Correlation of Early-Onset and Late-Onset Preeclampsia with Increased Lactic Dehydrogenase Serum Levels

Lois Tabitha Kezia Sitorus,[1] Edy Priyanto,[2] Zulvayanti[1]
[1]Department of Obstetrics and Gynecology, Hasan Sadikin General Hospital/ Universitas Padjadjaran
[2]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Soedirman
Corresponding: Lois Tabitha Kezia Sitorus, Email: kezsitorus@gmail.com

Abstract
Introduction: Preeclampsia is a hypertensive disorder during pregnancy that is associated with 2-8% of pregnancy-related complications worldwide. Lactate Dehydrogenase (LDH) is a dominant intracellular cytoplasmic enzyme of anaerobic glycolysis and is released into the general circulation during cell death. This enzyme is increased in preeclampsia due to glycolysis and chronic anoxemia due to placental ischemia. The effect of LDH on pregnancy-related complications, such as preeclampsia, is now gaining attention. This study aims to assess the difference in LDH serum levels in early- and late-onset preeclampsia.
Method: This is an analytical observational study with a retrospective approach and cross-sectional design. The sample consists of 106 patients with early- and late-onset preeclampsia at RSUD Prof Dr. Margono Soekarjo from July to December 2022. Data analyzed in this study was collected from medical records.
Results: This study found that 65.09% of the subjects were less than 35-years-old, 76.42% were multiparous, 64.15% had term birth, and 77.01% had a BMI >30. The mean LDH level in early-onset preeclampsia was 292.38 + 255.05 (141–1507), while the mean in late-onset preeclampsia was 181.60 ± 43.13 (103–319). The cut-off value for LDH levels in preeclampsia patients was 185.5 U/L. A significant correlation was found between mean BMI and LDH levels (p=0.0001) and between mean maternal age and LDH levels (p=0.0001).
Conclusion: There was a significant relationship between the onset of preeclampsia, mean BMI, and mean maternal age and LDH levels.

Keywords: Early-Onset Preeclampsia, Lactic Dehydrogenase, Late-Onset Preeclampsia, Preeclampsia

Hubungan antara Kejadian Preeklamsia Awitan Dini dan Lanjut dengan Peningkatan Serum Laktat Dehidrogenase

Abstrak
Pendahuluan: Preeklamsia adalah kelainan hipertensi pada kehamilan yang berhubungan dengan 2 – 8% komplikasi terkait kehamilan di seluruh dunia. Laktat dehidrogenase (LDH) adalah enzim sitoplasma intraseluler dominan dari glikolisis anaerobik dan dilepaskan ke sirkulasi umum selama kematian sel. Enzim ini meningkat pada preeklamsia akibat glikolisis dan anoksemia kronis akibat iskemia plasenta. Pengaruh LDH terhadap komplikasi terkait kehamilan seperti preeklamsia kini mulai mendapat perhatian. Studi ini bertujuan untuk menilai perbedaan kadar serum LDH pada preeklamsia awitan dini dan lanjut.
Metode: Penelitian ini merupakan penelitian observasional analitik dengan pendekatan retrospektif dan desain potong lintang. Sampel terdiri atas 106 pasien dengan preeklamsia awitan dini dan lanjut di RSUD Prof Dr. Margono Soekarjo periode Juli-Desember 2022. Data diperoleh dari rekam medis.
Hasil: Ditemukan bahwa 65,09% subjek berusia kurang dari 35 tahun, sebanyak 76,42% subjek multipara, sebanyak 64,15% subjek mengalami kelahiran aterm, sebanyak 77,01% subjek memiliki IMT >30. Rerata kadar LDH pada preeklamsia awitan dini ditemukan 292,38 ± 255,05 (141–1507), sedangkan rerata pada preeklamsia awitan lanjut adalah 181,60 ± 43,13 (103–319). Nilai *cut off* kadar LDH pada pasien preeklamsia ditemukan 185,5 U/L. Hubungan signifikan ditemukan antara rerata IMT dengan kadar LDH (p=0,0001) dan rerata usia ibu dengan kadar LDH (p=0,0001).
Kesimpulan: Terdapat hubungan signifikan antara awitan preeklamsia, rerata IMT dan rerata usia ibu dengan kadar LDH.

Kata kunci: Preeklamsia Awitan Dini, *Lactic Dehydrogenase*, Preeklamsia Awitan Lanjut, Preeklamsia

Introduction

Preeclampsia is a hypertensive disorder during pregnancy that is associated with 2-8% of pregnancy-related complications worldwide. Preeclampsia is defined as new-onset hypertension. Early identification parameters of preeclampsia were specifically defined as a systolic blood pressure equal to or more than 140 mmHg or a diastolic blood pressure equal to or more than 90 mm Hg on two occasions at least 4 hours apart or a shorter interval of systolic blood pressure equal to or more than 160 mmHg or diastolic blood pressure equal to or more than 110 mmHg, all of which must be identified after 20 weeks of pregnancy. Preeclampsia is a multisystem condition that triggers the possibility of severe hypertension and end-organ dysfunction or failure.[1] This disease causes around 9–26% of maternal deaths in low-income countries and around 16% in high-income countries. Preeclampsia accounts for approximately 63,000 maternal deaths each year worldwide.[2] In developed countries, the maternal mortality rate is reported to be 0–1.8%. Meanwhile, the maternal mortality rate reaches 14% in developing countries,[3,4] with fetal death rates vary from 13–30%. In India, the incidence of preeclampsia is reported to be 8–10% in pregnant women.[5,6]

There are several risk factors and predeterminants of preeclampsia. Some of these are parity, multi-para pregnancy, advanced maternal age of more than 35 years, in-vitro fertilization or other forms of assisted reproductive technology, maternal comorbidities (chronic hypertension, chronic kidney disease, diabetes mellitus, thrombophilia, obstructive sleep apnea, obesity with a pre-pregnancy BMI >30), family history, history of placental abruption or preeclampsia in a previous pregnancy, or intrauterine fetal growth restriction.[7–10]

The underlying etiology of preeclampsia is not well understood. The widely accepted cause of preeclampsia originates from the theory of placental abnormalities causing significant maternal physiological dysfunction. Abnormal placentation causes abnormal spiral artery remodeling, placental ischemia, hypoxia, and oxidative stress. These conditions lead to abnormal blood vessels and inadequate vascular accommodation for several organ systems, especially the cardiovascular, renal, and hepatic. This results in abnormal blood vessels and inadequate vascular accommodation for several organ systems, especially the cardiovascular, renal, and hepatic.[7,10]

The most common historical finding in patients with preeclampsia is a complaint of new-onset headache not attributable to an alternative diagnosis (such as a history of headaches or migraines), which is unresponsive to treatment. These complaints may or may not be accompanied by additional complaints of visual disturbances. In addition, patients may experience symptoms of right upper quadrant or epigastric pain, with associated nausea or vomiting. Shortness of breath and increased perceived swelling, both worsening the initial pregnancy-related symptoms, may also be reported.[1]

Clinical manifestations of preeclampsia often appear at gestational age approaching term. Other important findings that may not be part of the clinical presentation include proteinuria, signs of end organ damage, such as thrombocytopenia, impaired liver function, severe persistent right upper quadrant or epigastric pain, excluding all other alternative diagnoses, new onset headache not responsive to all forms of management, pulmonary edema, or renal insufficiency with abnormal laboratory values. Although preeclampsia usually presents with typical physical signs and symptoms, there are atypical presentations.[1] Patients with a single criterion or a combination of these history findings and manifestations should undergo a thorough physical examination. Complaints

usually begin with an evaluation of vital signs, specifically blood pressure. Patients with a systolic blood pressure of 140 mmHg or greater or a diastolic blood pressure of 90 mmHg or greater should raise suspicion for preeclampsia. In patients over 20 weeks gestation, blood pressure readings on two measurements at least 4 hours apart should be evaluated with further diagnostic exercises.[1]

Lactate Dehydrogenase (LDH) is the dominant intracellular cytoplasmic enzyme of anaerobic glycolysis and is released into the general circulation during cell death. This enzyme is increased in preeclampsia due to glycolysis and chronic anoxemia due to placental ischemia. The effect of LDH on pregnancy-related complications such as preeclampsia is now gaining attention.[11] Studies show high serum LDH levels correlate well with disease severity and outcome in preeclampsia patients. Mary et al. demonstrated increased serum levels of LDH, uric acid, and liver enzymes in severe preeclampsia. They concluded that LDH values greater than 800 U/L correlated with an increased risk of perinatal mortality.[12] Moreover, Munde et al. concluded that LDH can be effectively used as a biochemical marker because it reflects the severity of preeclampsia and can help in effective management.[13] There are still few published studies describing LDH levels in patients with early- and late-onset preeclampsia, especially in developing countries, including Indonesia. Therefore, considering the importance of knowing the LDH levels in early- and late-onset preeclampsia, the authors are interested in knowing how the serum LDH level is related to the incidence of early- and late-onset preeclampsia at RSUD Prof. Dr. Margono Soekarjo from July to December 2022.

Method

This is an analytical observational study with a retrospective approach and cross-sectional design. The study was performed after receiving ethical clearance from the Ethical Committee of the Faculty of Medicine Padjadjaran University and RSUD Prof. Dr. Margono Soekarjo. The research sample involves 106 patients with early- and late-onset preeclampsia at RSUD Prof. Dr. Margono Soekarjo from July–December 2022 who met the inclusion criteria. The inclusion criteria include patients with a history of preeclampsia, patients with early- and late-onset preeclampsia, and patients with preeclampsia at gestational age > 20 weeks without accompanying heart disease, liver disease, or complications of HELLP syndrome. Meanwhile, the exclusion criteria includes incomplete medical record data, not having LDH levels measurement, having a history of heart disease, liver disease, or complications of HELLP syndrome. This research uses secondary data, including maternal age, gestational age, onset of preeclampsia, and LDH levels obtained from medical records. Categorical data, including maternal age, parity, gestational age, body mass index (BMI), and education level, were presented as percentages. Numerical data (LDH level) was presented as mean. The correlation of the onset of preeclampsia with LDH level was analyzed using an independent t-test. In addition, the correlation of BMI with maternal age was analyzed using an independent t-test. Meanwhile, the diagnostic performance of LDH level in predicting the onset of preeclampsia was analyzed using Receiving Operator Characteristics (ROC) analysis. The odds ratio is presented to determine the strength of association between the onset of preeclampsia and LDH cut-off value. Data analysis was carried out using the SPSS version 27.0 for Mac.

Results

The total number of patients who gave

Table 1 General Characteristics of Patients Giving Birth at RSUD Prof. Dr. Margono Soekarjo

Variable	Preeclampsia			
	Yes		No	
	N=106	%	N=125	%
Maternal Age				
≥ 35 years	37	34.91	30	24
<35 years	69	65.09	95	76
Parity				
Primipara	25	23.58	52	41.6
Multipara	81	76.42	73	58.4
Gestational Age				
Preterm	38	35.85	11	8.80
Aterm	68	64.15	114	91.20
Body Mass Index				
>30	20	22.99	30	27.03
<30	67	77.01	81	72.97
Education				
Elementary school	78	73.59	93	74.40
Junior high school	22	20.75	28	22.40
Senior high school	6	5.66	4	3.20

Table 2 Correlation of the Onset of Preeclampsia with LDH Levels

Onset	Mean LDH Levels (min-max)	*P-value*
Early (N=34)	292.38 ± 255.05 (141–1507)	0.0026*
Late (N=53)	181.60 ±43.13 (103–319)	

*Significant if p<0.005. Analysis was carried out using an independent t-test

birth at RSUD Prof. Dr. Margono Soekarjo Purwokerto in July–December 2022 were 231 patients, with 106 of them diagnosed with preeclampsia (45.87%), while the remaining 125 were not diagnosed with preeclampsia (64.13%). Most of patients with preeclampsia were less than 35 years old (65.09%), multiparous (76.42%), BMI >30 (77.01%), and had primary school education (73.59%). Almost all patients with preeclampsia experienced term birth (91.2%) (Table 1).

Analysis of the correlation of the onset of preeclampsia with LDH levels shows that the mean LDH levels were higher in the group with early-onset preeclampsia, namely 292.38 ± 255.05 (141–1507), compared to the group with late-onset preeclampsia, namely 181.60 ± 43.13 (103–319). The significance of the correlation of the onset of preeclampsia with serum LDH levels was found in this study, indicated by a p-value <0.005 (Table 2).

Receiving Operator Characteristics (ROC) analysis shows that the cut-off number for LDH levels in patients with preeclampsia was 185.5 U/L. Patients with LDH levels < 185.5 had an odds ratio of 0.2x experiencing early-onset preeclampsia. Patients with LDH levels < 185.5 had a relative risk of 0.386x experiencing early-onset preeclampsia. Patients with LDH levels < 185.5 had a relative risk of 1.768x for patients experiencing late-onset preeclampsia (Figure 1 and Table 3).

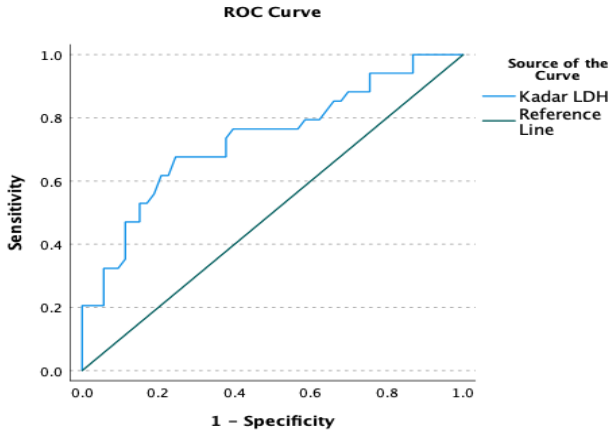

Figure 1 Receiving Operator Characteristics (ROC) curve

Table 3 Odds Ratio Analysis Results

Onset	LDH Levels (U/L)	*Odds Ratio*
Early (N=34)	<185.5	0.204
	>185.5	0.728
Late (N=53)	<185.5	1.230
	>185.5	2.541

The mean LDH level in patients with preeclampsia was 224.89 ± 160.41, the mean maternal BMI was 30.62 ± 6.04, and the mean maternal age was 32.05 ± 6.25. The significance of the correlation of mean BMI with mean maternal age on LDH levels was obtained in this study, with p<0.005 (Table 4).

Table 4 Correlation of BMI with Maternal Age with LDH Levels

Variable	Mean	Relationship with LDH levels (P-value)
LDH	224.89 ± 160.41	
BMI	30.62 ± 6.04	0.0001*
Maternal Age	32.05 ± 6.25	0.0001*

*Significant if p<0.005. Analysis was carried out using an independent t-test

Discussion

Preeclampsia is a pregnancy disease with potentially devastating consequences for both mother and child. Severe preeclampsia can cause serious complications such as eclampsia, HELLP syndrome, abruption, and even perinatal mortality and morbidity.[14] A study by Jaiswar et al. revealed a significant increase in LDH levels with increasing disease severity. Other studies also showed similar findings in preeclampsia and eclampsia in the study group.[15]

Neonatal complications, stillbirths, and perinatal deaths were significantly higher in mothers who had increased serum LDH levels. According to the findings of Jaiswar et al., LDH levels increase significantly in women with preeclampsia and eclampsia. Higher LDH levels have a significant correlation with disease severity and poor maternal and perinatal outcomes.[15] According to research by Amit et al., the average LDH level in preeclampsia was 356.46 ± 158.09, gestational hypertension 282.3 ± 120.98, normal pregnancy 151.57 ± 47.47 and control 130.5 ± 44.36.[16] Another study found statistical significance in the mean serum LDH between the control group (201.5 ± 125.9) and the study group (570.5 ± 270.9). Another study by Umasatyasri et al. assessed

the prognostic significance of serum LDH values as a marker of preeclampsia-eclampsia and severity. They found a mean LDH level in normotensives (n = 50) of 159.06 ± 41.93; preeclampsia (n = 30) 323.30 ±77.40; severe preeclampsia (n = 20) 636.20 ± 132.29; and eclampsia (n = 50) 649.32 ± 153.53.[16]

The result of this study is in line with another study. The results of this study show that the mean LDH level in patients with preeclampsia was 224.89 ± 160.41. Moreover, this study found that the mean maternal BMI was 30.62 ± 6.04, and the mean maternal age was 32.05 ± 6.25. A significant correlation of mean BMI and mean maternal age with LDH levels was obtained in this study with a p-value of 0.0001. Qublan et al. found that the mean LDH level in controls was 299±79 IU/l; while in patients with preeclampsia was 348±76 IU/l, and in severe preeclampsia was 774±69.61 IU/l. This shows that LDH levels and severe preeclampsia were significantly correlated. Similar results were described in studies conducted by Jaiswar et al., Hazari et al., and Gandhi et al.[15] They showed that LDH levels<600 IU/l were observed in 66% of preeclampsia patients and 36.73% of severe preeclampsia patients, while 9.8% of patients with preeclampsia and 30.61% of patients with severe preeclampsia had LDH levels >800 IU/l. LDH levels were found to be significantly higher in severe preeclampsia than in preeclampsia. This finding is in line with Sarkar et al.[17]

Research by Qublan et al. revealed a significant association between serum LDH levels and severe preeclampsia. An increased incidence of perinatal mortality was also observed in patients with elevated serum LDH levels. Intrauterine fetal death was seen in 4.8% of cases, intrauterine growth restriction in 33.9% and prematurity in 77.9%. Neonatal mortality was reported in 95.2% of the severe preeclampsia group.[15] Although there was a significant association between increased serum LDH and eclamptic complications, neonatal mortality and stillbirth were recorded in only 15%. Another study conducted by Sreelatha S et al. stated that increased LDH levels correlated with the severity of PIH and had poor perinatal outcomes. So, it can be considered as a biochemical marker.[18]

A study by Amit et al. concluded that serum LDH gradually increases with increasing disease severity. Routine monitoring of serum LDH levels in women with Hypertension in Pregnancy can provide clues to the severity of the disease.[16] In patients with higher LDH levels, vigilant monitoring and prompt management can reduce maternal and perinatal morbidity and mortality.[19] Serum LDH levels can be offered to all preeclampsia patients and can be used to predict the prognosis of preeclampsia.[20] Clinicians' ability to determine high-risk women and fetuses early in the disease course will allow them to effectively tailor individual management. Identifying women at risk of adverse outcomes will enable intensive monitoring or intervention and effective use of resources. Conversely, identifying low-risk women may reduce adverse maternal and neonatal iatrogenic outcomes by reducing unnecessary interventions and monitoring.[14]

The most plausible explanation of the pathogenesis of preeclampsia focuses on the placenta.[21] The initial events of placentation involve the formation of a non-invasive trophoblast shell, which progresses to an invasive phenotype, causing an exponential increase in the influx of oxygenated maternal blood into the intervillous space. Opening the intervillous space and the resulting increase in PO2 reduces HIF-1 alpha expression, augmenting trophoblastic differentiation along the invasive pathway.[22] Preeclampsia progresses through a proposed two-stage model that includes poorly fused placentation (Stage 1) resisting trophoblast invasion, increased vascular resistance and subsequent nutritional deprivation that modifies maternal metabolism to increase

nutrient availability. The inability to tolerate these modifications leads to the clinical manifestations of preeclampsia (Stage 2). Lactate Dehydrogenase (LDH), the dominant intracellular cytoplasmic enzyme of anaerobic glycolysis, is released into the general circulation during cell death and may be increased in preeclampsia due to vigorous glycolysis and chronic anoxemia as a result of placental ischemia. Furthermore, the LDH A gene is a well-characterized hypoxia-inducible gene and ineffective elevation/downregulation of HIF-1 alpha upregulates LDH A expression. Therefore, LDH may be a major candidate marker of ischemia and tissue damage associated with endothelial dysfunction and the severity of preeclampsia.[21]

Studies in the control group showed serum LDH within the recommended cutoff of 525 U/L, while women with preeclampsia showed a statistically significant increase. The difference in serum LDH between mild and severe preeclamptic groups was also statistically significant. The majority of normotensive pregnant women have serum LDH within the normal range. In contrast, the majority of preeclamptic women showed elevated levels, with serum LDH showing a sensitivity of 50% and a specificity of 80%.[21]

These findings are in accordance with many previous studies. Studies show that high serum LDH levels correlate well with disease severity and outcome in preeclampsia patients.[23] A study conducted by Mary et al. also demonstrated increased serum levels of LDH, uric acid and liver enzymes in severe preeclampsia. It concluded that LDH values greater than 800 U/L correlated with an increased risk of perinatal mortality.[12] The study by Purnima and Sonal and another study by Munde et al. showed that LDH can be effectively used as a biochemical marker because it reflects the severity of preeclampsia and can help in effective management.[13,17]

Preeclampsia is considered an idiopathic multisystem disorder. Prevention of preeclampsia is necessary to avoid complications, so it is necessary to diagnose the disease as early as possible. The effect of LDH on pregnancy-related complications such as preeclampsia is of concern. Various studies observed a significant increase in LDH levels in preeclampsia patients compared to control groups and that there was an increase in LDH values with increasing severity of preeclampsia.[24]

Statistically increased incidence of eclampsia, HELLP syndrome, and ICU transfer rates were found when comparing three subgroups of patients with LDH levels of 800 IU/l. In addition, the maximum number of complications was observed in preeclamptic women with LDH levels >800 IU/l, and more than one complication was present in one patient. Umasatyasri et al. observed an increase in maternal morbidity with increasing serum LDH levels. They observed that higher serum LDH levels were associated with increased incidence of maternal complications such as abruption, renal failure, and HELLP syndrome ($p<0.05$). Qublan et al. and Demir et al. concluded that there was a statistically significant association between maternal complications and high LDH levels.[25]

Previous research has shown an association of low-birth-weight babies with increased serum LDH levels. Jaiswar et al. noted that with LDH levels <600 IU/l, the average baby's weight was 2.42 ± 0.79% kg. In women with LDH levels of 600-800 IU/l, the average baby weight was 1.99±0.68 kg, while in the subgroup with LDH levels >800 IU/l, it was 1.979±0.787 kg (p 0.019).[31] Umasatysi et al. found that there was a decrease in mean birth weight with increasing LDH levels, as also depicted by a significant p-value <0.05. The average birth weight in patients with LDH <600 IU / l was 2.36 ± 0.60 kg; with LDH levels of 600-800 IU / l was 2.20 ± 0.52 kg and in patients with LDH levels > 800 IU /

l was 1.99±0.59 kg. The average Apgar scores at 1 minute and 5 minutes were deficient in cases with high LDH levels as in studies by Umasatyasri et al. and Jaiswar et al.[15,25] Qublan et al. observed a significant increase in the incidence of perinatal mortality in patients with elevated serum LDH levels ($p<0.001$).[4] The effects on perinatal outcomes were also studied in the studies of Jaiswar et al. and Bhave et al., showing a significant increase in stillbirths, neonatal deaths, and perinatal deaths with increasing serum LDH levels.[23] In the study, similar results were observed, showing a significant increase in neonatal mortality ($p<0.05$) and perinatal mortality ($p<0.001$), but no significant increase in stillbirths was found with higher LDH levels ($p>0.05$). It was observed that maternal and perinatal morbidity and mortality had a significant association with increased LDH levels. This suggests that LDH levels have a significant correlation with increased severity of preeclampsia with worse maternal and perinatal outcomes. This is in line with the results of this study, which found that there was a significant relationship between the onset of preeclampsia and serum LDH levels, and a significant relationship was also found between the incidence of preeclampsia and gestational age in this study.

Conclusion

This research shows a significant correlation of maternal age, gestational age, and a history of parity with the incidence of preeclampsia. In addition, this study found a significant correlation of the onset of preeclampsia, mean BMI, and mean maternal age with LDH levels.

Conflict Of Interest

No conflict of interest from the authors regarding the publication of this manuscript.

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