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The Relationship between Maternal Leukocyte Levels and Serum Interleukin-6 (IL-6) Levels and Duration of Premature Rupture of Membranes in Pregnant Women

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KEYWORDS

Preterm Premature Rupture of Membranes, Leukocytes, Interleukin-6, Intrauterine Infection, Inflammatory Biomarkers

ABSTRACT:

Introduction: Preterm premature rupture of membranes increases the risk of maternal and perinatal morbidity through an inflammatory response characterized by elevated maternal leukocyte counts and IL-6 levels as the duration of membrane rupture increases.

Objective: To analyze the relationship between maternal leukocyte count and serum IL-6 levels with the duration of rupture of membranes in pregnant women.

Methods: A cross-sectional study of 80 term pregnant women with PPL at Dr. Wahidin Sudirohusodo General Hospital and the University of Hasanuddin Faculty of Medicine network, dividing subjects based on the interval of membrane rupture (<8 to ≥24 hours), with leukocyte (hematology analyzer) and IL-6 (ELISA) testing, as well as analysis using the Kruskal–Wallis test and multinomial logistic regression.

Results: There were significant differences in leukocyte and IL-6 levels between the amniotic fluid rupture interval groups ($p < 0.05$). The proportion of leukocytosis increased gradually from 0% (<8 hours), 10% (8–12 hours), 85% (12–24 hours), to 100% (≥24 hours). The prevalence of elevated IL-6 levels also increased from 5% (<8 hours), 70% (8–12 hours), 90% (12–24 hours), to 100% (≥24 hours). Regression analysis showed that leukocyte levels (OR = 0.295) and IL-6 levels (OR = 0.832) differed significantly, particularly in the 12–24-hour interval compared to ≥24 hours, indicating a pattern of increasing inflammation corresponding to the duration of membrane rupture.

Conclusion: Maternal leukocyte and IL-6 levels are significantly associated with the duration of preterm rupture of membranes. IL-6 increases earlier than leukocytes, thus better reflecting early-phase intrauterine inflammation, whereas leukocytes better reflect systemic inflammation in the later phase. The combination of both provides a more comprehensive picture of the progression of inflammation in preterm rupture of membranes.

1. Introduction

Premature rupture of membranes (PROM) is a condition in which the amniotic membranes rupture before labor begins, characterized by the discharge of amniotic fluid through the vagina, either suddenly or gradually, and is classified as Premature Rupture of Membranes (PROM) if it occurs in a term pregnancy and Preterm PROM (PPROM) if it occurs before 37 weeks of gestation[1]. This condition remains a common obstetric problem and significantly contributes to increased maternal and perinatal morbidity and mortality. The loss of the amniotic membranes' function as a natural barrier against microorganisms allows for intrauterine infections which can progress to chorioamnionitis, endometritis, and even neonatal sepsis. Additionally, PROM can lead to other complications such as umbilical cord prolapse, neonatal respiratory distress, and an increased risk of perinatal mortality[2]. Therefore, the management of PPL must be carried out promptly and appropriately through monitoring of the mother's and fetus's condition, administration of prophylactic antibiotics, and determination of the optimal timing and method of delivery, as delayed intervention can increase the risk of infection, while premature intervention in an immature fetus can cause respiratory complications and developmental disorders[3].

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Intrauterine infection is the most common and dangerous complication of PID, especially if the interval between membrane rupture and delivery exceeds 12 hours, as microorganisms from the vagina can enter the amniotic cavity and trigger both local and systemic inflammatory responses[4–6]. This inflammatory process involves the release of various mediators, including pro-inflammatory cytokines such as interleukin-6 (IL-6), which are known to increase earlier than clinical symptoms of infection and thus serve as a sensitive biomarker for detecting subclinical infection[7]. Additionally, the inflammatory process also leads to the release of proteolytic enzymes such as matrix metalloproteinases (MMP-8 and MMP-9), which damage the collagen and elastin structures of the amnion-chorion membrane, thereby weakening the integrity of the amniotic membranes and triggering spontaneous rupture. The activation of cytokines such as IL-1β and TNF-α further stimulates IL-6 production and increases leukocyte infiltration, which exacerbates membrane damage[8–10].

Leukocytes, or white blood cells, are the primary components of the immune system responsible for the body's defense against infection. Elevated leukocyte levels (leukocytosis) in pregnant women with preeclampsia may indicate an immune response to microbial invasion; however, interpretation must be done cautiously, as normal pregnancy can also cause physiological leukocytosis[11,12]. Leukocyte counts, which are part of the complete blood count (CBC), are frequently used as an initial indicator of infection; however, they are nonspecific as they can be influenced by various conditions such as stress, trauma, or medication use[13]. Therefore, leukocyte evaluation should be combined with other parameters, such as IL-6 or C-reactive protein (CRP), to improve accuracy in detecting infection in KPD[14,15]. In addition to the total white blood cell count, a white blood cell differential count is also important for identifying the type of immune response, where neutrophils play a dominant role in bacterial infections, lymphocytes in viral infections, and monocytes, eosinophils, and basophils in certain inflammatory conditions[16,17].

Interleukin-6 (IL-6) itself is a multifunctional cytokine produced by various cells such as macrophages, fibroblasts, and endothelial cells in response to infection, trauma, or tissue stress[18,19]. During pregnancy, IL-6 plays a role in maintaining a balance between immune tolerance toward the fetus and protection against infection. However, excessively elevated IL-6 levels may reflect pathological inflammatory processes associated with various obstetric complications, including preeclampsia and preterm labor[20,21]. Additionally, IL-6 is involved in various systemic diseases such as autoimmune diseases, type 2 diabetes, and cancer, highlighting its broad role not only in inflammation but also in metabolic regulation[22]. In the context of PID, IL-6 is considered a more sensitive biomarker than leukocytes because its levels rise more rapidly in response to infection, even before clinical manifestations appear.

Several studies indicate that the longer the interval of membrane rupture, the higher the risk of intrauterine infection, characterized by increased levels of IL-6 and maternal leukocytes in the amniotic fluid. This suggests a relationship between the duration of membrane rupture and the degree of inflammation occurring. Therefore, measuring IL-6 and leukocyte levels holds significant clinical value in assessing inflammatory conditions in mothers with preterm labor and helps determine the appropriate timing for obstetric intervention to prevent further complications[8]. Thus, research on the relationship between maternal leukocyte and IL-6 levels and the duration of rupture of membranes is important for evaluating the role of these two parameters as diagnostic indicators in detecting subclinical infection in PPL, thereby improving the quality of management and reducing the risk of maternal and perinatal morbidity and mortality[10].

2. Methods

This study is an analytical observational study with a cross-sectional design aimed at analyzing the relationship between serum leukocyte and interleukin-6 (IL-6) levels and the duration of membrane rupture in pregnant women. The study was conducted at Dr. Wahidin Sudirohusodo General Hospital in Makassar and the Hasanuddin University Faculty of Medicine network from December 2024 to November 2025, with laboratory testing performed at the Hasanuddin University Hospital. This study has obtained ethical approval from the Ethics Committee for Biomedical Research on Humans at the Hasanuddin University Faculty of Medicine and the Health Research Ethics Committee (KEPK) of RSPTN UH–RSWS under letter

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number 634/UN4.6.4.5.31/PP36/2025. The population consists of full-term pregnant women with preterm premature rupture of membranes (PPROM), and samples were collected using consecutive sampling until 80 subjects were reached, divided into four groups based on the interval of membrane rupture (<8 hours, 8–12 hours, 12–24 hours, ≥24 hours). Leukocyte counts were performed using a hematology analyzer, while IL-6 levels were measured by ELISA from serial venous blood samples collected at specific time intervals. Sample size was calculated using the unpaired numeric-categorical formula, with a minimum requirement of 16 subjects per group, increased to 20 to enhance statistical power.

Inclusion criteria included pregnant women aged 18–35 years with term pregnancies and uncomplicated preeclampsia without other inflammatory complications, while exclusion criteria included systemic infectious diseases, autoimmune disorders, malignancies, and immunosuppressive conditions. Data were collected through medical history, clinical examination, and laboratory tests, then analyzed using SPSS with descriptive tests, difference tests (ANOVA/Kruskal–Wallis), correlation tests (Pearson/Spearman), as well as multivariate analysis and ROC to determine the diagnostic value of leukocytes and IL-6. Results were considered significant if $p < 0.05$. This study obtained ethical approval and informed consent from all subjects. The research hypothesis stated that there is a significant association between leukocyte and IL-6 levels and the duration of membrane rupture, with IL-6 having better diagnostic value in detecting infection compared to leukocytes.

Table 1. Operational Definitions

Variables	Operational Definition	Measurement Method	Scale	Category/Outcome
Duration of Rupture of Membranes	Time interval from rupture of membranes to examination	Medical history, speculum examination, nitrazine test	Categorical	<8 hours; 8–12 hours; 12–24 hours; ≥24 hours
IL-6 levels	Inflammatory cytokine reflecting the immune response	ELISA	Numeric	Normal <30 pg/ml; elevated ≥30 pg/ml
White Blood Cell Count	White blood cell count as an indicator of inflammation	Automated Hematology	Numerical	Normal <10×10³/µL; leukocytosis ≥10×10³/µL
Socioeconomic	Economic status based on income	Medical history	Categorical	<2 million; ≥2 million
Education	Level of formal education	Medical history	Categorical	Low–high
Parity	History of number of pregnancies	Medical history	Categorical	Primigravida; multigravida
BMI	Body mass index (kg/m²)	Physical measurements	Numeric	Underweight–obesity

3. Results

This study involved 80 pregnant women diagnosed with preterm premature rupture of membranes (PPROM) who met the inclusion criteria. The subjects were divided into four groups based on the time interval from the rupture of membranes to the initial examination, namely: < 8 hours (n = 20), 8–12 hours (n = 20), 12–24 hours (n = 20), > 24 hours (n = 20) Table 2.

Table 2. Characteristics of Study Subjects

Variable	N	Percentage
Age		
• 20–25	20	25%
• 26–30	29	36.25%
• > 30	31	38.75%
Parity		
• Primigravida	43	53.75%
• Multigravida	37	46.25%
Education		
• High School	12	15%
• High School	45	56.25%
• College	23	28.75%

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Socioeconomic Status		
• Low	33	41.25%
• Medium	47	58.75%
BMI		
• Underweight (<18.5)	1	1.25%
• Normal weight (18.5–24.9)	41	51.25%
• Overweight (>24.9)	38	47.5%
KPD Interval		
• < 8 hours (n = 20)	20	25%
• 8–12 hours (n = 20)	20	25%
• 12–24 hours (n = 20)	20	25%
• > 24 hours (n = 20)	20	25

The largest age group among respondents was 26–30 years old, comprising 31 people (38.75%). Most respondents were primigravidas (43 people, 53.75%), had a high school education (45 people, 56.25%), and were in the middle socioeconomic category (47 people, 58.75%). Body mass index (BMI) values fell into the normal-overweight category for 41 participants (51.25%).

Table 3. Results of Bivariate Analysis between Leukocyte Count and Duration of Ruptured Membranes

		Duration of Rupture of Membranes				
		< 8 Hours	8–12 Hours	12–24 Hours	> 24 Hours	*p-value*
White Blood Cell Count	Leukocytosis	0 (0%)	2 (10%)	17 (85%)	20 (100%)	0.000
	Normal	20 (100%)	18 (90%)	3 (15%)	0 (0%)	

There is a significant association between leukocyte levels and the duration of membrane rupture (p=0.000), with a pattern of increase from the early phase (<8 hours)—which remains normal due to a limited local inflammatory response—to the late phase (>24 hours), where leukocytosis is observed throughout as a manifestation of systemic inflammation. This increase occurs through the activation of the innate immune pathway (TLR–NF-κB), neutrophil recruitment, and stimulation of granulopoiesis by cytokines such as IL-6 and G-CSF, reflecting the progression of intrauterine infection as the duration of membrane rupture increases.

Table 4. Results of Bivariate Analysis between IL-6 Levels and Duration of Ruptured Membranes

		Duration of Ruptured Membranes				
		< 8 Hours	8–12 Hours	12–24 Hours	> 24 Hours	*p-value*
IL-6 levels	Increased	1 (5%)	14 (70%)	18 (90%)	20 (100%)	0.000
	Normal	19 (95%)	6 (30%)	2 (10%)	0 (0%)	

There is a significant association between IL-6 levels and the duration of membrane rupture (p=0.000), with a pattern of gradual increase from the early phase (<8 hours)—which remains predominantly normal due to limited local inflammation—to the late phase (>24 hours), where levels are uniformly elevated, reflecting systemic inflammation and a potential intrauterine infection. This increase occurs through the activation of the innate immune pathway (TLR–NF-κB), cytokine release, and stimulation of prostaglandins and MMPs, which exacerbate inflammation and are associated with an increased risk of maternal and neonatal complications.

Table 5. Results of Multinomial Logistic Regression Analysis of Duration of Ruptured Membranes on Leukocyte Count and IL-6 Levels

Duration of Rupture of Membranes		***B***	***p-value***	***Exp(B)***
< 8 Hours	Leukocyte Count	-5.567	0.000	0.004
	IL-6 Level	-0.742	0.000	0.476

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8–12 hours	White Blood Cell Count	-2.979	0.000	0.051
	IL-6 level	-0.269	0.000	0.764
12–24 hours	White Blood Cell Count	-1.222	0.010	0.295
	IL-6 Level	-0.184	0.009	0.832
> 24 hours	White Blood Cell Count	-0.432	0.015	0.369
	IL-6 Level	-0.044	0.011	0.948

There were significant differences in leukocyte and IL-6 levels across all KPD time intervals (<8 hours, 8–12 hours, 12–24 hours) compared to the ≥24-hour group as a reference, with the most pronounced differences observed in the early phase (<8 hours), as indicated by p=0.000 and very low ORs (leukocytes 0.004; IL-6 0.476). Although the magnitude of the differences decreased with increasing duration (OR increased at 8–12 hours and 12–24 hours), both biomarkers continued to show significant changes, confirming the presence of distinct inflammatory dynamics at each interval of preterm rupture of membranes.

4. Discussion

The characteristics of the subjects in this study present a clinically and epidemiologically representative profile of the population of pregnant women with preterm premature rupture of membranes (PPROM). The majority of respondents were within the optimal reproductive age range (26–30 years), who theoretically have good biological tissue conditions, yet remain at risk of PPROM due to other factors such as infection or inflammatory processes. The literature indicates that although extreme ages (<20 or >35 years) are often associated with pregnancy complications, PPL still occurs frequently within the healthy reproductive age range[11],[12] because its primary mechanism involves membrane structural degradation due to biochemical and inflammatory processes. This suggests that age is not the sole determinant but rather part of a set of predisposing factors that interact with other biological conditions.

The parity distribution in this study shows a slightly higher proportion of primigravidas compared to multigravidas. Theoretically, primigravidas face certain risks due to the cervical and uterine tissues not yet being fully adapted to pregnancy, making them more susceptible to changes in intrauterine pressure and mechanical stress on the amniotic membranes[13]. However, several studies indicate that the relationship between parity and preterm birth is inconsistent, as infectious and inflammatory factors play a more dominant role in the pathogenesis of preterm birth compared to obstetric factors alone[14]. Therefore, parity is more appropriately viewed as an additional contributing factor that can modulate risk, rather than as the primary cause.

Educational characteristics and socioeconomic status in this study indicate that the majority of respondents were at the upper secondary education level and had a middle socioeconomic status. These factors are important in the context of public health as they relate to health literacy levels, access to healthcare services, and the speed in seeking medical assistance when PPD occurs[15]. Individuals with higher educational levels tend to have a better understanding of pregnancy danger signs, enabling earlier intervention. However, preeclampsia can still occur in all social groups because its etiology is largely influenced by biological factors such as microbial infections and inflammatory responses[16].

The body mass index (BMI) of the respondents was mostly in the normal to overweight range. Nutritional status plays a crucial role in maintaining the structural integrity of collagen in the amniotic membrane. Deficiencies in certain nutrients can lead to tissue weakness, while being overweight or obese can trigger a state of low-grade chronic inflammation that increases the production of pro-inflammatory cytokines[17]. This condition can accelerate the degradation of the extracellular matrix in the amniotic membrane through the activation of proteolytic enzymes such as matrix metalloproteinases (MMPs), thereby increasing the risk of membrane rupture[18]. Thus, BMI acts as a biological factor that can influence susceptibility to PPL through inflammatory mechanisms.

The even distribution of subjects based on the interval of membrane rupture provides methodological strength in evaluating the relationship between the duration of PID and the inflammatory response. Pathophysiologically, the longer the interval of membrane rupture, the higher the risk of intrauterine infection due to the entry of microorganisms from the vagina into the amniotic

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cavity[19]. This process triggers activation of the maternal immune system, characterized by increased levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and leukocyte activation. IL-6 is a key mediator in the acute inflammatory response, produced by macrophages and tissue cells in response to infection and tissue damage[20]. Elevated IL-6 levels are known to occur earlier than clinical manifestations of infection, making it a sensitive biomarker for detecting subclinical infections in PID[21].

Leukocytes, as a primary component of the immune system, also increase in CPD as a response to microbial invasion. However, interpreting leukocyte levels during pregnancy has limitations due to the presence of physiological leukocytosis, which normally occurs during pregnancy, particularly in the third trimester[22]. This condition makes leukocytes less specific as an indicator of infection when used alone. Therefore, combining leukocyte counts with other biomarkers such as IL-6 or C-reactive protein (CRP) is recommended to improve diagnostic accuracy[23]. Several studies indicate that IL-6 has higher sensitivity and specificity than leukocyte counts in detecting intrauterine infection, particularly in the early stages before clinical symptoms appear[8].

The biological mechanisms underlying PID are closely associated with inflammatory processes that cause damage to fetal membrane structures. Bacterial infection triggers the release of pro-inflammatory cytokines such as IL-1β and TNF-α, which subsequently stimulate IL-6 production and leukocyte activation. These cytokines also induce the production of MMP-8 and MMP-9, which play a role in the degradation of collagen and elastin in the amnio-chorionic membranes[9],[18]. This degradation weakens the membrane structure, making it more prone to spontaneous rupture. Additionally, oxidative stress and an imbalance between proteolytic and antiproteolytic factors also contribute to this process[10].

The characteristics of the subjects in this study indicate that PPD is a multifactorial condition influenced by the interaction between demographic factors, nutritional status, and inflammatory biological processes. Factors such as age, parity, education, socioeconomic status, and BMI act as predisposing factors that can influence susceptibility to PPD; however, the primary mechanisms remain linked to inflammatory processes and intrauterine infection. The clinical implication is the importance of using inflammatory biomarkers, particularly IL-6, as a tool for the early detection of subclinical infection in PID, especially in cases with prolonged rupture of membranes. This approach is expected to assist clinicians in determining the appropriate timing of intervention to reduce the risk of maternal and perinatal complications[8],[10].

5. Conclusion

This study confirms that leukocyte and interleukin-6 (IL-6) levels are associated with intrauterine inflammatory processes in preterm premature rupture of membranes (PPROM), where IL-6 serves as a more sensitive indicator for detecting early-phase inflammation, while leukocytes better reflect systemic inflammatory responses in the later phase. Nevertheless, leukocyte testing remains relevant as an initial screening tool because it is simple, inexpensive, and widely available, while IL-6 is more appropriately used as an adjunct test to improve diagnostic accuracy in specific conditions. Therefore, the combination of these two parameters can support a more comprehensive clinical assessment and aid in decision-making regarding the management of PPL. Based on this, it is recommended that clinicians consider the use of IL-6, particularly in cases with a higher risk of infection; healthcare facilities increase the availability of inflammatory biomarker testing; future research develops studies with stronger designs and evaluates combinations of other biomarkers; and educational institutions utilize these findings as learning materials regarding the role of inflammatory biomarkers in KPD.

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