RESEARCH ARTICLE

Elevation of miR-210 Expression and Mean Arterial Pressure as Early-onset Pre-eclampsia Biomarkers, while Elevation of Matrix Metalloproteinase-2 as Late-onset Pre-eclampsia Biomarker

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Abstract

BACKGROUND: Pre-eclampsia has varying onset patterns, which are challenging to determine due to their association with diverse clinical parameters, including blood pressure regulation, vascular remodeling, and placental hypoxia. These parameters influence the expression of key biomarkers such as microRNAs, metalloproteinases, and arterial pressure indices. Therefore, understanding the associations is crucial for improving early diagnosis and management. This study was conducted to compare miR-210 expression, mean arterial pressure (MAP), and matrix metalloproteinase (MMP)-2 levels between early-onset pre-eclampsia (EOPE) and late-onset pre-eclampsia (LOPE).

METHODS: Pregnant women with EOPE (20–34 weeks) and LOPE (35 weeks to term) were included in this cross-sectional comparative study, and their blood samples were collected. miR-210 expression was quantified with reverse transcription polymerase chain reaction (RT-PCR), MAP was measured using sphygmomanometer, while MMP-2 levels were measured using enzyme-linked immunosorbent assay (ELISA).

RESULTS: miR-210 expression was more frequently observed in the EOPE group (87.5%) compared to the LOPE group (77.5%), with a significant difference identified between the two groups. The odds ratio for miR-210 expression in EOPE compared to LOPE was 2.03 (95% CI: 1.06–6.72). The MAP was notably higher in the EOPE group (121.15 mmHg) than in the LOPE group (116.15 mmHg), with a significant difference observed. Conversely, MMP-2 levels were significantly higher in the LOPE group (390.99 ng/mL) compared to the EOPE group (271.35 ng/mL).

CONCLUSION: There are significant differences in miR-210 expression, MAP and MMP-2 between EOPE and LOPE. These findings suggest that miR-210, MAP, and MMP-2 could be useful biomarkers for distinguishing between EOPE and LOPE, potentially guiding more effective management and intervention strategies.

KEYWORDS: miR-210, MAP, MMP-2, EOPE, LOPE, pre-eclampsia

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Introduction

Pre-eclampsia is a pregnancy-specific hypertensive disorder that significantly contributes to maternal and neonatal morbidity and mortality worldwide. This condition, which affects 2–8% of pregnancies, is characterized by high blood pressure and proteinuria after 20 weeks of gestation. It is a leading cause of maternal deaths, particularly in low- and middle-income countries, and can also lead to serious

complications such as fetal growth restriction and preterm birth.(1) Despite extensive research, the pathophysiology of pre-eclampsia remains incompletely understood, with various hypotheses suggesting contributions from genetic, immunologic, and environmental factors.(1,2)

In clinical practice, pre-eclampsia is classified based on gestational age at the time of diagnosis, with early-onset pre-eclampsia (EOPE) cases occurring before 34 weeks and late-onset pre-eclampsia (LOPE) cases occurring at or beyond 34 weeks. However, this terminology primarily reflects the timing of delivery rather than the actual onset, which is often unknown. Additionally, pre-eclampsia can be categorized as mild or severe, depending on factors such as blood pressure levels, proteinuria, and other clinical manifestations, including organ dysfunction.(3) These subtypes differ not only in their clinical presentations and outcomes but also in their underlying pathophysiological mechanisms. EOPE is often associated with severe maternal and fetal complications, including intrauterine growth restriction (IUGR) and higher rates of preterm delivery, while LOPE is typically associated with more favorable outcomes.(4)

Over the past decade, numerous studies have explored the molecular mechanisms underlying pre-eclampsia, with particular focus on microRNAs (miRNAs) as potential biomarkers. Among them, miR-210 has been widely recognized as a key regulator of hypoxic responses in the placenta, with studies demonstrating its upregulation in pre-eclamptic pregnancies and its role in impairing trophoblast function and mitochondrial activity.(5,6) Despite these findings, miR-210 has not yet been fully integrated into clinical diagnostics, as its specificity and predictive value remain under investigation. Recent studies have expanded the search for additional biomarkers, identifying matrix metalloproteinase (MMP)-2 as a critical factor in extracellular matrix remodeling and vascular function in pre-eclampsia.(7-9) While MMP-2 has shown promise in differentiating between EOPE and LOPE, further research is needed to validate its clinical utility.(10) Moreover, miR-210 is thought to contribute to the dysregulation of mitochondrial function and increased production of reactive oxygen species (ROS), further exacerbating placental dysfunction.(11)

Another crucial aspect of pre-eclampsia is the alteration in vascular function, often assessed through mean arterial pressure (MAP). Elevated MAP is a hallmark of pre-eclampsia and reflects the systemic endothelial dysfunction and vasoconstriction associated with the disease. Studies have shown that MAP is typically higher in EOPE compared to LOPE, correlating with the severity and adverse outcomes associated with the former.(12) Dysregulation of MMP-2 activity in pre-eclampsia has been linked to increased vascular stiffness and reduced nitric oxide (NO) bioavailability, contributing to elevated MAP. MMP-2 can degrade elastin and collagen within the vascular wall, leading to impaired vascular remodeling and increased arterial resistance, which further elevates blood pressure.(13) The distinction in MAP between EOPE and LOPE underlines the importance of precise blood pressure monitoring in pregnant women as a critical aspect of clinical management and risk stratification.

MMPs, particularly MMP-2, have recently emerged as significant contributors to the pathophysiology of pre-eclampsia. MMP-2 plays a pivotal role in extracellular matrix remodeling and angiogenesis, processes critical for placental development.(11,12) Alterations in MMP-2 activity have been associated with placental dysfunction in pre-eclampsia. However, the specific differences in MMP-2 levels between EOPE and LOPE remain under-explored, creating a critical gap in the understanding of its role in these distinct subtypes.(12) In LOPE, the higher levels of MMP-2 may reflect a compensatory mechanism aimed at maintaining vascular integrity, whereas in EOPE, lower MMP-2 levels could indicate severe placental insufficiency with limited adaptive vascular remodeling. (14) Identifying the variations in MMP-2 expression might provide new insights into the molecular mechanisms driving the differences in clinical outcomes between EOPE and LOPE.

Given the distinct pathophysiological profiles and clinical outcomes of EOPE and LOPE, there is a growing interest in exploring specific biomarkers and physiological markers that can aid in early diagnosis and management. While miR-210 and MAP have been studied extensively, the role of MMP-2 in differentiating EOPE and LOPE has not been thoroughly investigated. This study was conducted to compare the expression of miR-210, MAP, and MMP-2 in EOPE and LOPE. By examining how miR-210 regulates vascular function through hypoxia and endothelial dysfunction, how MMP-2 contributes to vascular remodeling, and how these factors collectively influence MAP, this study seeks to establish a mechanistic link between these biomarkers. By addressing this research gap, hopefully it can enhance the understanding of these biomarkers' roles and their potential utility in improving diagnostic accuracy and developing targeted therapeutic strategies, ultimately advancing maternal and neonatal outcomes.

Methods

Study Design

This study employed a cross-sectional comparative design, conducted at the Inpatient Care Unit of Dr. M. Djamil General Hospital in Padang for clinical data collection, and at the Biomedical Laboratory of the Faculty of Medicine, Universitas Andalas, Padang, for the analysis of miR-210 expression, MAP, and MMP-2. The study sample comprised pregnant patients diagnosed with either EOPE or LOPE who met the inclusion criteria. The protocol of this study was approved by the Ethics Review Board of Dr. M. Djamil General Hospital, Padang (No. DP.04.03/D.XVI. XI/542/2023).

Sampling Criteria and Sample Size Calculation

Pregnant women presenting at Dr. M. Djamil Hospital, those diagnosed with EOPE (gestational age 20–34 weeks) or LOPE (gestational age 35–40 weeks) were included in the study. However, pregnant women with chronic diseases such as diabetes mellitus, heart disease, kidney disease, malignancies, and autoimmune disorders, as well as those who withdrew before sample collection or had damaged or incomplete samples were excluded from the study. The sample size was determined using the formula for comparing two means, resulting in a requirement of 40 subjects per group (EOPE and LOPE), with a total of 80 subjects. Consecutive sampling was employed as the sampling technique.

Subjects Recruitment and Data Collection

The medical history of the subjects was obtained to collect characteristic data, including name, address, age, last menstrual period, and parity. In addition, laboratory parameters such as hemoglobin (g/dL), leukocytes (/µL), platelets (/µL), urea (mg/dL), creatinine (mg/dL), serum glutamic oxaloacetic transaminase (SGOT) (U/L), serum glutamic pyruvic transaminase (SGPT) (U/L), prothrombin time (PT) (seconds), activated partial thromboplastin time (APTT) (seconds), albumin (g/dL), total protein (g/dL), globulin (g/dL), and lactate dehydrogenase (LDH) (U/L) were also obtained.

Upon hospital admission, a pregnancy examination was conducted, and the diagnosis of pre-eclampsia was confirmed based on clinical criteria. Patients that met the inclusion and exclusion criteria were selected as study participants. After all data collection, patients were managed according to the applicable standard operating procedures at Dr. M. Djamil General Hospital based on their clinical condition.

Measurement of miR-210 Expression

To analyze miR-210 expression, 5 mL of venous blood was collected, processed according to procedural guidelines, and sent to the Biomedical Laboratory at the Faculty of Medicine, Universitas Andalas, Padang. miR-210 is a single-stranded noncoding RNA involved in gene regulation, particularly in hypoxia-related pathways.(5,6) RNA extraction was performed using Trizol reagent (Cat. No. 339306 YP00204333; Invitrogen, Waltham, MA, USA), and cDNA synthesis was carried out using the RevertAid First Strand cDNA Synthesis Kit (Thermo Fisher Scientific, Waltham, MA, USA). Quantification was conducted using qPCR with SYBR Master Mix (Takara, Dalian, China). The primers used for miR-210-3p were forward: 5′-TAACACTGTCTGGTAACGATGT and reverse: 5′-CATCTTACCGGACAGTGCTGGA. The expression of miR-210 was measured using absolute quantification and categorized as either present or absent.

Measurement of MAP

MAP, which represents the average arterial pressure during a single cardiac cycle, including both systolic blood pressure (SBP) and diastolic blood pressure (DBP), was measured using a validated sphygmomanometer. Measurements were taken in a sitting position after the patient had rested for at least five minutes. SBP and DBP were then recorded, and MAP was calculated using the formula: MAP = DBP + 1/3 (SBP−DBP).(12)

Measurement of MMP-2 Levels

MMP-2, an enzyme from the matrix metalloproteinase family involved in extracellular matrix remodeling and angiogenesis, was measured using plasma samples obtained from collected blood.(8,9) Samples were processed and stored at −80°C until analysis. MMP-2 levels were quantified using an enzyme-linked immunosorbent assay (ELISA) kit (Cat. No. E0904Hu; Abcam, Cambridge, UK) according to the manufacturer's protocol. The results were expressed in nanograms per milliliter (ng/mL), and all measurements were performed in duplicate to ensure accuracy.

Statistical Analysis

Descriptive data analysis for categorical variables was presented as frequencies and percentages, while numeric variables were presented as medians, minimums, and maximums. Bivariate analysis was conducted using the

Chi-square test and Mann-Whitney test, with a $p<0.05$ considered statistically significant. Data analysis was performed using SPSS version 23.0 (IBM Corporation, Armonk, NY, USA).

Results

Characteristics of the Study Subjects

In this current study, 40 EOPE subjects and 40 LOPE subjects were included. There were no statistically significant differences in age, BMI, parity, hemoglobin levels, leukocyte count, platelet count, and albumin levels between the two groups, suggesting that these general characteristics were relatively similar in both EOPE and LOPE subjects (Table 1). However, significant differences were observed in renal function and LDH levels, with higher urea levels in EOPE (27 mg/dL) compared to LOPE (22.5 mg/dL), with a $p=0.004$, indicating greater renal impairment in EOPE cases. Although creatinine levels were not significantly different, the trend toward higher levels in EOPE suggestsed possible subclinical kidney dysfunction. LDH levels were also significantly elevated in EOPE (436.5 U/L) compared to LOPE (265.5 U/L), with a $p=0.020$. LDH is a marker of cellular damage and oxidative stress, and its elevation in EOPE suggests greater endothelial dysfunction, hypoxia, and hemolysis in this group, consistent with the more severe systemic involvement observed in early-onset cases. Liver function markers (SGOT, SGPT), coagulation parameters (PT, APTT), and total protein levels showed no statistically significant differences between EOPE and LOPE.

miR-210 Expression between EOPE and LOPE

The miR-210 expression was more frequently found in the EOPE group (87.5%) compared to the LOPE group (77.5%) (Table 2). Statistical analysis indicated a significant difference in miR-210 expression between EOPE and LOPE ($p=0.026$), with an odds ratio (OR) of 2.03 (95% CI: 1.06–6.72).

The Difference in MAP between EOPE and LOPE

MAP was higher in EOPE at 121.15 mmHg (110.30 mmHg - 134.70 mmHg) compared to LOPE at 116.15 mmHg (94.70 mmHg - 123.00 mmHg) (Figure 1). The Mann-Whitney test showed a significant difference in MAP between EOPE and LOPE ($p=0.000$).

The Difference in MMP-2 between EOPE and LOPE

The MMP-2 was higher in LOPE at 390.99 ng/mL (206.70 ng/mL - 2706.43 ng/mL) compared to EOPE at 271.35 ng/mL (166.99 ng/mL - 2354.50 ng/mL) (Figure 2). The Mann-Whitney test showed a significant difference in MMP-2 between EOPE and LOPE ($p=0.007$).

Table 1. Characteristics of the study subjects.

Characteristic	Median (Min-Max)		*p*-value
	EOPE	LOPE	
Age (years)	32.5 (15-41)	29.5 (22-41)	0.647
BMI (kg/m^2)	25 (18.4-35.6)	26.3 (22.6-37.6)	0.671
Parity (n)	2 (0-4)	1 (0-3)	0.088
Hb (g/dL)	12.7 (10-16)	12.7 (9.8-14.5)	0.376
Leukocytes (/µL)	12,700 (7,460-55,100)	12,295 (5,490-98,423)	0.411
Platelets (/µL)	212,000 (7,000-347,000)	217,000 (86,000-387,000)	0.057
Urea (mg/dL)	27 (11-82)	22.5 (4-56)	0.004*
Creatinine (mg/dL)	0.8 (0.4-1.7)	0.7 (0.1-17)	0.116
SGOT (U/L)	19 (10-128)	23.5 (9-307)	0.390
SGPT (U/L)	14.5 (6-64)	19 (4-158)	0.346
PT (seconds)	9.1 (8.2-10.8)	9.3 (8.4-10.2)	0.143
APTT (seconds)	27.1 (10.2-41.8)	26.2 (22.2-140.2)	0.184
Albumin (g/dL)	2.9 (2.1-29.0)	2.8 (1.3-30.0)	0.810
Protein total (g/dL)	5.8 (4.7-7.0)	6.1 (3.2-7.6)	0.478
Globulin (g/dL)	2.9 (2.1-4.0)	3.1 (1.4-4.3)	0.434
LDH (U/L)	436.5 (235-925)	265.5 (149-1415)	0.020*

*$p<0.05$ indicates statistical significance.

Table 2. miR-210 expression between EOPE and LOPE.

miR-210 Expression	n (%)		*p*-value	OR (95% CI)
	EOPE	LOPE		
Present	35 (87.5)	31 (77.5)	0.026	2.03 (1.06-6.72)
Not present	5 (12.5)	9 (22.5)		Ref

Discussion

miR-210, a noncoding RNA involved in hypoxic responses and angiogenesis, demonstrated distinct expression patterns between EOPE and LOPE in this study. miR-210 was detected in 87.5% of EOPE cases compared to 77.5% of LOPE cases (p=0.026), with an odds ratio (OR) of 2.03 (95% CI: 1.06–6.72). This indicates that pregnant women with EOPE are approximately 2.03 times more likely to have miR-210 overexpression compared to those with LOPE.

The overexpression of miR-210 is known to negatively impact trophoblast function by inhibiting cell migration and invasion, leading to defective placentation and impaired spiral artery remodeling. These disruptions contribute to placental hypoxia, oxidative stress, and endothelial dysfunction, which are hallmarks of EOPE. In contrast, lower miR-210 expression in LOPE suggests a milder degree of placental hypoxia and better-preserved trophoblast invasion. Previous studies have reported significantly lower miR-210 expression in normotensive pregnancies, indicating that its upregulation is largely driven by hypoxic stress in pre-eclampsia.(6,8)

These findings align with previous research, which has shown that miR-210 is upregulated in pre-eclampsia and plays a key role in hypoxia adaptation by regulating gene expression under oxygen-deficient conditions.(12,15) Higher miR-210 expression has been reported in pre-eclamptic placentas compared to normotensive pregnancies, with studies linking its upregulation to trophoblast dysfunction, mitochondrial impairment, and increased production of ROS.(15) Another study identified miR-210 as a potential biomarker for pre-eclampsia, as its elevated levels correlate with increased disease severity and poor pregnancy outcomes.(16)

The current study results support these findings and further suggest that miR-210 overexpression is more strongly associated with EOPE than LOPE, likely due to the more severe placental hypoxia and angiogenic failure seen in early-onset cases. The higher miR-210 expression in EOPE may reflect a more pronounced response to severe hypoxic conditions, leading to greater trophoblast dysfunction, vascular dysregulation, and fetal growth restriction compared to LOPE.(17) These findings suggest that miR-210 could serve as a valuable biomarker for distinguishing EOPE from LOPE, particularly in early risk stratification and diagnosis. Further research should explore potential miR-210 cut-off values that could be used in clinical practice to differentiate EOPE from LOPE with high sensitivity and specificity.

MAP, reflecting the average arterial pressure during a cardiac cycle, was significantly higher in EOPE (121.15 mmHg) than in LOPE (116.15 mmHg). This finding is consistent with the clinical observation that EOPE tends to present with more severe hypertension compared to LOPE. Elevated MAP in EOPE may be attributed to the more acute and severe nature of the condition, leading to higher systemic vascular resistance and impaired blood flow.(18,19) The results of this study corroborate previous

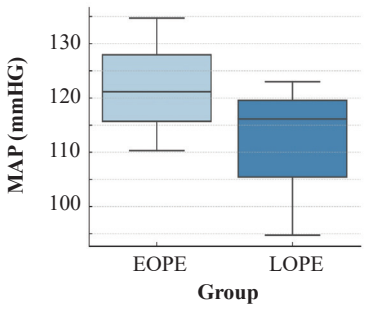

Figure 1. The difference in MAP between EOPE and LOPE.

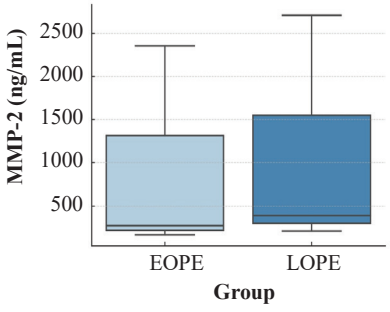

Figure 2. The difference in MMP-2 between EOPE and LOPE.

studies linking elevated MAP with adverse outcomes in pre-eclampsia. In normotensive pregnancies, MAP levels generally range between 80–100 mmHg, further highlighting the substantial increase in MAP observed in pre-eclampsia cases, particularly in EOPE.(12) The significant difference in MAP between EOPE and LOPE underscores the potential severity of early-onset pre-eclampsia and its implications for maternal and fetal health.

MMP-2, an enzyme involved in extracellular matrix remodeling and angiogenesis, also exhibited distinct patterns between EOPE and LOPE in this study. We observed significantly higher levels of MMP-2 in LOPE (390.99 ng/mL) compared to EOPE (271.35 ng/mL). Previous studies have highlighted the role of MMP-2 in placental development and its dysregulation in pre-eclampsia.(13,20) Increased MMP-2 activity has been associated with compensatory mechanisms in response to vascular dysfunction in LOPE, where placental abnormalities are typically less severe compared to EOPE.(14) In the normotensive pregnancies, MMP-2 levels are generally higher than those found in EOPE, suggesting that the marked reduction in EOPE may contribute to impaired placentation and vascular dysfunction, exacerbating disease severity.(9-11) Elevated MMP-2 levels in LOPE cases, suggesting that MMP-2 may reflect a distinct pathophysiological pathway in this subtype, characterized by milder hypoxia and a greater reliance on angiogenic repair processes.(12) Conversely, reduced MMP-2 activity in EOPE aligns with the more severe placental and vascular dysfunction in this subtype, where the hypoxic environment and insufficient angiogenesis are predominant features.(15) The differential expression of MMP-2 between EOPE and LOPE further underscores the distinct mechanisms driving these subtypes of pre-eclampsia.

The observed differences in miR-210 expression, MAP, and MMP-2 between EOPE and LOPE have important clinical implications.(20,21) miR-210 could serve as a novel biomarker for differentiating between EOPE and LOPE, potentially aiding in the early diagnosis and risk stratification of pre-eclampsia.(8) Elevated miR-210 levels could indicate more severe disease, prompting closer monitoring and intervention.(22-24) Similarly, the higher MAP in EOPE cases highlights the need for aggressive management of hypertension in EOPE to prevent complications.(25) Regular monitoring of MAP and miR-210 levels could help clinicians tailor treatment strategies and improve outcomes for women with pre-eclampsia.(26) The observed differences in MMP-2 levels between EOPE and LOPE also have critical implications.(27) The higher MMP-2 levels in LOPE suggest a potential role in compensatory vascular remodeling, reflecting milder placental dysfunction and angiogenesis repair processes compared to EOPE.(28) Conversely, the lower levels of MMP-2 in EOPE may highlight more severe disruptions in extracellular matrix remodeling and angiogenesis, which are characteristic of this subtype.(29) Given these findings, MMP-2 could be explored as an additional biomarker to differentiate between EOPE and LOPE, providing further insights into the underlying pathophysiological mechanisms.(30) Monitoring MMP-2 levels, in conjunction with miR-210 and MAP, could improve the precision of pre-eclampsia diagnosis, guide therapeutic interventions, and facilitate better risk stratification. Further research is needed to validate the clinical utility of MMP-2 in predicting disease severity and outcomes in pre-eclampsia.

This study directly compares EOPE and LOPE, providing insight into their distinct pathophysiological mechanisms. By evaluating miR-210, MAP, and MMP-2 simultaneously, it contributes to the biomarker-based differentiation of pre-eclampsia subtypes. However, the absence of a normotensive pregnancy control group limits the generalizability of findings, as baseline biomarker levels remain unclear. Future studies should include a matched control group to enhance validity. Additionally, potential errors in MAP measurements require further verification. Future research should focus on validating these biomarkers in larger, multi-center cohorts and exploring their combined predictive value. Determining the cut-off values for miR-210 and MMP-2 could improve diagnostic accuracy, while longitudinal studies may clarify their role in disease progression and treatment response.

Conclusion

This study demonstrates significant differences in miR-210 expression, MAP, and MMP-2 levels between EOPE and LOPE. Higher miR-210 expression and MAP in EOPE suggest more severe hypoxia, angiogenesis impairment, and hypertension, reinforcing miR-210 as a potential biomarker for early diagnosis and risk stratification. In contrast, elevated MMP-2 levels in LOPE indicate a compensatory response to milder placental dysfunction. These findings highlight the potential of miR-210, MAP, and MMP-2 as biomarkers for distinguishing EOPE from LOPE, which could improve diagnosis and clinical management of pre-eclampsia subtypes.

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Authors Contribution

NN, Y and JS were involved in concepting and planning the research. NN and YY performed the data acquisition/collection. NN performed the data analysis. YY and JS aided in interpreting the results. J, AA, A, and EG provided substantial suggestions to enhance the study data. NN, YY and JS drafted the manuscript and designed the figures and tables. All authors took parts in giving critical revision of the manuscript.

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