



RESEARCH ARTICLE

Neutrophil Gelatinase Associated Lipocalin Levels in Normal Pregnancy and Preeclampsia Subtypes

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Abstract

Objective: To determine the differences in neutrophil gelatinase-associated lipocalin (NGAL) expression in normal pregnancy, early-onset preeclampsia (EOP), and late-onset preeclampsia (LOP).

Method: This was an observational analytic study with a cross-sectional design conducted from April 2024 to June 2025. The study population included pregnant women aged ≥ 20 weeks presenting to the Obstetrics Department at Dr. M. Djamil General Hospital, Andalas University Hospital, and Dr. Reksodiwiryo Hospital in Padang. Samples were divided into three groups: normal pregnancy, EOP, and LOP. Exclusion criteria included history of malignancy, infection, premature rupture of membranes, or comorbidities. NGAL levels were measured from venous blood samples using the ELISA method. Data were analyzed using One-way ANOVA.

Result: The study included 36 samples: 12 normal pregnancies, 13 EOP, and 11 LOP. Demographic characteristics were similar across groups, with a mean age of 31 years, predominantly multiparous, obese, and housewives. The mean NGAL levels were 2.45 ± 0.73 ng/ml in normal pregnancy, 3.61 ± 1.12 ng/ml in EOP, and 3.63 ± 1.12 ng/ml in LOP. Statistical analysis showed a significant difference in NGAL expression between normal pregnancy and both preeclampsia groups ($p = 0.01$) Post-hoc analysis confirmed significant differences between normal vs. EOP ($p = 0.021$) and normal vs. LOP ($p = 0.027$) but no significant difference was found between EOP and LOP ($p = 1$).

Conclusion: Significant differences in NGAL expression were found between normal pregnancy and preeclampsia (both early and late onset). However, NGAL levels did not differ significantly between early-onset and late-onset preeclampsia.

Keywords: Preeclampsia, Early onset, Late onset, NGAL, Biomarker

INTRODUCTION

Hypertension in pregnancy, particularly preeclampsia, remains a serious global health issue and is a leading cause of maternal morbidity and mortality. Worldwide, approximately 10% of pregnant women experience hypertension during pregnancy. Preeclampsia itself accounts for 5-10% of all pregnancies and is responsible for 14% of maternal deaths and over 500,000 fetal deaths annually.¹⁻⁴

In Indonesia, hypertension ranked as the second leading cause of maternal death after hemorrhage in 2019. Local data from Dr. M. Djamil General Hospital Padang (the national referral hospital for the Central Sumatra region) recorded 432 cases of severe preeclampsia during the 2018-2020 period. The long-term impact of preeclampsia is significant, including the risk of future non-communicable diseases for both mother and child, perinatal death, preterm birth, and low birth weight.^{4,5}

Clinical diagnosis of preeclampsia is generally established through findings of hypertension and proteinuria. However, challenges arise because proteinuria does not always accompany preeclampsia, and clinical symptoms often vary. This drives the need for more sensitive and specific biomarkers for early detection and accurate diagnosis.^{2,6}

One promising biomarker is *Neutrophil Gelatinase-Associated Lipocalin* (NGAL). NGAL is a 25-kDa protein expressed by neutrophils, kidneys, and other cells in response to endothelial damage, ischemia, and inflammation. In obstetrics, elevated NGAL is associated with maternal kidney damage and systemic endothelial dysfunction due to inflammation in preeclampsia. Several studies suggest that NGAL is superior to creatinine as a marker of renal impairment in pregnancy and has the potential to be an early predictor of preeclampsia. Nevertheless, research findings regarding NGAL remain controversial; some studies found significant increases in preeclampsia, while others found no significant differences.⁷⁻¹⁰

Preeclampsia is a hypertensive disorder of pregnancy characterized by the new onset of elevated blood pressure—defined as systolic pressure of 140 mmHg or higher, or diastolic pressure of 90 mmHg or higher—occurring after 20 weeks of gestation. This rise in blood pressure must be accompanied by either proteinuria or specific signs of maternal organ dysfunction. Proteinuria typically reflects renal involvement, but even in its absence, preeclampsia can be diagnosed when there is evidence of thrombocytopenia, impaired kidney function, elevated liver enzymes indicating hepatic injury, pulmonary edema, or neurological symptoms such as severe headache or visual disturbances. These diagnostic criteria reflect the systemic nature of the disease and its potential to affect multiple organ systems, underscoring the importance of early recognition and timely management to prevent severe maternal and fetal complications.¹¹

The pathogenesis of preeclampsia is widely described using a two-stage model that differentiates early-onset preeclampsia (EOP) from late-onset preeclampsia (LOP). In the first stage, which is placental in origin, the underlying mechanisms differ between EOP and LOP. In EOP, abnormal placentation occurs due to a failure of the spiral arteries to remodel into the large-caliber,

low-resistance vessels required for adequate uteroplacental perfusion. This defective remodeling leads to placental ischemia and oxidative stress early in pregnancy. In contrast, LOP is characterized not by a primary placental defect but by a mismatch between the growing metabolic and oxygen demands of the fetoplacental unit in late pregnancy and the mother's ability to increase perfusion. This mismatch is often associated with maternal comorbidities such as obesity, chronic hypertension, diabetes, or other cardiovascular and metabolic conditions that limit adaptive hemodynamic responses.^{12,13}

The second stage of the model represents the development of the maternal syndrome. Once the placenta becomes ischemic—whether from early structural abnormalities or late physiological mismatch—it releases a cascade of circulating factors into the maternal bloodstream. Key among these are anti-angiogenic substances such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng), along with a range of inflammatory mediators. These factors disrupt normal endothelial function throughout the maternal vascular system, resulting in widespread endothelial dysfunction. This systemic endothelial injury underlies the clinical manifestations of preeclampsia, including hypertension, proteinuria, end-organ involvement, and the potential progression to severe disease.^{12,13}

Neutrophil gelatinase-associated lipocalin (NGAL) plays a multifaceted role in the pathophysiology of preeclampsia, rising in response to heightened immune activation, endothelial injury, and renal involvement. In preeclampsia, an exaggerated maternal inflammatory response leads to marked neutrophil activation, during which neutrophils release structures known as Neutrophil Extracellular Traps (NETs). These NETs contribute to vascular damage and simultaneously serve as a source of circulating NGAL. Endothelial dysfunction further amplifies NGAL levels, while kidney injury—both glomerular and tubular—adds an additional stimulus for its production. Among its measurable forms, serum NGAL appears to have stronger diagnostic value compared to urinary NGAL, reflecting its closer association with systemic inflammation and endothelial damage characteristic of preeclampsia.^{14–16}

This study aims to evaluate differences in NGAL levels across three groups: normal pregnancy, early-onset preeclampsia (EOP), and late-onset preeclampsia (LOP) in the West Sumatra population, considering that the pathogenesis of EOP and LOP has fundamental differences but results in a similar maternal syndrome.

METHODS

This study employed an analytical observational approach with a cross-sectional design to evaluate NGAL levels among different groups of pregnant women. The research was conducted over a period extending from April 2024 to June 2025, during which both sample collection and laboratory analyses were completed. This design allowed the researchers to capture data at a single point in time from participants who met the study criteria.

The study was carried out across several clinical settings to ensure adequate sample representation. Samples were collected from the Emergency Room, inpatient wards, and the

Obstetrics and Gynecology Polyclinic of Dr. M. Djamil General Hospital Padang. Additional samples were obtained from network hospitals, including Universitas Andalas Hospital and Dr. Reksodiwiryo Hospital. All laboratory examinations, specifically the analysis of NGAL levels, were conducted at the Biomedical Laboratory of the Faculty of Medicine, Universitas Andalas, ensuring standardized processing and reliable laboratory outputs.

The study population consisted of all pregnant women with a gestational age of 20 weeks or more who presented to Dr. M. Djamil General Hospital Padang. Using a consecutive sampling technique, participants who met the inclusion criteria were enrolled sequentially until the intended sample size was reached. Based on the formula for comparing two proportions, the minimum required sample size was calculated to be nine subjects per group. To anticipate a potential 10% dropout, the number was rounded up to ten subjects per group, resulting in a minimum total of 30 participants.

Inclusion criteria consisted of normal pregnancies of at least 20 weeks' gestation, pregnancies complicated by early-onset preeclampsia (occurring between 20 and <34 weeks), and pregnancies with late-onset preeclampsia (≥ 34 weeks). All participants were required to have an intrauterine pregnancy and provide informed consent. Women were excluded if they had a history of malignancy or infectious disease, premature rupture of membranes, or comorbid conditions such as cardiovascular disease, chronic kidney disease, or diabetes mellitus. Blood samples showing evidence of lysis were also excluded from analysis.

Operational definitions were established to ensure clarity and consistency. Early-onset preeclampsia was defined as hypertension with systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg accompanied by proteinuria or signs of organ dysfunction before 34 weeks of gestation. Late-onset preeclampsia followed the same diagnostic criteria but occurred at or beyond 34 weeks. NGAL was defined as the concentration measured in venous serum using the ELISA method and expressed in ng/mL.

The study procedures involved several standardized steps. Participants underwent informed consent, detailed anamnesis, physical examination including blood pressure measurement, and screening for eligibility. Blood samples were collected by drawing 5 mL from the median cubital vein, which were then placed into EDTA tubes and centrifuged at $1000\times g$ for 15 minutes to obtain serum or plasma. Laboratory analysis using ELISA involved adding samples and standards to microplate wells, followed by incubation, washing, application of detection reagents, and measurement of optical density within ten minutes of adding the stop solution.

Data processing was conducted using SPSS software. Univariate analysis summarized demographic characteristics using frequency distributions, means, and standard deviations. Normality of the numerical variables was assessed using the Shapiro–Wilk test. As NGAL values were normally distributed, mean comparisons across the three study groups were performed using One-Way ANOVA. A p-value of less than 0.05 was considered statistically significant. For significant ANOVA results, a Bonferroni Post Hoc test was carried out to evaluate pairwise differences between groups.

RESULTS

Sample Characteristics

A total of 36 pregnant women were included in this study, consisting of 12 normal pregnancies, 13 cases of early-onset preeclampsia (EOP), and 11 cases of late-onset preeclampsia (LOP). The demographic characteristics across the groups demonstrated a relatively homogeneous age distribution, with mean ages around 31–32 years, thereby reducing the likelihood of age-related confounding on NGAL levels. Parity analysis revealed that multigravida women predominated in all three groups, although the proportion varied, with the highest in normal pregnancy (91.7%) and lower but still substantial proportions in the EOP (61.5%) and LOP (81.8%) groups. Body mass index (BMI) findings showed that obesity was highly prevalent, affecting 75% of normal pregnancies and more than 80% of women with preeclampsia, reflecting the strong metabolic risk profile in the sampled population. Most participants had a high school level education and were predominantly housewives (IRT), suggesting a relatively similar socioeconomic background among the study population.

NGAL Levels (Neutrophil Gelatinase–Associated Lipocalin)

The examination of NGAL levels revealed distinct differences between normal pregnancies and those complicated by preeclampsia. Normal pregnant women had a mean serum NGAL concentration of 2.45 ± 0.73 ng/mL, with values ranging from 1.64 to 4.25 ng/mL. In contrast, both preeclampsia groups exhibited markedly higher levels. The EOP group demonstrated an average NGAL level of 3.61 ± 1.12 ng/mL (range: 2.03–5.92 ng/mL), while the LOP group showed a similar mean value of 3.63 ± 1.12 ng/mL (range: 1.99–5.12 ng/mL). These findings indicate a consistent elevation of NGAL in preeclamptic pregnancies, regardless of the timing of disease onset.

Statistical Analysis (Difference Test)

Statistical testing using One-Way ANOVA demonstrated a significant overall difference in NGAL levels across the three study groups, with a p-value of 0.01. Post Hoc analysis using the Bonferroni correction confirmed that NGAL levels were significantly higher in both EOP and LOP compared with normal pregnancies. The comparison between normal and EOP yielded a p-value of 0.021, while normal versus LOP showed a p-value of 0.027, both indicating statistically significant differences. However, the comparison between EOP and LOP resulted in a p-value of 1.000, suggesting no significant difference in NGAL expression between the two forms of preeclampsia.

DISCUSSION

Interpretation of Demographic Characteristics

The relative similarity in maternal age among participants is an important methodological strength, as NGAL levels are known to rise more noticeably in women above 45 years. The predominance of multiparous women in the preeclampsia groups differs from classical obstetric theories, which often emphasize primigravidity as a major risk factor. This discrepancy highlights the multifactorial nature of preeclampsia, where new paternal exposure, long interpregnancy

intervals, advancing maternal age, and metabolic factors may contribute to risk in multiparous women. The high prevalence of obesity—affecting over three-quarters of participants in every group—further underscores the metabolic background of the study population. Obesity is well documented to promote systemic inflammation and endothelial dysfunction, mechanisms central to the development of preeclampsia.^{17–19}

Analysis of NGAL Levels in Normal Pregnancy

Normal pregnancies in this study exhibited NGAL levels averaging 2.45 ± 0.73 ng/mL, consistent with physiological elevation during gestation. Several mechanisms account for this increase: enhanced glomerular filtration rate (GFR) leads to greater NGAL reabsorption dynamics, while the heightened oxidative metabolic demands of pregnancy stimulate mild neutrophil activation and chemotaxis. Despite these physiological changes, NGAL levels in normal pregnancy remained significantly lower than those observed in preeclampsia, confirming the usefulness of normal pregnancy values as a baseline reference.^{20–22}

Analysis of NGAL Levels in Preeclampsia (EOP and LOP)

Both forms of preeclampsia demonstrated a clear elevation in NGAL levels, with similar mean values in EOP (3.61 ng/mL) and LOP (3.63 ng/mL). The rise in NGAL is explained by several pathophysiological mechanisms. Preeclampsia is marked by systemic endothelial dysfunction and placental ischemia, both of which drive the release of pro-inflammatory cytokines that activate neutrophils. Activated neutrophils produce NGAL as part of the acute-phase inflammatory response. Additionally, renal involvement—particularly glomeruloendotheliosis—impairs tubular reabsorption or stimulates increased renal synthesis of NGAL, further elevating systemic levels. These findings align with previous literature, including analyses by Sisti et al. (2023) and D’Anna et al. (2010), which consistently report elevated serum NGAL in preeclampsia due to oxidative stress and endothelial injury.^{7,9,14,23}

Comparison of NGAL Between EOP and LOP

Although theoretical models suggest that EOP, with its more pronounced placental pathology, should exhibit higher NGAL levels than LOP, this study did not observe a significant difference between the two groups. This finding suggests that despite differing origins—EOP being primarily placental and LOP more often associated with maternal metabolic factors—the downstream systemic effects are comparable once the disease becomes clinically apparent. Both types of preeclampsia ultimately produce substantial endothelial damage and systemic inflammation, which lead to similar NGAL elevations. Another plausible explanation is the tertiary referral nature of Dr. M. Djamil General Hospital, where both EOP and LOP patients may present with more severe conditions, narrowing biomarker differences that might otherwise be seen in community-based populations.^{2,16,18,24–26}

Limitations of the Study

This study has several notable limitations. First, NGAL levels were only assessed during the third trimester at the time of diagnosis; thus, the study does not provide insight into the predictive

value of NGAL for early identification of preeclampsia. Second, this research focused exclusively on serum NGAL without evaluating urinary NGAL, which may provide additional information regarding the relative contributions of renal injury versus systemic inflammation. Future studies incorporating longitudinal sampling and dual-matrix (serum and urine) analysis may help clarify the temporal progression and diagnostic utility of NGAL in preeclampsia.

CONCLUSION

Pregnant women with preeclampsia at Dr. M. Djamil General Hospital Padang in this study were generally around 31 years old, multiparous, obese, and predominantly housewives, reflecting a population with several established risk factors for preeclampsia. Normal pregnancies demonstrated a mean serum NGAL level of 2.45 ± 0.73 ng/mL, representing physiological changes in neutrophil activity and renal function. In contrast, NGAL levels were significantly elevated in both early-onset (3.61 ± 1.12 ng/mL) and late-onset preeclampsia (3.63 ± 1.12 ng/mL), confirming a marked increase in inflammatory and endothelial dysfunction markers among affected pregnancies. The significant difference between normal pregnancy and preeclampsia underscores NGAL's potential as a biomarker for disease pathology, while the absence of differences between EOP and LOP suggests that, despite differing initiating mechanisms, both forms ultimately produce a comparable degree of systemic endothelial damage and inflammation in the study population.

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