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Research

Premature Rupture of Membrane Outcome Determinants in Reproductive Age Women

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ABSTRACT

Background: Premature Rupture of Membrane (PROM) may cause maternal and neonatal morbidity and mortality. This study aimed to investigate the risk factors related to PROM in pregnant women below <35 years old.
Subjects and Method: This cross-sectional study was conducted in Kertha Usada General Hospital, North Bali, Indonesia. We collected 224 repoductive women using consecutive sampling. The dependent variable was premature rupture of membrane. The independent variables were gravidity status, gestational age, body mass index (BMI), history of caesarean section, miscarriage, infection, and anemia. Data of infection was obtained from examination, such as neutrophil, lymphocyte, platelet, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR). We also obtained Hb, MCV, and MCH as laboratory parameter of anemia. The data were analyzed by a multiple logistic regression.
Results: Multigravida (OR= 0.04; 95% CI= 0.01 to 0.27; p= 0.001) and MCH >34 pg (OR= 0.10; 95% CI= 0.01 to 0.86; p= 0.036) decreased the risk of premature of rupture membrane in women of reproductive age.
Conclusion: Multigravida and MCH >34 pg decrease the risk of premature of rupture membrane in women of reproductive age.

Keywords: premature rupture membrane

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BACKGROUND

Premature rupture of membranes (PROM) is a rupture of membranes over the age of 28 weeks of pregnancy but prior to the onset of labor. PROM is classified into premature rupture of membranes (PROM) and preterm premature rupture of membranes (PPROM). PROM occurs at gestational age above 37 weeks but prior to the onset of labor. PPROM occurs when gestational age <37 weeks. Rupture of membranes more than 24 hours referred to as prolonged rupture of membranes (Dutta, 2015). The diagnosis of PROM is established through anamnesis and internal examination, which is the watery fluid comes from genital or there are pool of fluids on the speculum examination. Other supporting diagnostic tests are nitrazin test (vaginal fluid PH examination), ferning test, ultrasound examination of amniotic fluid, and fetalfibronectin (Olabi and Lucy, 2016).

PROM may cause maternal and neonatal morbidity and mortality. In the study conducted by 17.8% of patients had chorioamnionitis (Yu et al., 2015). The other study conducted at the 24-31 week gestational age who underwent PPROM, there was a choriamnionitis in 9.8% of twin pregnancies, and 23.2% of single pregnancies. As well as, 35.9% of chorioamnionitis on twin fetal placenta and 67.7% in single fetal placenta. Other frequent complications are IVH, RDS, PVL, sepsis, NEC, and mortality in neonates (Yu et al., 2015). Some studies have reported various factors that may increase the incidence of PROM, including cervical incompetence, multiple pregnancies, infection, cervical length, prior birth history, and weight gain (Lee et al, 2018; Musaba et al, 2017; Vyas et al, 2013; Lai et al, 2017; Zeng, 2014; Shainker 2016; Derakhshi, 2016; Hung et al 2015; Masho et al, 2013). Our study aimed to investigate the most influential risk factors that have been related to PROM and PPROM.

SUBJECTS AND METHOD

1. Study Design

This is the analytical observational study with cross-sectional design. The study was conducted on April 2018 within 1 month from Kertha Usada Hospital, Singaraja, Bali.

2. Population and Sample

A total of 224 reproductive women were selected by consecutive sampling.

3. Study Variables

The dependent variable was premature rupture membrane. The independent variables were gravidity status, gestational age, body mass index (BMI), history of caesarean section, miscarriage, infection, and anemia.

The inclusion criteria were the patients diagnosed with PROM and PPROM that were previously established through anamnesis and internal examination. Other supporting diagnostic tests are nitrazin test (vaginal fluid examination test) ferning test, and ultrasound examination of amniotic fluid.

4. Operational Definition of Variables

We described women in reproductive age was below 34 years old. Whereas, the advance age was above 35 years old.

Gravidity status was classified into primigravida, the women who had a pregnant only once, and multigravida.

Gestational age was classified into below 37 weeks and above 37 weeks.

Body mass index (BMI) was classified into normal, overweight, and obese. We did not get an underweight data.

We also extract the participants data based on the history of caesarean section and miscarriage.

5. Study Instruments

The data were obtained from medical record. We used laboratory parameter from infection and anemia. There were four indicators of infection, such as neutronphil, lymphocyte, platelet value, neutrophil-to-lymphocyte (NLR), and platelet-to-lymphocyte ratio (PLR). We also obtained Hb, MCV, and MCH as the benchmark of anemia.

6. Data Analysis

The data were analyzed by a multiple logistic regression.

7. Research Ethics

Ethics committee approval was received for this study from the ethics committee of Kertha Usada General Hospital, Buleleng, Bali (Ethics number: 0054/RSU-KU/V/2018).

RESULTS

1. Univariate analysis

Respondents aged ≤35 years contained 193 people (86.2%), while age>35 years contained 31 people (13.8%).

Table 1. Frequency distribution of participants

Independent Variables	n	%
Gravida		
Multigravida	129	87.05
Primigravida	95	12.96
Gestational Age		
<37 weeks	15	6.69
≥37 weeks	229	93.31
BMI		
25-29.9 kg/m^2	89	39.73
≥30 kg/m^2	37	16.52
18.5-24.99 kg/m^2	98	43,75
Sectio Cesaria History		
Yes	30	13.39
No	194	86.61
Miscarriage History		
Yes	31	13.84
No	193	86.16
Neutrophil		
>8 x10^3/uL	140	62.5
<2 x10^3/uL	1	0.45
2-8 x10^3/uL	83	37.05
Lymphocyte		
>5 x10^3/uL	3	1.34
<1 x10^3/uL	1	0.45
1-5 x10^3/uL	220	98.21
Platelet		
<150 x10^3/uL	8	3.57
>450 x10^3/uL	1	0.45
150-450 x10^3/uL	215	95.98
NLR		
≥6.48	37	16.52
<6.48	187	83.48
PLR		
>117.14	104	46.43
≤117.14	120	53.57
Hb level		
7-8.99 g/dl	2	0.89
9-11 g/dl	48	20.08
>11 g/dl	174	79.03
MCV		
<80 fL	19	8.48
>100 fL	4	1.78
80-100 fL	201	89.74
MCH		
<26 pg	22	9.82
>34 pg	5	2.23
26-34 pg	197	87.95
Maternal age		
<35 years	193	86.20
≥35 years	31	13.80

2. The result of multivariat analysis

Table 2 showed the results of multivariate analysis on the determinants of premature rupture membrane. Table 2 showed that multigravida (OR= 0.04; 95% CI= 0.01 to 0.27; p= 0.001) and MCH >34 pg (OR= 0.10; 95% CI= 0.01 to 0.86; p= 0.036) decreased the risk of premature of rupture membrane in women of reproductive age.

Table 2. Multivariate analysis on the determinants of premature rupture membrane

Independent Variables	Maternal age				OR	95% CI		p
	<35 years		≥35 years			Lower limit	Upper limit	
	n	%	n	%				
Gravida								
Multigravida	99	76.7	30	23.3	0.04	0.01	0.27	0.001
Primigravida	94	98.9	1	1.1				Reference
Gestational Age								
<37 weeks	14	93.3	1	6.7	1.15	0.12	11.07	0.902
≥37 weeks	179	85.6	30	14.4				Reference
BMI								
25 kg/m² to 29.9 kg/m²	80	89.9	9	10.1	1.94	0.74	5.07	0.177
≥30 kg/m²	30	81.1	7	18.9	1.06	0.33	3.48	0.918
18.5kg/m² to 24.99 kg/m²	83	84.7	15	15.3				Reference
History if Cesarian Section								
Yes	25	83.3	5	16.7	1.15	0.37	3.56	0.814
No	168	86.6	26	13.4				Reference
Miscarriage History								
Yes	23	74.2	8	25.8	1.04	0.36	2.97	0.945
No	170	88.1	23	11.9				Reference
Infection Parameter								
Neutrophil								
>8 x10³/uL	121	86.4	19	13.6	1.02	0.37	2.76	0.975
<2 x10³/uL	1	100	0	0.0	-	-	-	1
2x10³/uL to 8 x10³/uL	71	85.5	12	14.5				Reference
Lymphocyte								
>5 x10³/uL	3	100.0	0	0.0	-	-	-	0.999
<1 x10³/uL	0	0.0	1	100	-	-	-	1
1x10³/uLto 5 x10³/uL	190	86.4	30	13.6				Reference
Platelet								
<150 x10³/uL	7	87.5	1	12.5	0.68	0.06	7.45	0.755
>450 x10³/uL	1	100.0	0	0.0	-	-	-	1
150x10³/uL to450 x10³/uL	185	86.0	30	14.0				Reference
NLR								
≥6.48	30	81.1	7	18.9	0.81	0.24	2.76	0.734
<6.48	163	87.2	24	12.8				Reference
PLR								
>117.14	89	85.6	15	14.4	0.68	0.28	1.63	0.385
≤117.14	104	86.7	16	13.3				Reference
Anemia								
Hb level								
7 g/dl to 8.99 g/dl	2	100.0	0	0.0	-	-	-	0.999
9 g/dl to 11 g/dl	44	91.7	4	8.3	2.45	0.64	9.42	0.192
>11 g/dl	147	84.5	27	15.5				
MCV								
<80 fL	16	84.2	3	15.8	0.09	0.01	5.21	0.248
>100 fL	2	50.0	2	50.0	4.22	0.07	271.10	0.498
80-100 fL	175	87.1	26	12.9				Reference
MCH								
<26 pg	19	86.4	3	13.6	0.76	0.19	3.04	0.705
>34 pg	2	40.0	3	60.0	0.10	0.01	0.86	0.036
26pg to 34 pg	172	87.3	25	12.7				Reference

DISCUSSION

There are various factors that affect advance maternal age to be more prone toward rupture of membrane. We all known that the higher maternal age will decrease the elasticity and density of collagen protein and the

other protein containing matrix tissue. On the contrary, we believe thatreproductive age have a lower risk of rupture of membrane which could be considered as insignificant condition in pregnant women. Our analysis found that multigravida has a significant value as a protective factor 0.035 times.The other study from Okeke et al. has a pretty same results with primigravidahas a higher risk for PROM especially PPROM. The increasing number of parities does not have a significant value for higher risk PPROM. As well as the study from Koo et al. (2015) and Koo et al. (2012), that primigravida was a risk factor for PROM event with $p<0.001$.

In this study, we found that there was insignificant relationship between BMI (underweight, overweight and obesity) with PROM in woman of reproductive age. For underweight, there was no respondent were found. The respondent with overweight BMI has the highest percentage with 80 patients (89.9%) compared with age over 35 years. The riskof PROM with BMI had insignificant value as a protective factor with 1.94 times - for overweight and 1.064 times for obesity. Even though, this study has not any data about the weight before the pregnancy, which has to be adjusted with IOM criteria about Gestational Weight Gain (GWG) in 2009.

The study from Sung et al. (2015) about the risk of spontaneous preterm birth on a twin pregnancy according to BMI maternal showed a significant relationship between BMI especially overweight or obesity with a preterm birth event because of PROM (12.5%) about 1.58 times. Otherwise, the underweight showed an increased risk for preterm birth but had not a significant relationship compared to normal weight, as well as the respondent with spontaneous preterm birth or iatrogenic rupture. These correspond with this study in which the underweight had not a significant relationship.

Obesity on pregnancy may cause an increase cytokine pro-inflammatory in which IL-1 and TNF-αcaused constriction of myometrium and weakened of the membrane. Insulin resistant also play a role on preterm birth that was associated with CRP and cytokine pro-inflammatory (IL-1, IL-6, and TNF-α) increasing on insulin resistance. Otherwise, woman with obesity were said to have a greater risk for urinary tract infection leading to greater risk forchorioamnionitis. Furthermore, the cytokine pro inflammatory will also increase. Underweight were said to have a greater risk of spontaneous preterm birth (Sung et al, 2018).

A study from Parker et al. had a significant results between BMI before pregnancy and spontaneous PTB, such as underweight 54 persons (5.8%), overweight 269 persons (28.9%), and obesity 163 persons (17.5%). Significant results was obtained on Gestational Weight Gainaccording to IOM criteria 2009. The weight gain during pregnancy was 18 persons (12.7%) not adequate and 306 persons (32.9%) was excessive weight gain (Parker et al, 2014). Underweight BMI has a greater risk for spontaneous PTB but not significant about 1.46 times. On the other hand, obesity has significant risk reduction about 0.76 times. Ifchorioamnionitis combined with BMI index, underweight has a greater risk but not significant to late spontaneous PTB about 1.48 times. Underweightshowed a greater risk for spontaneous PTB because of lack of important nutrition in pregnancy for fetal and placental growth. However,obesity showed a reduction to inflammation marker that may caused spontaneous PTB.

The study about maternal characteristic and pregnancy outcome in third trimester, showed significantly related between history of CS and PROM in 27 respondents (4.7%) and PPROM in 20 respondents (14.6%). There after, A study classified history of CS to PPROM into gestational age 28-31 weeks

about 6 people (28.6%) and 32-26 weeks about 14 people (12.1%) with p=0.04 which said to be statistically significant. Breech presentation with history of CS may impact to PPROM rather than PROM (p<0.05) (Chandra and Lizhou, 2017).

In contrast tothis study that there was insignificant relation between history of CS and PROM. However, there was a higher risk of about 1.146 times higher. Conversely, the study conducted in Tehran, Iran also said that there was a significant relationship between higher risk of history of CS as protective factor about 0.6 times higher with preterm birth of any causes with (Halimi et al, 2017). However, in this study, gestational week was classified into <37 weeks and ≥37 weeks, in which <37 weeks should be classified into extremely preterm (<28 weeks), very preterm (28-32 weeks), and moderate-to-late preterm (32-<37 weeks) that may affect the risk factors of PROM or PPROM.

History of miscarriage were said to have a greater risk of PROM with the mechanism of latent local inflammation process because of miscarriage surgery or dilatation of cervix that leads to cervical incompetence with the risk of urinary tract infection. A study from Moreau et al. said that there was an increasing risk of severe premature birth because of PROM in woman with history of miscarriage by pregnancy induction (Moreau et al, 2005).

This study showed an insignificant increasing risk of miscarriage towards PROM about 1.038 times. Even so, this study was also has the same result with Makhlouf et al. about pregnancy in woman with history of miscarriage with or without induction. The results showed there wasansignificant increasing risk of preterm PROM about 2.9 timesin woman with history of 2 or more miscarriage. Greater gestation age when spontaneous miscarriage occur will have a poor prognosis for the next pregnancy (Makhlouf 2014).

The study from Seol et al. (2008) in Korea showed decreasing regulatory T cell which is CD4+CD25 bright might cause PROM on third trimester of pregnancy. These study also compared the group from patient with a third trimester pregnancy that has PROM complication with a group patient on third trimester pregnancy without complication and labor. The study showed that regulatory t-cell were significantly decrease in a group patient with third trimester pregnancy that had PROM complication (p <0.001) and p<0.026 when compared the group patient on third trimester without complication with a group of patient on third trimester with labor. The increasing of regulatory T-cell on early pregnancy might be related to implantation process period (Seol et al, 2008).

The relation between neutrophil or lymphocyte with PROM and PPROM in ≤35 years old women was insignificant. There was an increaserisk for neutrophil as a risk factor 1.016 times higher at level >8 x103/uL. However, neither neutrophil nor lymphocyte was insignificant as protective or risk factors at any level. In contrast to the study from Kim, et al. that there was a significant value for neutrophil and lymphocyte as a maternal inflammatory response predictive marker (Kim et al., 2015).

Chronic chorioamniotic is a condition where there is an infiltration of mononuclear cells to chorioamnionitic membrane. The feature of chronic chorioamnionitic lesion showed broad infiltration of maternal CD8+ cells. In acute chorioamnionitic lesion, the degree of t-cells infiltration was lower than neutrophil cells. The study from Kim, et al.showed that chronic chorioamnionitic resulted from increasing of CXCL10, CXCL9, and CXCL11 in chorioamnionitic membrane. That was caused by chemotactic gradient that appear after T-cells migration from decidua to cho-

rioamniotic gradient (Kim et al, 2014 and Kim et al, 2015).

Study from United States showed significantly higher level of CD40L from respondent with preterm labour in all subgroup (p<0.001) than normal labour. Women with normal labor also said had higher level of sCD40L than non-pregnant women (p=0.05) with the normal median 369.5 pg/ml (63.5–1848.7) and non-pregnant median 270.4 pg/ml (94.2–568). Platelet express CD40L on its membrane then cleave and become soluble substance in plasma sCD40L, whereas sCD40L might be detected in plasma. Activated platelet express more than 90% sCD-40Lin plasma, in which this cytokine is a platelet activation marker. Increasing level of CD40L in respondent with preterm labor because of platelet play a role in acute and chronic inflammation process, in which platelet degranulation and direct contact of platelet with monocyte in circulating system make activation of inflammatory process. Preterm labor causing platelet activation by platelet activation mechanism. However, in normal labor especially in third trimester, platelet decreased in a significant way and related to increasing platelet consumption in utero-placenta (Erez et al, 2008).

In contrast with this research, in which platelet level <150 x 103/uL is insignificant as protective factors 0.684 times higher. However, platelet level >450 x103/uL also was not statistically significant as a risk factor or protective factor. Eventhough, study from Cho et al. showed that PPROM with or without chorioamnionitis was not significant (p=-0.704) (Cho et al, 2017).

The causal of premature labor with or without PROM or PPROM said to be an infectious process, in which the organisms produce collagenases, mucinases, and proteases that may weakened the amnion and chorionic membrane and after that may cause membrane rupture. The mechanism that underlie the infectious process with premature labor is caused by prostaglandin biosynthesis stimulation and then activation of phospholipase A2 and C, or indirectly by IL-1, TNF, and platelet factor activation, that may be identified in infected amniotic fluid (Menezes, 2009).

The study conducted by Kim et al. (2014), about Placental Inflammatory Response (PIR), showed a significant result with positive NLR ≥6.48. NLR predicted PIR about 5.18 times. Systemic inflammation process and stress may increase the immune response with increasing the leukocyte followed by neutrophil, in which NLR plays a role as an inflammatory marker. The study conducted in Turkey, also had a significant value for NLR as a risk factor of PPROM (Toprak et al, 2017). Whereas this study showed NLR ≥6.48 wasinsignificant protective factor about 0.808 lower in women age ≤35.

NLR is a marker of inflammatory process with increasing of white blood cells count ≥50 x 109/I or absolute neutrophil count ≥30 x 109/I in neonatal. The study conducted by Duranetal.showed that neonatal with higher NLR usually occurs with mother infected by chorioamnionitic (p <0.001) and with mother infected by PROM (p= 0.02) because of normal delivery (p= 0.01). Moreover, in low birth weight infants, NLR said to be related with some morbidities, including higher frequency of PROM, chorioamnionitis, low APGAR score, prolong mechanical ventilation, sepsis, IVH,BPD, and higher mortality rate (Duran et al, 2010).

The study conducted by Toprak et al. (2017), on PPROM inflammatory markers showed PLR >117.14 significant value in causing PPROM. A study reported that PLR is an inflammatory marker that has been widely used in predicting coronary thrombosis events, inflammatory processes, and malignancies. The other study showed that PLR was less significant between latent periods <72 hours and>72 hours. In chronic

inflammatory processes, megakaryocytes proliferate rapidly with decreased lymphocyte counts due to severe apoptotic processes, resulting in an influence on the number of blood cells, for example in PLR.

Research conducted by Bencaiova et al. in Switzerland regarding mild anemia and pregnancy outcomes showed insignificant association between PPROM and iron deficiency anemia, women with iron reserves depletion without anemia, and anemia due to other causes compared with women without anemia (Bencaiova and Christian, 2014). It showed insignificant relationship between anemia of any kind with PPROM incidence. However, the study was inconsistent with epidemiological characteristics of preterm birth outcomes having a significant association between anemia during pregnancy and preterm birth with 49.59% PPROM of respondents (Gimenez et al., 2016).

Our study showed insignificant relationship between the severities of anemia with PROM in women of reproductive age. Similarly, the morphology of Hb (MCV) showed insignificant effect on the incidence of PROM. Nevertheless, the number of respondents with mild anemia were 91.7% in women with a PROM less than 35 years. In addition, MCH>34 pg showed a significant association of PROM about 0.101 times as a protective factor.

Physiological plasma expansion resulting in decreasingHb and Ht that occured in the first and second trimesters. The lowest plasma volume expansion occurs at the end of the second and third trimester. The increase of plasma volume is continue until at term gestational age. Thus, it can be concluded that the best time to detect anemia in pregnant women is in the early of first trimester. Twenty weeks gestation examination showed the decrease in Hb and Ht are due to pregnancy which is not representative to diagnose anemia in pregnant women. Research showed that mild anemia in pregnancy does not lead to poor outcome of maternal and neonatal (Bencaiova and Christian, 2014).

There was some limitations of the present study. First, this study was not excluded the comorbidity of the respondents. Second, this study was not classified the dependent variable into PROM and PPROM. Third, this study was not classified the maternal age as a dependent variable into adolescent, adult, and elderly. Fourth, this study was not classified the independent variables in its subgroups.

Our study obtained that multigravida and MCH>34 pgwere thesignificant value as protective factors of reproductive age women with PROM and PPROM. These results were generate a question about the association between the elasticity of collagen with the higher gravidity status which will decrease the risk of membranerupture or vice versa. Likewise, our results showed that macrocytic erythrocyte was not correlated the high risk of membrane rupture, as the oxygen level was dependent on erythrocyte quantity and quality. However, further research is needed in larger samples and populations, as in this study, most of the respondents' data were taken from the patient's medical record that were control in the minimal recommendation of antenatal care at least 3 times. In addition, most of the respondents in this study were pregnant women in reproductive age ≤35 years, which consist of 193 people (86.2%). While women aged > 35 years count as 31 people (13.8%), which showed unequal distribution of age in the study.

AUTHOR CONTRIBUTION

Sarah Chairani Zakirah contributed on concept and design, acquisition of data, data analysis and interpretation, drafting and revising the article, and final proofreading. Putri Chairani Eyanoer made concept, draft-

ing and revising the article, final proofreading, approval of the final manuscript, and supervising. Chairul Nurdin Azali drafted and revised the article. Budi Wiweko did final proofreading and supervising.

CONFLICT OF INTEREST

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

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