy rather than an isolated rise in blood pressure. Abnormal placental function and maternal endothelial injury act together to generate vasoconstriction, oxidative stress, inflammatory signaling, and angiogenic imbalance, ultimately contributing to maternal and fetal complications [1,2]. Endothelin-1 (ET-1) is especially relevant within this pathway because it is a powerful endogenous vasoconstrictor and a marker of endothelial activation [5,6].

Maternal adiposity may amplify this vascular disturbance. Large epidemiologic analyses show a graded increase in preeclampsia risk as pre-pregnancy body mass index (BMI) rises [3]. At the biological level, excess adipose tissue is accompanied by insulin

resistance, adipocyte hypoxia, oxidative stress, chronic low-grade inflammation, and reduced nitric-oxide availability. These processes overlap substantially with the mechanisms that drive endothelial dysfunction in preeclampsia [4,7,8].

The endothelin pathway may therefore represent a point of convergence between obesity and preeclampsia. Metabolic dysfunction and adipose-tissue inflammation can stimulate ET-1 expression, whereas placental malperfusion, antiangiogenic activity, and maternal endothelial stress provide additional stimuli in preeclampsia [5,7-9]. Previous clinical work has mainly shown that ET-1 is higher in preeclamptic than in normotensive pregnancies [10,11,14]. Far less is known about whether obesity is associated with a further shift in ET-1 among women who already share the same severe preeclamptic phenotype.

The present study was designed around that within-disease question. Severe preeclampsia was held constant, and circulating ET-1 was compared according to pre-pregnancy obesity status. We also assessed whether ET-1 differed between class I and class II obesity. Our a priori expectation was that obesity would be accompanied by higher ET-1, while a simple stepwise relation across obesity classes might be less evident because severe preeclampsia itself produces substantial endothelial activation.

2. MATERIALS AND METHODS

2.1 Study design and setting

We performed a multicenter analytical cross-sectional study in four hospitals in South Sulawesi, Indonesia: Dr. Wahidin Sudirohusodo Hospital, Hasanuddin University Hospital, Siti Khadijah Hospital, and Fatimah Regional General Hospital. Enrollment and study procedures took place between May 2025 and March 2026. Reporting was organized with reference to STROBE principles for observational research.

2.2 Participants and sampling

Pregnant women diagnosed with severe preeclampsia who received care at any of the four participating hospitals were screened consecutively during the study period using the same prespecified eligibility criteria across centers. The source population comprised women with severe preeclampsia receiving care at these hospitals. Hospital records from 2024, used to characterize the center-specific recruitment base, documented 126 women with severe preeclampsia: 52 at Dr. Wahidin Sudirohusodo Hospital, 25 at Hasanuddin University Hospital, 27 at Siti Khadijah Hospital, and 22 at Fatimah Regional General Hospital. These 2024 figures represent verified source-population caseloads and not the distribution of participants ultimately included in the analysis. Recruitment continued from May 2025 to March 2026 until the prespecified minimum sample of 82 participants (41 per comparison group) had been exceeded. Following application of the eligibility criteria and assessment of data completeness, 88 women were included in the final analysis, comprising 44 women with obesity and 44 women without obesity. Center-specific counts for the final analyzable sample were not retained and therefore were not estimated. Eligibility required a singleton pregnancy, fulfillment of the severe-preeclampsia criteria used by the Indonesian Society of Obstetrics and Gynecology, and written informed consent. Maternal demographic, obstetric, and clinical information was obtained through structured interview, clinical examination, and review of medical records.

Women were excluded if they had chronic hypertension, diabetes mellitus, renal disease, thyroid disease, autoimmune disease, use of lipid-modifying medication such as statins or fibrates, or a history of alcohol use. Participants were excluded from the final analysis if the blood sample was damaged or the laboratory result could not be reliably interpreted.

2.3 Obesity classification and clinical data

Pre-pregnancy BMI was calculated as preconception body weight (kg) divided by height squared (m^2). The preconception weight and height values used for this calculation were documented in the study demographic questionnaire. BMI categories were defined a priori according to the Asia-Pacific classification used in Indonesian clinical practice [16]: non-obesity, BMI <25.0 kg/m^2; class I obesity, BMI 25.0–29.9 kg/m^2; and class II obesity, BMI ≥30.0 kg/m^2. For the prespecified primary comparison, class I and class II obesity were combined as the obesity group (BMI ≥25.0 kg/m^2) and compared with the non-obesity group; the secondary comparison examined class I versus class II obesity. Maternal age, gestational age, parity, medical history, blood pressure, and relevant medication information were obtained from structured interview, clinical examination, and medical records.

2.4 Blood collection and ET-1 measurement

Approximately 3 mL of peripheral venous blood was collected into an EDTA-containing tube and transported under cooled conditions in a cooler box for laboratory processing. Circulating ET-1 was quantified using the Human ET-1 (Endothelin 1) ELISA Kit, 96T (Elabscience Biotechnology Inc., Houston, TX, USA; catalog no. E-EL-H0064), according to the manufacturer's instructions. The assay uses a sandwich colorimetric ELISA principle, with optical-density measurement at 450 ± 2 nm and concentration estimation from the assay standard curve. ET-1 was defined as the concentration measured in maternal venous blood by ELISA. Concentrations were recorded directly from the assay output and reported in pg/mL, consistent with the calibration worksheet.

2.5 Statistical analysis

Statistical processing was undertaken in SPSS after the dataset had been checked for missing entries, duplication, implausible values, and data-entry errors. Categorical variables are summarized as counts and percentages. The distribution of ET-1 was assessed using the Kolmogorov-Smirnov test together with graphical inspection. Because ET-1 was not normally distributed, concentrations are reported as median with interquartile range (IQR), and rank-based non-parametric tests were selected. The Mann-Whitney U test was used for comparisons between two independent groups (obesity versus non-obesity, class I versus class II obesity, and preterm versus term gestation) because the outcome distribution was non-normal and the groups were independent. The Kruskal-Wallis test was used for comparisons across more than two independent categories, including maternal-age and parity groups. Categorical distributions were compared using the chi-square test when expected cell counts were adequate and Fisher's exact test when sparse cells made the chi-square approximation inappropriate. A supportive Spearman rank analysis was performed using the ordered BMI categories (non-obesity, class I obesity, and class II obesity); because this ordinal analysis overlapped substantially with the primary group comparisons, it was treated as secondary rather than as an independent line of evidence. All tests were two-sided, and $p<0.05$ was considered statistically significant.

3. RESULTS AND DISCUSSION

3.1 Baseline profile of participants

Table 1. Participant characteristics stratified by obesity status

Characteristic	Total (n=88)	Obesity (n=44)	Non-obesity (n=44)	p-value
Age, years				0.878
<20	5 (5.7%)	2 (4.5%)	3 (6.8%)	
20–35	60 (68.2%)	31 (70.5%)	29 (65.9%)	
>35	23 (26.1%)	11 (25.0%)	12 (27.3%)	
Education				0.653
<9 years	58 (65.9%)	28 (63.6%)	30 (68.2%)	
≥9 years	30 (34.1%)	16 (36.4%)	14 (31.8%)	
Parity				0.612
Nulliparous	35 (39.8%)	20 (45.5%)	15 (34.1%)	
Primiparous	24 (27.3%)	11 (25.0%)	13 (29.5%)	
Multiparous	28 (31.8%)	13 (29.5%)	15 (34.1%)	
Grand multipara	1 (1.1%)	0 (0.0%)	1 (2.3%)	
Gestational age				0.127
Preterm	35 (39.8%)	21 (47.7%)	14 (31.8%)	
Term	53 (60.2%)	23 (52.3%)	30 (68.2%)	

Data are n (%). Categorical comparisons used chi-square testing or Fisher's exact test when required.

3.2 Circulating ET-1 according to obesity status

The analysis included 88 women, evenly divided between the obesity and non-obesity groups. Overall, 68.2% were 20-35 years of age, 39.8% were nulliparous, and 60.2% had reached term gestation.

None of the measured baseline distributions for age, education, parity, or gestational-age category showed a statistically detectable difference between obesity groups (all $p>0.05$). These non-significant tests indicate an absence of detected differences; they do not demonstrate formal equivalence between groups.

The main signal was a marked separation in ET-1 according to obesity status. Median (IQR) ET-1 was 3.38 (0.65-27.11) pg/mL in women with obesity and 0.76 (0.49-2.70) pg/mL in those without obesity ($p=0.019$). Thus, despite all participants sharing severe preeclampsia, the distribution of circulating ET-1 was shifted upward in the presence of obesity. A supportive Spearman rank analysis across the ordered BMI categories (non-obesity, class I obesity, and class II obesity) showed a weak positive association with ET-1 ($r_s=0.215$, $p=0.044$). Because this secondary analysis used ordinal BMI categories rather than continuous BMI, it was not interpreted as evidence of a linear dose-response relationship.

Table 2. ET-1 concentrations by obesity status and obesity class

Comparison	n	ET-1, median (IQR), pg/mL	p-value
Obesity	44	3.38 (0.65–27.11)	0.019
Non-obesity	44	0.76 (0.49–2.70)	
Class I obesity	26	3.77 (0.70–22.40)	0.567
Class II obesity	18	3.28 (0.51–37.01)	

Mann-Whitney U test. ET-1 values are presented as median (IQR), pg/mL.

This pattern is consistent with known vascular biology. The endothelin system is an important determinant of vascular tone and endothelial behavior [6]. In obesity, oxidative stress, insulin resistance, adipose inflammation, and loss of nitric-oxide bioavailability can favor greater endothelin signaling [7,8]. Severe preeclampsia activates overlapping mechanisms through placental ischemia, antiangiogenic factors, immune dysregulation, and widespread endothelial injury [5,9,15]. The higher ET-1 observed in the obesity group is therefore compatible with superimposed metabolic-inflammatory stress on an already activated endothelial state.

The findings also connect two strands of prior Indonesian evidence. Simanjuntak et al. documented higher ET-1 in preeclampsia than in normotensive pregnancy and linked ET-1 with mean arterial pressure [11], whereas Hartopo et al. reported associations between ET-1 and obesity-related anthropometric measures in Indonesian women [12]. The current analysis brings these observations together by studying obesity-related variation in ET-1 only among women with severe preeclampsia. This within-condition comparison addresses biological heterogeneity that is not captured when the sole contrast is preeclampsia versus normal pregnancy.

3.3 ET-1 pattern across obesity classes

Within the obesity subgroup, ET-1 values were not statistically different between class I and class II obesity ($p=0.567$). This should not be read as proof that obesity severity has no biological effect. Only 26 women had class I obesity and 18 had class II obesity, the ET-1 distribution was broad, and the study was not designed primarily to detect a graded BMI-response relation. The data therefore neither confirm nor exclude a nonlinear or threshold pattern.

A possible explanation is that coexisting obesity and severe preeclampsia already engage multiple endothelial stress pathways to a substantial degree. Adipose hypoxia, inflammatory mediators, oxidative stress, impaired nitric-oxide signaling, placental malperfusion, and antiangiogenic activity can all converge on the endothelin system. Once these processes are active, additional increments in BMI may have less influence on circulating ET-1 than the presence of the combined phenotype itself. Mechanistic

reviews support a link between metabolic dysfunction and endothelin biology [7,8], whereas clinical evidence is not uniform: a recent Indonesian adolescent study found no significant difference in ET-1 across obesity and hypertension groups [13]. This context dependence makes a simple linear BMI-ET-1 dose-response relation uncertain.

3.4 ET-1 in relation to maternal and obstetric characteristics

Table 3. ET-1 concentrations across selected maternal and obstetric categories

Characteristic	ET-1, median (IQR), pg/mL	**p-value**
Age <20 years	8.88 (0.92–60.94)	0.501
Age 20–35 years	0.86 (0.60–7.96)	
Age >35 years	1.63 (0.59–16.61)	
Nulliparous	1.04 (0.59–12.28)	0.628
Primiparous	0.87 (0.61–4.99)	
Multiparous	1.26 (0.51–27.11)	
Grand multipara	25.15*	
Preterm	2.77 (0.62–20.80)	0.167
Term	0.82 (0.59–5.34)	

*Only one participant was grand multiparous, preventing calculation of an IQR. Kruskal-Wallis testing was used for age and parity; Mann-Whitney U testing was used for gestational-age category.

No statistically significant ET-1 differences were detected across the examined categories of maternal age, parity, or gestational age. These secondary analyses are descriptive rather than definitive. The modest sample, categorization of continuous characteristics, and the strong endothelial disturbance inherent to severe preeclampsia may have obscured smaller associations.

3.5 Interpretation, study contribution, and limitations

The contribution of this study lies in the comparator chosen. Demonstrating that ET-1 is elevated in preeclampsia itself would add little because that relationship is already established [10,11,14]. Here, all participants had severe preeclampsia, yet women with obesity showed higher ET-1. The observation points to metabolic-endothelial heterogeneity within the severe disease phenotype and supports future work that integrates adiposity, metabolic status, angiogenic factors, renal indices, and vascular biomarkers rather than assuming that severe preeclampsia is biologically uniform.

Several design features strengthen the analysis, including recruitment from multiple centers, balanced group sizes for the principal comparison, classification using pre-pregnancy BMI, and exclusion of major chronic comorbid conditions likely to alter endothelial biology. Important constraints nevertheless remain. The cross-sectional design cannot establish temporal sequence or causality, and ET-1 was measured at a single time point. The overall sample was modest, and the obesity-class subgroups were smaller (26 women with class I obesity and 18 with class II obesity), limiting power to detect a graded BMI-response relation or to perform robust center-stratified analyses. Non-significant baseline comparisons do not establish equivalence between groups. Moreover, no multivariable model was fitted, so residual confounding by continuous gestational age, blood-pressure severity, renal function or proteinuria, metabolic characteristics, timing of blood sampling, and treatment exposure cannot be excluded. Although chronic hypertension, diabetes mellitus, renal, thyroid, and autoimmune disease and use of statins or fibrates were excluded by design, other medication exposures, less overt comorbidities, and treatment differences were not comprehensively characterized and may have contributed to the observed ET-1 distributions. The primary rank-based between-group comparisons are unaffected by unit scaling; however, future studies should preserve complete plate-level quality-control records, calibration data, dilution factors, and assay-range documentation.

The multicenter design broadens the clinical setting but also introduces potential center-level heterogeneity. Referral patterns, case mix, timing relative to diagnosis or treatment, pre-analytical handling, and local clinical pathways may differ across hospitals. In addition, center-specific counts for the final analyzable sample were not retained, precluding assessment of

recruitment balance across centers. Hospital-specific effects were not modeled, and the study was not powered for center-stratified inference; consequently, a center effect cannot be excluded. Future multicenter studies should standardize sampling and processing across sites, retain center-level recruitment data, and incorporate center in adjusted analyses when sample size permits.

For these reasons, the present data do not justify describing ET-1 as an established prognostic or predictive biomarker. Future studies should use longitudinal designs, standardize the timing and technique of ET-1 sampling across centers, model BMI as a continuous exposure, document medication and comorbidity profiles in greater detail, and apply multivariable adjustment for clinically relevant covariates and center effects. Serial biomarker measurement linked to maternal and neonatal outcomes would be required to determine whether an obesity-associated ET-1 signal provides prognostic information beyond conventional measures of disease severity.

4. CONCLUSION

In women already affected by severe preeclampsia, pre-pregnancy obesity was associated with higher circulating ET-1, while no additional increase was demonstrated between class I and class II obesity. The results are consistent with endothelial heterogeneity in the presence of maternal adiposity, but they do not establish causation, a BMI threshold, or clinical predictive value. Longitudinal studies incorporating standardized biomarker measurement across centers, continuous adiposity measures, detailed medication and comorbidity data, multivariable analysis, and maternal-neonatal outcomes are needed before the association can be translated into clinical use.

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AUTHOR CONTRIBUTIONS

ETA: study conception, investigation, participant recruitment, and preparation of the initial manuscript. EL and NA: study conception, supervision, and critical revision of the manuscript. RBL, IS, and SS: formal analysis, interpretation, supervision, and critical manuscript revision.

CONFLICT OF INTEREST

The authors report no competing interests.

ETHICS STATEMENT

Approval was granted by the Ethics Committee of the Faculty of Medicine, Hasanuddin University (No. 490/UN4.6.5.31/PP36/2025). Written informed consent was obtained from every participant. Participation was voluntary, confidentiality safeguards were applied, and declining or withdrawing from the study did not affect clinical care.

DATA AVAILABILITY STATEMENT

De-identified study data may be obtained from the corresponding author on reasonable request, subject to ethics approval, privacy safeguards, and relevant institutional regulations.

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