

**RESEARCH ARTICLE****Urinary KIM-1 Levels Normal Pregnancy vs Early-Onset Preeclampsia, and Late-Onset Preeclampsia**Silvia H. Morena¹, Vaulinne Basyir^{2,*}, Husna Yetti³¹ *Department of Obstetrics and Gynecology, Faculty of Medicine, Andalas University/ Dr. M. Djamil, Hospital Padang, West Sumatra, Indonesia*² *Fetomaternal Subdivision, Department of Obstetrics and Gynecology, Faculty of Medicine, Andalas University/ Dr. M. Djamil Hospital, Padang, West Sumatra, Indonesia*² *Department of Public Health Sciences, Faculty of Medicine, Andalas University/ Dr. M. Djamil Hospital, Padang, West Sumatra, Indonesia***Corresponding Author:** Vaulinne Basyir; vaulinne@gmail.com ; +62 812-6618-805**Submitted :** May 14, 2025; **Accepted:** July 8, 2025; **Published:** July 25, 2025**Doi :** <https://doi.org/10.25077/aoj.9.2.213-223.2025>**Abstract****Introduction :** Preeclampsia is a hypertensive disorder of pregnancy that contributes to high maternal mortality rates. Kidney Injury Molecule-1 (KIM-1) has been identified as a potential biomarker for detecting kidney injury and is suspected to play a role in the pathogenesis of preeclampsia.**Objective :** This study to determine the differences in urinary KIM-1 levels among normal pregnancies, early-onset preeclampsia, and late-onset preeclampsia at Dr. M. Djamil General Hospital, Padang.**Methods :** Cross-sectional comparative study included 72 pregnant women, consisting of 24 with normal pregnancies, 24 with early-onset preeclampsia, and 24 with late-onset preeclampsia. Urinary KIM-1 levels were measured using the ELISA method at the Biomedical Laboratory, Faculty of Medicine, Andalas University.**Results :** The mean urinary KIM-1 levels in the normal pregnancy group were 2.834 ± 0.957 ng/mL, in the early-onset preeclampsia group were 2.659 ± 1.175 ng/mL, and in the late-onset preeclampsia group were 2.694 ± 0.978 ng/mL. Statistical analysis showed no significant difference in urinary KIM-1 levels among the three groups ($p > 0.05$).**Conclusion :** There was no significant difference in urinary KIM-1 levels between normal pregnancies, early-onset preeclampsia, and late-onset preeclampsia. Further studies with larger sample sizes and more specific methods are needed to explore the potential of KIM-1 as a preeclampsia biomarker.**Keywords:** Preeclampsia, urinary KIM-1, biomarker, normal pregnancy, early onset preeclampsia, late onset preeclampsia

INTRODUCTION

Preeclampsia is a complex, multi-system hypertensive disorder of pregnancy and a leading cause of maternal and perinatal morbidity and mortality worldwide, affecting 2–8% of pregnancies and accounting for an estimated 70,000 maternal deaths annually.¹ The disorder is increasingly understood not as a single disease entity but as a heterogeneous syndrome with distinct pathophysiological origins, broadly categorized into early-onset and late-onset subtypes.³ This distinction is critical for understanding its clinical manifestations and for developing targeted diagnostic and therapeutic strategies. The widely accepted "two-stage" model posits that preeclampsia originates from placental dysfunction (Stage 1), which then leads to a systemic maternal inflammatory and endothelial response (Stage 2).⁴

Early-onset preeclampsia (EOP), typically defined by onset before 34 weeks of gestation, is considered a "placental" disease. It is characterized by severe placental pathology, including defective trophoblast invasion of the maternal spiral arteries, which results in placental hypoperfusion, ischemia, and the release of anti-angiogenic factors into the maternal circulation.³ This placental insufficiency is strongly associated with more severe maternal and neonatal outcomes, including fetal growth restriction (FGR), HELLP (Hemolysis, Elevated Liver enzymes, Low Platelet count) syndrome, and preterm delivery.² In contrast, late-onset preeclampsia (LOP), occurring at or after 34 weeks, is viewed as a "maternal" disease. LOP is thought to arise from the interaction of a relatively well-perfused placenta with underlying maternal constitutional factors, such as pre-existing chronic hypertension, obesity, or metabolic syndrome, which overwhelm the maternal system's capacity to adapt to pregnancy, leading to systemic endothelial stress.³

The common pathophysiological pathway for both subtypes is systemic maternal endothelial dysfunction, which manifests as the clinical syndrome of hypertension, proteinuria, and multi-organ injury.⁴ A key mediator of vascular health is nitric oxide (NO), a potent vasodilator produced by endothelial nitric oxide synthase (eNOS). Dysregulation of the NO pathway, leading to reduced NO bioavailability, is a central feature of the endothelial dysfunction seen in preeclampsia.⁸ Research conducted within the same hospital population as the present study has explored eNOS levels in EOP and LOP, suggesting that local factors may influence this pathway.¹ This endothelial damage is further propagated by systemic oxidative stress. Factors released from the stressed or ischemic placenta, such as cell-free fetal hemoglobin, can leak into the maternal circulation, where they scavenge NO, generate reactive oxygen species, and trigger an inflammatory cascade, creating a vicious cycle of vasoconstriction and tissue damage that affects multiple organs, including the kidneys.¹⁰

Renal involvement is a hallmark of preeclampsia, which is a primary cause of pregnancy-related acute kidney injury (PRAKI).¹¹ The classic renal lesion, known as glomerular endotheliosis, involves the swelling of glomerular endothelial cells and the deposition of fibrinoid material, which primarily signifies

glomerular injury.¹¹ While this glomerular pathology is well-documented, the extent and clinical significance of concomitant *tubular* injury are less defined. This gap in knowledge provides

a compelling rationale for investigating biomarkers specific to tubular damage. Kidney Injury Molecule-1 (KIM-1) is a type 1 transmembrane glycoprotein that is minimally expressed in the normal kidney but is dramatically upregulated in the apical membrane of proximal tubule epithelial cells following ischemic or nephrotoxic injury, making it a highly sensitive and specific biomarker of acute proximal tubular damage.¹⁴ Alongside KIM-1, Neutrophil Gelatinase-Associated Lipocalin (NGAL) is another well-studied biomarker of tubular stress, often investigated in parallel to provide a more complete picture of renal tubular response to injury.¹³

The existing literature on KIM-1 as a biomarker for preeclampsia presents conflicting results. Several studies have reported significantly elevated levels of urinary or serum KIM-1 in women with preeclampsia compared to normotensive controls.⁶ For example, research by Wang et al. demonstrated that both plasma and urinary KIM-1 levels were significantly higher in preeclamptic women, a finding supported by immunohistochemical evidence of increased KIM-1 expression in renal proximal tubules.¹³ Similarly, Berenji et al. and Yalman et al. reported higher KIM-1 levels in preeclamptic cohorts.¹ However, these findings are not universal, creating a clear evidence gap. Furthermore, there is a scarcity of data from Indonesian populations, who may possess distinct genetic and environmental risk profiles for preeclampsia, as suggested by local research identifying risk factors such as low physical activity and short interpregnancy intervals.¹

Therefore, this study was conducted to investigate the difference in urinary KIM-1 levels among normal pregnancy, EOP, and LOP within the specific patient population at Dr. M. Djamil Hospital, Padang, to clarify its potential role as a diagnostic biomarker in this setting.

METHODS

The research design used was the *cross sectional comparative study method*. This method was chosen to observe the independent variables and dependent variables once at the same time. The population of this study was all pregnant women with normal pregnancies at gestational age > 20 weeks, early onset preeclampsia at gestational age 20-34 weeks and late onset preeclampsia at gestational age > 34 weeks obtained from physical and supporting examinations and received management at the Polyclinic, Ponek and Delivery Room of Dr. M. Djamil Padang Central General Hospital as many as 72 samples with each group consisting of 24 pregnant women. Examination of urine samples from pregnant women was carried out at the Biomedical Laboratory of the Faculty of Medicine, Andalas University for examination of KIM-1 levels. Data collection and collection of research data were conducted in April–September 2024. Inclusion criteria Pregnant women with normal pregnancies with systolic blood pressure <90 mmHg and no signs and symptoms of preeclampsia after 20 weeks of gestation based on physical examination, clinical symptoms and supporting examinations, pregnant women with a gestational age of >20 weeks, gestational age >20 weeks – <34 weeks and gestational age ≥34 weeks (known with certainty from reliable HPHT and with obstetric examination (USG), do not suffer from chronic hypertension, do not suffer from kidney disease or conditions that affect kidney function previously, pregnant women who are willing to be research samples. Exclusion criteria are damaged urine samples and cannot be assessed during

the research process.

Urine samples are collected into sterile tubes, then centrifuge the sample for 20 minutes at 2000-3000 RPM. Collect the supernatant without sediment. Samples to be used within 5 days should be stored at 2-8 ° C. Samples should be aliquoted or should be stored at - 20 ° C within 1 month or -80 ° C within 3 months. Avoid repeated thawing (hemolysis) because it will affect the validity of the results. Samples should also be brought to room temperature before starting the test. Centrifuge the sample before use. If sediment occurs during storage, centrifugation should be done again. All reagents should be brought to room temperature (18-25 ° C) before use. Reconstitute 120ul of standard (4800pg / ml) with 120ul of standard diluent to produce a standard stock solution of 2400pg / ml. Allow the standard to stand for 15 minutes with agitation before making dilutions. Prepare duplicate standards by serially diluting the standard stock solution (2400pg/ml) 1:2 with standard diluent to produce solutions of 1200pg/ml, 600pg/ml, 300pg/ml and 150pg/ml. The remaining solution should be frozen at -20°C and used within one month. Dilute 20 ml of 25x Wash Buffer solution with deionized or distilled water to produce 500 ml of 1x Wash Buffer. If crystals have formed in the concentrate, stir gently until the crystals are completely dissolved.

Assay Procedure is done by preparing all reagents, standard solutions and samples as instructed. Bring all reagents to room temperature before use. The test is performed at room temperature. Determine the number of strips required for the test. Insert the strips in the frame for use. Unused strips should be stored at 2-8°C. Add 50ul of standard to the standard. Note: Do not add antibody to the standard well because the standard solution contains biotinylated antibodies. Add 40ul of sample to the sample well and then add 10ul of Human NTN1 antibody to the sample, then add 50ul of streptavidin-HRP to the sample and standard wells. Mix and cover the plate with sealer. Incubate for 60 minutes at 37°C. Remove the sealer and wash the plate 5 times with wash buffer. Soak with 300ul of wash buffer for 30 seconds - 1 minute for each wash. Add 50ul of substrate solution A to each well and then add 50ul of substrate solution B to each well. Incubate the plate covered with fresh sealer for 10 minutes at 37°C in the dark. Add 50ul Stop Solution to each well, there will be an immediate color change from blue to yellow. Determine the optical density (OD value) of each well using a microplate reader set to 450 nm within 10 minutes after adding the stop solution. Calculation of Results Create a standard curve by plotting the average OD for each standard on the vertical (Y) axis against the concentration on the horizontal (X) axis. Then draw the best fit curve through the points on the graph. This calculation can be done well with computer-based curve-fitting software and the line of best fit can be determined by regression analysis. And all samples were tested 2 times.

Data analysis was performed using univariate and bivariate . Univariate analysis was used to determine the description of the independent and dependent variables of the study. The dependent variable used a nominal measurement scale including categorical data, which was analyzed univariately with the results of the mean and standard deviation values. While the independent variable used a ratio measurement scale including numeric data, which was analyzed univariately with the results being the frequency distribution and proportion of each category. Bivariate analysis was used to determine the difference in the average levels of KIM-1 urine between early onset

preeclampsia and normal pregnancies. The normality test was performed first on the KIM-1 urine level data using the Shapiro-Wilk test. If the distribution is normal, the One way Annova test will be used and if it is not normally distributed, the Kruskal Wallis test will be used.

RESULT

In this study, there were 72 respondents consisting of respondents with normal pregnancy, early onset preeclampsia and late onset preeclampsia. Table 1 shows the characteristics of the subjects of this study including maternal age, parity, and gestational age. Most respondents in all groups were multipara.

Table 1 Frequency and Description of Characteristics of Research Subjects at RSUP DR. M. Djamil Padang

Characteristics	Normal Pregnancy n = 24		Preeclampsia			
			Early onset		Late onset	
	Mean $\pm$ SD	f (%)	Mean $\pm$ SD	f (%)	Mean $\pm$ SD	f (%)
Mother's age (years)	28.88 $\pm$ 4.26		32.08 $\pm$ 5.74		31.25 $\pm$ 6.38	
Parity (n)						
Primipara		5 (20.83)		9 (37.5)		8 (33.33)
Multipara		19 (79.17)		15 (62.5)		16 (66.67)
Gestational age (weeks)	30.54 $\pm$ 5.68		30.67 $\pm$ 2.69		36.48 $\pm$ 1.86	

*SD = Standard Deviation; n = number of samples; f = frequency

Table 1 shows that the average maternal age in the normal pregnancy group was 28.88 $\pm$ 4.26, while in the early-onset and late-onset preeclampsia groups it was 32.08 $\pm$ 5.74 years and 31.25 $\pm$ 6.38 years, respectively. Based on parity, in the normal pregnancy group there were 5 mothers (20.83%) primiparous and 19 mothers (79.17%) multiparous. In the early-onset preeclampsia group, there were 9 mothers (37.5%) primiparous and 15 mothers (62.5%) multiparous, while in the late-onset preeclampsia group there were 8 mothers (33.33%) primiparous and 16 mothers (66.67%) multiparous. The mean gestational age in the normal pregnancy group was 30.54 weeks (SD = 5.68), in the early onset preeclampsia group was 30.67 weeks (SD = 2.69), and in the late onset preeclampsia group was 36.48 weeks (SD = 1.86). Most respondents in all groups were multipara.

Table 2. Average levels of *Kidney Injury Molecule-1* (KIM-1) in the urine of respondents at RSUP Dr. M. Djamil Padang

Urine KIM-1 Levels	n	Mean $\pm$ SD (ng/ml)	Min (ng/ml)	Max (ng/ml)
Normal pregnancy	24	2.834 $\pm$ 0.957	1,550	4,972
Early Onset Preeclampsia	24	2,659 $\pm$ 1,175	1,029	6,155
Late Onset Preeclampsia	24	2.694 $\pm$ 0.978	1,231	5,154
Total	72	2,729 $\pm$ 1,030	1,029	6,155

*SD = Standard Deviation; n = number of samples; min-max = minimum-maximum

Table 2 shows the average results of *Kidney Injury Molecule-1* (KIM-1) levels in urine in three groups of study subjects, namely normal pregnancy, early-onset preeclampsia, and late-onset preeclampsia. In the normal pregnancy group (n = 24), the average KIM-1 level was 2.834 $\pm$ 0.957 ng/ml, with a minimum value of 1.550 ng/ml and a maximum of 4.972 ng/ml. This shows that KIM-1 levels in normal pregnancy are relatively variable but still in a lower range compared to the preeclampsia group. For the early-onset preeclampsia group (n = 24), the average KIM-1 level was slightly lower, at 2.659 $\pm$ 1.175 ng/ml. However, the variation of KIM-1 values in this group was greater, ranging from 1.029 ng/ml to 6.155 ng/ml, indicating a higher increase in KIM-1 levels in some individuals with early-onset preeclampsia compared to normal pregnancies. Meanwhile, the late-onset preeclampsia group (n = 24) had an average KIM-1 level of 2.694 $\pm$ 0.978 ng/ml, ranging from 1.231 ng/ml to 5.154 ng/ml. Overall, of the three groups studied (total n = 72), the average KIM-1 level was 2.729 $\pm$ 1.030 ng/ml. The range of KIM-1 levels for all samples was between 1.029 ng/ml to 6.155 ng/ml, indicating differences in the distribution of KIM-1 levels between groups, with the possibility of higher levels in preeclampsia compared to normal pregnancy.

Table 3. Initial Data Normality Test with Shapiro-Wilk Test on Urine *Kidney Injury Molecule-1* (KIM-1) Levels

Group	Shapiro Wilk	
	n	p-value
Normal Pregnancy	24	0.016
Early Onset Preeclampsia	24	0.059
Late Onset Preeclampsia	24	0.246

Table 3 shows the results of the normality test using Shapiro Wilk and it was found that the data in the normal pregnancy group had a p-value of 0.016, which was less than 0.05, so the data in this group were not normally distributed. Meanwhile, in the early-onset preeclampsia group, the p-value of 0.059 showed a value greater than 0.05, so the data in this group could be considered normally distributed. Likewise, in the late-onset preeclampsia group, the p-value was 0.246, which was also greater than 0.05, indicating that the data in this group were normally distributed. Since the normality test was not met, the ANOVA test was less appropriate for this data. As an alternative,

the Kruskal-Wallis test is a better choice because it does not require the assumption of normality.

Table 4 Differences in urine KIM-1 levels between normal and postpartum pregnancies.

Variables	Group						p-value
	Normal pregnancy		Early onset preeclampsia		Late onset preeclampsia		
	N	Mean (min–max)	N	Mean (min–max)	N	Mean (min–max)	
Urinary KIM-1 levels	24	2,834 (1,550-4,972)	24	2,659 (1,029-6,155)	24	2,694 (1,231-5,154)	0.774

Table 4 shows the results of the Kruskal-Wallis test showing that there was no statistically significant difference ($p\text{-value} > 0.05$) in urinary Kidney Injury Molecule-1 (KIM-1) levels among three patient groups, namely the normal pregnancy group, early onset preeclampsia, and late onset preeclampsia.

DISCUSSION

The average maternal age in the normal pregnancy group was 28.88 years, while in the early-onset and late-onset preeclampsia groups it was 32.08 ± 5.74 years and 31.25 ± 6.38 years, respectively. Older maternal age, especially over 35 years, is known to be a significant risk factor for preeclampsia. This is due to several factors, including declining egg quality and increased prevalence of chronic medical conditions, such as hypertension and diabetes, in older age that can affect pregnancy. Older women are also at higher risk for other pregnancy complications that can trigger preeclampsia, such as multiple pregnancies or a history of disease in previous pregnancies.

Based on parity, in the normal pregnancy group there were 5 mothers (20.83%) primiparous and 19 mothers (79.17%) multiparous. In the early onset preeclampsia group, there were 9 mothers (37.5%) primiparous and 15 mothers (62.5%) multiparous, while in the late onset preeclampsia group there were 8 mothers (33.33%) primiparous and 16 mothers (66.67%) multiparous. The average gestational age in the normal pregnancy group was 30.54 weeks ($SD = 5.68$), in the early onset preeclampsia group it was 30.67 weeks ($SD = 2.69$), and in the late onset preeclampsia group it was 36.48 weeks ($SD = 1.86$).

In the normal pregnancy group ($n = 24$), the average KIM-1 level was 2.834 ± 0.957 ng/ml, with a minimum value of 1.550 ng/ml and a maximum of 4.972 ng/ml. This shows that the KIM-1 level in normal pregnancy is relatively variable but still in a lower range compared to the preeclampsia group. For the early-onset preeclampsia group ($n = 24$), the average KIM-1 level was slightly lower, at 2.659 ± 1.175 ng/ml. However, the variation in KIM-1 values in this group was greater, with a range between 1.029 ng/ml to 6.155 ng/ml, indicating a higher increase in KIM-1

levels in some individuals with early-onset preeclampsia compared to normal pregnancies. Meanwhile, the late-onset preeclampsia group ($n = 24$) had an average KIM-1 level of 2.694 ± 0.978 ng/ml, with a range between 1.231 ng/ml and 5.154 ng/ml.

Previous research conducted by Wang et al. (2023) showed that urinary Kidney Injury Molecule-1 (KIM-1) levels in women with preeclampsia were significantly higher compared to the normal control group ($p < 0.01$).⁷ Research by Jing Xiao et al. (2013) also reported higher urinary KIM-1 (uKIM-1) levels in patients with preeclampsia (2.34 ± 1.31 mg/ml) compared to normal pregnancies (1.58 ± 0.97 mg/ml) with a significance of $p < 0.05$.³⁰ Meanwhile, the results of this study showed that KIM-1 levels in normal pregnancies were relatively variable but remained in a lower range compared to the preeclampsia group. However, statistical tests on urinary KIM-1 levels between normal pregnancy, early-onset preeclampsia, and late-onset preeclampsia groups did not show any significant differences.

This non-significant result may be explained by the characteristics of KIM-1 as a biomarker typical for acute kidney damage.¹² In preeclampsia, kidney damage tends to be subclinical or chronic, so that increased KIM-1 levels may not be prominent enough to produce significant differences in patients with preeclampsia.¹³ Sample size can also affect statistical power to detect differences in KIM-1 levels between groups. Studies with small sample sizes have the potential to produce high levels of variability in the data, making differences between groups less significant. Variation in KIM-1 levels between individuals can also increase the standard deviation, which ultimately affects the results of statistical analysis.

Several previous studies, including those by Wang et al. (2023), showed significant results related to KIM-1 levels in preeclampsia. Wang et al.'s (2023) study revealed that KIM-1 levels in the urine and blood of women with preeclampsia were significantly higher than those in normal pregnancies. This study used comprehensive methods, such as measuring KIM-1 and NGAL levels in plasma and urine via ELISA, as well as analyzing KIM-1 expression in renal proximal tubular epithelial cells via immunostaining and electron microscopy.⁶ Other studies with different designs, such as populations with certain preeclampsia severity or larger samples, may also contribute to the detection of clearer differences in KIM-1 levels.

The results of this study provide a basis for further research, such as increasing the number of samples, exploring additional biomarkers, and analyzing combinations of several biomarkers to obtain a more comprehensive picture of preeclampsia. A combination of biomarkers or a biomarker panel approach may provide higher sensitivity and specificity in detecting preeclampsia and evaluating its severity.

CONCLUSION

In this study, there was no significant difference in urinary KIM-1 levels in the normal pregnancy, early and late onset preeclampsia groups. The average maternal age in the normal pregnancy group was lower compared to the early and late onset preeclampsia groups, with the early onset preeclampsia group having a higher proportion of primiparas compared to late onset

preeclampsia and normal pregnancies. In the normal pregnancy group at Dr. Soetomo General Hospital. M. Djamil Padang, the average urinary KIM-1 level was 2.834 ± 0.957 ng/mL, with a range of values 1.550-4.972 ng/mL, while in the early-onset preeclampsia group, the average urinary KIM-1 level was 2.659 ± 1.175 ng/mL, with a range of values 1.029–6.155 ng/mL and in the late-onset preeclampsia group, the average urinary KIM-1 level was 2.694 ± 0.978 ng/mL, with a range of values 1.231–5.154 ng/mL.

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