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Original Article

Histopathological Difference of Inflammatory Cells Infiltration into Fetal Membranes of PROM and Non-PROM

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ABSTRACT

Introduction: *Premature rupture of membranes (PROM) remains one of several causes of premature birth that increases both maternal mortality ratio and neonatal mortality rate. Inflammation of fetal membranes leads to release of inflammatory mediators and resulting in weakness of fetal membranes, particularly the amniotic membrane. The amniotic membrane in PROM has a focal weakness, which differs from the membrane in non-premature rupture of membrane (non-PROM) that has a generalized weakness. This research aimed to determine histopathological difference of inflammatory cells infiltration into fetal membranes of PROM and non-PROM.* ***Methods:*** *Quantitative observation was applied to this research. Cross-sectional design was used for analyzing data. Primary data was collected from the delivery room and operating theater of Emergency Department in dr. Ramelan Central Naval Hospital (RSPAL dr. Ramelan) Surabaya. Data collection started from August to November 2019 using total population sampling technique.* ***Results:*** *A total of 40 samples histopathologically examined showed that 11 out of 20*

(55%) fetal membranes in PROM had polymorphonuclear (PMN) cells infiltration and 9 (45%) did not have PMN cells infiltration, 1 out of 20 (5%) fetal membranes in non-PROM had PMN cells infiltration and 19 (95%) did not have PMN cells infiltration. The prevalence ratio (PR) of PROM based upon the presence of PMN cells infiltration into fetal membranes was 2.85 (PR>1). The significance level of Chi-square test was 0.001 (ρ>0.05). ***Conclusions:*** *The difference of inflammatory cells infiltration into fetal membranes of PROM and non-PROM was statistically significant.*

1. INTRODUCTION

Premature rupture of membranes (PROM) refers to the spontaneous rupture of fetal membranes before the onset of labor, irrespective of gestational age.[1] World Health Organization (WHO) estimated the incidence of PROM worldwide was variable, complicated approximately 8% of full-term pregnancies (gestational age range of $37^{0/7}$ to $42^{6/7}$ weeks) and increased risk of perinatal morbidity.[1,2] Premature rupture of membranes (PROM) can occur at term (gestational age of ≥37 weeks) or preterm (gestational age of <37 weeks), termed as preterm PROM (PPROM).[3]

Maintaining the integrity of fetal membranes is crucial throughout the gestation.[4] These membranes exhibit distinctive morphological features in a resctricted area known as the “zone of altered morphology”. A significant change in the thickness of the fetal membranes was found in the zone of altered morphology. Therefore, this zone was indicated as the rupture site during labor.[5] When PROM developed, various factors such as stretching, infection, inflammation and local hypoxia of the fetal membranes were potentially accelerate the process of membranes weakening.[6] Pregnancy outcomes strongly associated with gestational age at delivery. More than 20% prenatal morbidity and mortality rate are associated with PPROM.[7] The impact of PROM complicates the outcome of both the mother and neonate. The most common complications on the mother with PROM that may occur include infection, placental abruption, and cesarean birth. The most common complications on the neonate including prematurity and low birth weight which has a substantial contribution to the perinatal mortality rate.[8]

Diagnosis of PROM is clinically established.[9] Typically, the diagnosis of PROM is confirmed by the clinicians via sterile speculum examination. Speculum examination is performed to objectively identify these three clinical signs: (1) inspection of fluid accumulation in the posterior fornix of vagina or fluid leaking from the cervical ostium which indicates membrane rupture; (2) an alkaline pH of the cervicovaginal fluid reflects amniotic fluid, which is suggested by nitrazine paper test turns into blue; (3) microscopic ferning test of the cervicovaginal fluid to confirm the presence of amniotic fluid crystals.[10] The gold standard to diagnose PROM is using indigo carmine injection. However, indigo carmine injection is considered as highly invasive procedure to be routinely practiced. An accurate diagnosis of PROM depend upon the clinician’s expertise to identify the clinical signs using minimally invasive procedure.[3]

The infiltration of polymorphonuclear (PMN) cell(s) into the chorionic and amniotic membrane was termed chorioamnionitis. It occurred in 0.1 – 2% of all pregnancies, 25 – 40% of all preterm births, and 40 – 70% of cases of spontaneous labor due to PROM. Obstetricians often defined acute chorioamnionitis as a clinical syndrome consists of fever, maternal or fetal tachycardia, tenderness in the uterus, and malodorous amniotic fluid.[11] The term histological chorioamnionitis was inserted into the medical lexicon to distinguish it from clinical chorioamnionitis, which is diagnosed clinically based upon clinical symptoms and signs. Histological chorioamnionitis confirmed histopathologically based upon microscopic examination.[12] There is no consensus regarding standard definition for diagnosing chorioamnionitis.[13] Sometimes the diagnosis of chorioamnionitis during pregnancy is difficult to establish, due to lack of clincal signs of inflammation.[14] However, the presence of inflammatory markers, such as white blood cells (WBC) and C-reactive protein (CRP) are used to make an early diagnosis of chorioamnionitis.[15] Histopathological examination of the fetal membranes might show the presence of PMN cell(s) infiltration into both amniotic and chorionic membrane and indicated a histological chorioamnionitis. The clinical course of histological chorioamnionitis is often asymptomatic. However, the process of PMN cells infiltration into fetal membranes is still ongoing, which in turn leads to increase complications of pregnancy. This research aimed to determine the difference of PMN cells infiltration into fetal membranes of PROM and non-PROM.

2. METHODS

Analytical observational study was applied to this research. Cross-sectional design was used for analyzing data. This research aimed to determine histopathological difference of inflammatory cells infiltration into fetal membranes of PROM and non-PROM. Quantitative study method was used for determining PR, ratio between prevalence of PROM in fetal membranes with PMN cells infiltration and PROM in fetal membranes without PMN cells infiltration.

Primary data collection was conducted in the delivery room and operating theater of Emergency Department in RSPAL dr. Ramelan Surabaya, started from 28 August 2019 to 28 November 2019. Accessible population of this research was the patients who gave birth due to PROM and non-PROM both spontaneously and via cesarean delivery. We included all patients who met following criteria: (1) maternal aged 18 – 44-year-old, by reason of marriage before the age of 18-year-old is prohibited and pregnancy in maternal aged ≥45-year-old have been reported to be associated with adverse pregnancy outcomes, including PROM and PPROM; (2) gestational age $20^{0/7}$ – $41^{6/7}$ weeks, as normal gestation period and; (3) singleton gestation, by reason of multiple gestation increases the risk of pregnancy complications, including PROM and PPROM. Expectant mothers with pre-eclampsia, gestational diabetes and history of PROM in previous pregnancies, pregnancies with fetal abnormalities, and those who repudiated partaking in this research were excluded. We excluded maternal whose past medical history listed above in consideration of risk factors for PROM. A total population sampling technique was used for taking this research samples. Data of maternal age, gestational age, gravidity and number of fetuses were collected directly from the subjects. Data of maternal medical history, mode of delivery and fetal abnormalities were obtained from their medical records. The research data confidentiality was ensured by labelling all

samples with sequential number corresponding to the order of the subject's participation in this research.

In this study, PROM was described as rupture of the fetal membranes (amnion and chorion) spontaneously prior to the onset of labor. Diagnosis of PROM was established from symptoms, physical findings and litmus testing for vaginal pH evaluation. Gestational age was projected by referring to the date of last menstrual period. Singleton gestation was diagnosed using ultrasonography (USG) during antenatal care (ANC) on the third trimester of gestation or the latest USG result. Fetal abnormalities were discovered directly after the neonate was born.

Following delivery, the fetal membranes were cut using mayo scissors in the necessary and required size as a sample. Samples were immersed in 10% neutral buffered formalin solution as fixative method. The fixed specimens were prepared and embedded in paraffin tissue blocks in the Anatomical Pathology Laboratory of the RSPAL dr. Ramelan Surabaya. Sections of formalin-fixed paraffin-embedded tissue blocks were stained using Hematoxylin and Eosin (H&E). Thereafter, the microscopic examination was inspected by the anatomical pathologist in five high-power fields (hpf). According to the fetal membranes histopathological findings, infiltration of ≥1 PMN cell(s) per 5 hpf was defined as a positive finding.

The maternal age, gestational age, gravidity and mode of delivery were recorded in a table form. A 2×2 table was displayed to calculate the PR of PROM. Histopathological findings of the samples were analyzed using a statistical software. Statistical analysis was performed by Chi-square test, aimed to assess the significance level of histopathological difference of inflammatory cells infiltration into fetal membranes of PROM and non-PROM. The statistical significance level was specified at $\rho<0.05$.

3. MAIN HEADING OF THE ANALYSIS OR RESULTS

During this research period, forty subjects were included by dint of meeting the inclusion criteria. Of the 40 enrolled subjects, 20 (50%) developed PROM and 20 (50%) non-PROM. The characteristics and distribution of this research subjects were listed in **Table 1**. Maternal age, mode of delivery, and gravidity were similar between PROM and non-PROM group and did not evaluate statistically.

Table 1. Characteristics and distribution of subjects (n = 40)

Variable	Category	PROM (n = 20)		Non-PROM (n = 20)	
		n	%	n	%
Meternal age (year-old)	18 – 24	2	10	3	15
	25 – 29	8	40	7	35
	30 – 34	4	20	6	30
	35 – 39	3	15	3	15
	40 – 44	3	15	1	5
Mode of delivery	Spontaneous	17	85	18	90
	Cesarean section	3	15	2	10
Gravidity	Primigravid	6	30	7	35
	Multigravid	14	70	13	65

Source: Primary data, 2019.

PROM: premature rupture of membranes; Non-PROM: non-premature rupture of membranes

On the report of the histopathological findings on 40 samples of fetal membranes, PMN cell(s) infiltration into fetal membranes were observed in 12 (30%) samples, and negative findings on the remaining 28 (70%) samples. The results were summarized in **Table 2**. Among the 12 samples with PMN cell(s) infiltration, 11 were collected from PROM subjects and only 1 from non-PROM. The prevalence of PROM in the fetal membranes with PMN cell(s) infiltration was 92% (**Figure 1**). Among the 28 samples without PMN cell infiltration, 9 were collected from PROM subjects, while the remaining 19 from non-PROM. The prevalence of PROM in the fetal membranes without PMN cell infiltration was 32% (**Figure 2**).

Table 2. 2×2 table of histopathology of inflammatory cells in fetal membranes from PROM and non-PROM

		PROM		Total
		Yes	No	
Inflammatory cell(s)	Positive	11	1	12
	Negative	9	19	28
Total		20	20	40

Source: Primary data, 2019.
PROM: premature rupture of membranes

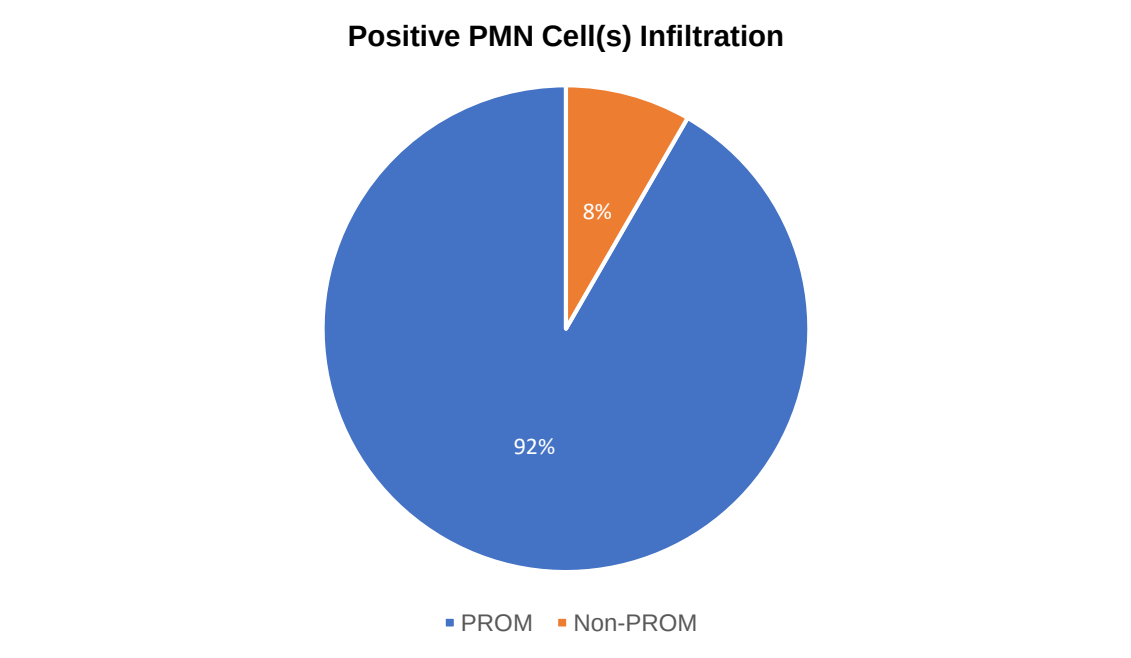

Figure 1. Prevalence of PROM in the fetal membranes with PMN cell(s) infiltration
Source: Primary data, 2019.
PMN: polymorphonuclear; PROM: premature rupture of membranes; Non-PROM: non-premature rupture of membranes

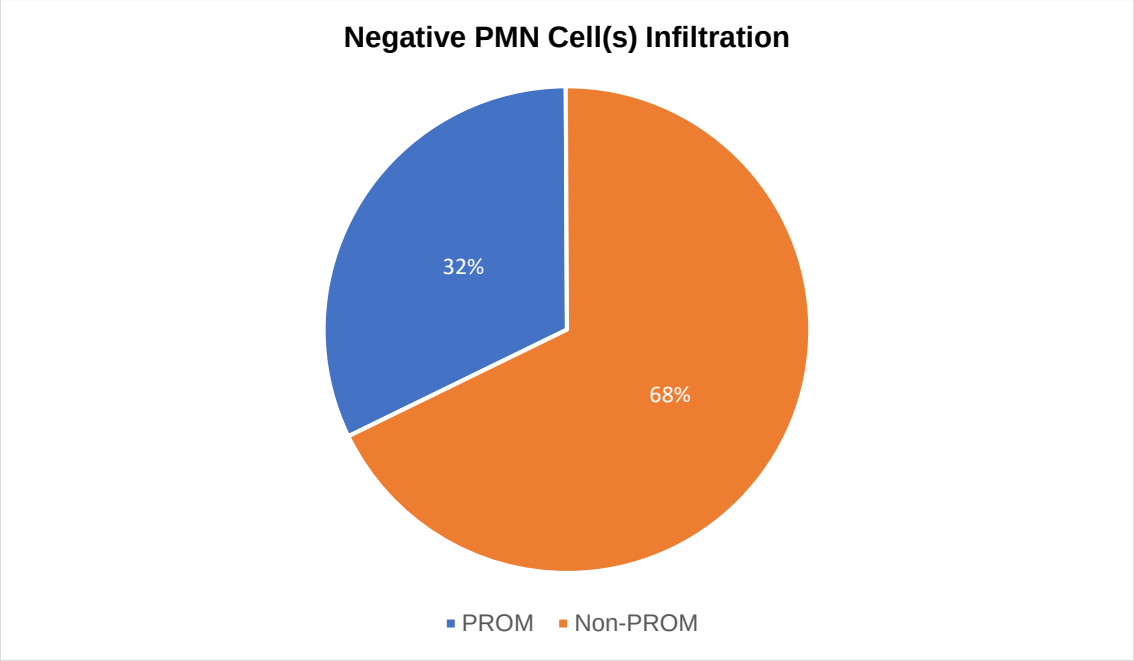

Figure 2. Prevalence of PROM in the fetal membranes without PMN cell infiltration
Source: Primary data, 2019.
PMN: polymorphonuclear; PROM: premature rupture of membranes; Non-PROM: non-premature rupture of membranes

Subsequent calculation resulted in prevalence ratio of 2.85 (PR>1). The prevalence ratio established that the infiltration of PMN cell(s) into fetal membranes was one of the risk factors of PROM. This research showed that infiltration of PMN cell(s) into fetal membranes increased 2.85 times the prevalence of PROM compared to fetal membranes without infiltration of PMN cell. The Chi-square test revealed ρ value = 0.001 (ρ<0.05). The difference of inflammatory cells infiltration into fetal membranes of PROM and non-PROM was statistically significant.

Table 3. Chi-square test

	Value	df	Asymptomatic Significance (2-sided)
Pearson Chi-Square	11.905[a]	1	.001

df: degree of freedom; a: 0 cells (0.0%) have expected count less than 5.
The minimum expected count is 6.00

4. DISCUSSIONS

The fetal membranes, composed of the amnion and chorion, play a critical role in maintaining a healthy pregnancy.[16] The amniotic membrane, the innermost layer, produces the amniotic fluid that cushions and protects the fetus. This avascular membrane, lacking nerves and lymphatic vessels, consist of five distinct layers, with the intermediate layer interfacing with the chorion.[16,17] While the junction between the amnion and chorion is not clearly defined, the fetal membranes could be separated manually after delivery.[18] The chorion, in contact with the maternal decidua, is typically thicker than the amnion but possesses less tensile strength.[16,18] Its metabolically active

cells contribute significantly to fetal protection by guarding against infection and regulating.[4]

During normal pregnancy, extracellular matrix (ECM) has a crucial contribution to maintain the fetal membranes integrity. Infection of fetal membranes, PROM and at term birth induce activation a group of enzymes, namely matrix metalloproteinases (MMPs). Matrix metalloproteinase-9 and MMP-2 are known to be the main mediators of ECM.[19] Infection-related PROM might develop through down-regulation of genes essential for tensile strength within the fetal membranes.[20] Prostaglandin plays a pivotal role in the rupture of fetal membranes, by upregulating MMP-9.[21] The fetal membranes of at term pregnancies have a relatively weak area in the zone that overlies the cervix. This zone comprises a numerous amount of collagen remodeling and apoptosis.[18]

During pregnancy, the main source of prostaglandin is the amniotic membrane. Prostaglandin has a crucial role in the labor process by stimulating cervical ripening and myometrial contraction.[21] Elevation of prostaglandin E2 (PGE2) level in the amniotic fluid only occurred when preterm labor is associated with microbial invasion of the amniotic membrane in women with PROM.[22] Intra-amniotic infection during pregnancies with preterm labor and PPROM could be detected using a sample of amniotic fluid. Transabdominal amniocentesis is performed to obtain amniotic fluid. This procedure is carried out in some institutions to test the amniotic fluid directly for subclinical intra-amniotic infection in patients with preterm labor or PPROM, or in the research field. Transabdominal amniocentesis is not regularly used for diagnosing intra-amniotic infection.[19,23]

Chorioamnionitis or intra-amniotic infection, stands as a prevalent cause of PROM.[24] While prophylactic antibiotics have shown promise in prolonging the latency period between membrane rupture and delivery, thereby reducing maternal and neonatal morbidity.[25] It is crucial to recognize that infection is not the sole culprit behind histological chorioamnionitis.[26] “Sterile” inflammation stemming from extra-placental factors can also contribute to this condition.

Fetal membrane rupture arises from a complex interplay of physiological weakening and various stressors. While tensional forces due to myometrial contractions are inherent to the process, factors like cervical insufficiency, polyhydramnios, trauma, and amniotic fluid infection can accelerate the process.[27] Inflammatory mediators, including interleukin-6 (IL-6), play a pivotal role in both membrane disruption and myometrial contractions, further emphasizing the intricate link between inflammation and PROM.[28]

Diagnosing PROM clinically relies on a combination of patient history, sterile speculum examination, and ancillary tests like the nitrazine test to detect amniotic fluid. However, each method has limitations.[6] Diagnosing chorioamnionitis during pregnancy presents a greater challenge due to the lack of a definitive consensus and the non-specific nature of its clinical manifestations.[9,28] Ultimately, histopathological examination of the fetal membranes post-delivery, particularly the presence of PMN cell(s), provides the definitive diagnosis.[12,29]

The supracervial area, where the fetal membranes overlie the cervical ostium, exhibits a heightened vulnerability to rupture in PPROM.[27] This susceptibility stems from anatomical and histological alterations in the amniotic membrane within this region, leading to compromised membrane integrity and increased bacterial colonization.

Importantly, while myometrial contractions exert tensional forces on the membranes, they alone are insufficient to cause rupture. Pre-existing weakening factors, particularly enzymatic degradation of collagen within the fetal membranes, play a crucial role in setting the stage for PPROM.[18]

Once membrane rupture occurs, the risk of ascending infection from the lower reproductive tract becomes a significant concern.[30] Urinary tract infections, for instance, can serve as a bacterial reservoir, with microorganism ascending through the vagina to the fetal membranes, triggering inflammation and further enzymatic degradation. This localized inflammation, in turn, fuels prostaglandin release, creating a vicious cycle of mild myometrial contractions, increased tensional forces at the already weakened supracervical area, and ultimately, PPROM.[31] Given these risks, clinicians are advised to avoid digital cervicovaginal examinations before labor to minimize the risk of introducing infection.[32]

Furthermore, diagnosing chorioamnionitis in PROM cases presents a significant challenge.[32] A systematic review by Etyang *et al.* revealed that relying solely on CRP levels for diagnosis is not widely recommended.[13] This limitation necessitates a more reliable diagnostic approach, such as histopathological examination of fetal membranes, to confirm chorioamnionitis accurately. This study will utilize histopathological examination to overcome the limitations of CRP-based diagnosis and ensure an accurate assessment of chorioamnionitis in the study population. Several researches have consistently published that a history of PROM in prior pregnancies increases the proclivity for recurrence.[32] Therefore, authors exclude the expectant mothers with history of PROM in their previous pregnancies. Marković *et al.* have reported that 2 – 4% of all singleton pregnancies and 7 – 20% of twin pregnancies complicated with PPROM. The research reported by Marković *et al.* suggested that multiple gestations increases the risk for PROM and considered as an exclusion criteria in this research.[33] The correlation between mode of delivery—either spontaneous vaginal delivery or cesarean section—and neonatal outcomes in preterm births due to PROM are not well disclosed.[27]

There are several studies discussing correlation between histopathological chorioamnionitis and PROM. Nguyen *et al.* found there was an increasing activation of some collagenases, such as MMP-1, MMP-8 and MMP-13 in the amniotic fluid of PROM. Futhermore, they observed a significant correlation between PMN cells and MMP level in the amniotic fluid of PROM, supporting its relationship to chorioamnionitis.[34] Cobo *et al.* observed a high level of CRP in the cervical compartment in patients with PPROM, reflecting an inflammation process in the amniotic cavity.[35] Our study revealed the infiltration of PMN cells into fetal membranes between patients with PROM and non-PROM are significantly (ρ value = 0.001 ($\rho<0.05$)) difference. The higher number of PMN cells in fetal membranes in patients with PROM indicating there is a histopathological chorioamnionitis. Patients with histopathological chorioamnionitis may present without clinical symptoms. Untreated chorioamnionitis may lead to PROM and cause preterm birth. Histopathological chorioamnionitis is confirmed after birth by histopathologically examining the fetal membranes. Since chorioamnionitis is not always related to microbial invasion, a routine administration of antibiotic is not recommended.

5. CONCLUSION

This research revealed a statistically significant difference in inflammatory cells infiltration into fetal membranes between PROM and non-PROM groups. Notably, our findings indicate that PMN cells infiltration into fetal membranes serves as a significant risk factor for PROM. However, the majority patients with PROM develop histopathological chorioamnionitis and present without any clinical symptom of chorioamnionitis. Therefore, asymptomatic chorioamnionitis is most often undiagnosed and left untreated. Further studies must be considered to establish the diagnosis of asymptomatic histopathological chorioamnionitis during pregnancy to prevent and reduce the incidence of PROM.

While this research provides valuable insights into the role of PMN cells in PROM, further prospective studies with larger sample sizes are crucial to solidify these findings. Future research should also explore the precise mechanisms by which PMN cells infiltration contributes to membrane weakening and subsequent PROM. Additionally, investigating potential interventions targeting PMN cells activity could pave the way for novel preventative and therapeutic strategies form PROM.

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