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Original Research Article

Prediction of preterm premature membrane rupture by the platelet-lymphocyte ratio

Nargis Sultana[1]*, Farha Karim[2], Mohammad Khalilur Rahman[3]

[1]Department of Obstetrics & Gynecology, Keraniganj Upazila Health Complex, Dhaka, Bangladesh
[2]Department of Obstetrics & Gynecology, Jinjira 20 Bedded Hospital, Dhaka, Bangladesh
[3]Department of Surgery, Shaheed Tajuddin Ahmed Medical College Hospital Gazipur, Bangladesh

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***Correspondence:**
Dr. Nargis Sultana,
E-mail: nargissultanamunni@gmail.com

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ABSTRACT

Background: Premature rupture of membranes is a significant obstetric problem. Evaluating platelet -lymphocyte ratio is expected to illuminate the potential scope of early prediction of PPROM. This study showed that PLR could be a new inflammatory marker for diagnosing preterm PROM.
Methods: The study place was the Department of Obstetrics and Gynaecology, Sir Salimullah Medical College & Mitford Hospital, Dhaka, Bangladesh, from May 2019 to October 2019.
Results: It was a case-control study. All mothers were selected by purposive sampling who were PPROM as cases. Age-matched non-PPROM pregnant women at term were also enrolled as control. Afterward, they were scrutinized according to eligibility criteria, and 200 mothers were enrolled. Among them, 100 were cases, and the other 100 were in control. A pre-tested, observation-based, peer-reviewed data collection sheet was prepared before the study. Data regarding clinical, biochemical, and surgical profiles were recorded. Data were compiled, edited, and analyzed. The P-value was determined by the chi-square test (categorical variables) and the student's t-test (continuous variables). The p-value was significant at <0.05.
Conclusions: The mean age of 100 patients from the case was 24.39±2.81 (age range: 18-36) years, and that of the control, like 100 normal pregnant women, was 24.31±2.34 (age range: 19-35) (p=0.49). The mean parity of case and control were 2.1±0.9 (range: 0-5) and 1.98±0.2 (range: 0-3). The mean gravida of case and control were (3.1±1.2 vs. 3.4±1.4). Platelet count was found to be significantly higher in preterm PROM group (case) than control (241.6±58.7×1000/mm³ vs. 201.7±65.9 ×1000/mm³), p value is <0.001 which is statistically significant. So, PLR might be an excellent inflammatory biomarker to predict preterm PROM.

Keywords: Platelet, Lymphocyte, PROM, Preterm, Inflammatory, Biomarker

INTRODUCTION

Preterm Premature rupture of membranes (PROM), is defined as the spontaneous rupture of fetal membranes before labour begins before 37 weeks gestation. It affects approximately 3% of all Pregnancies.[1] It is closely related to significant maternal and fetal morbidity and mortality. Preterm PROM is one of the most common causes of preterm delivery and is associated with maternal and neonatal infections.[2] The risk of chorioamnionitis is approximately 6-10% and increases to 40% if it prolongs over 24 hours.[3] Moreover, neonatal infection risk is two times greater in patients without chorioamnionitis.[4] Infection risk increases with preterm PROM. Neonatal hypoxia and jaundice are also more common in this condition.[5] Early diagnosis is crucial to provide maternal and fetal well-being because of these severe complications.[6] It usually occurs as a result of a

physiological process, such as uterine contractions, fetal movements, and biochemical changes decreasing collagen in the Chorio-amniotic membranes, which in turn weaken the chorio-amniotic membranes.[7]

Overall, it has been hypothesized that the presence of chronic inflammation could trigger premature rupture. Several inflammatory markers have been evaluated in the pathogenesis of PPROM, and there are shreds of evidences that show increased proliferation of megakaryocytic series, and severe apoptosis is associated with decreased lymphocyte counts.[8] In chronic inflammatory process, megakaryocyte proliferates increasingly due to substance produced by interaction of host and agents. Also inflammatory cytokines such as IL 1,IL 6 activates megakaryocytes, Cytokines that participate in inflammatory reactions have been reported to be associated with preterm PROM which is responsible for the rise in platelet count.[9] Therefore, the evaluation of platelet-lymphocyte ratio (PLR) is expected to throw light on the potential scope of early prediction of PPROM. With this background, the present study was carried out to compare the PLR among preterm PPROM and healthy controls to evaluate the predictive role of PLR.

METHODS

This study was conducted among women attending the Department of Obstetrics & Gynecology from May 2019 to October 2019 in Sir Salimullah Medical College & Mitford Hospital, Dhaka, Bangladesh, who were diagnosed with preterm PROM.

It is a case-control study, and the sample size is determined by the following formula:[9]

$$n = (Z\alpha + Z\beta)2\, x\, (\sigma 12 + \sigma 22) / (\mu 1 - \mu 2)\, 2$$

Where n=desired sample size, μ_1=mean of control group=106.9, μ_2=mean of PRETERM PROM group=126.3, σ_1=SD of control group=49.4, σ_2=SD of preterm PROM group=68.9, Z_α=Z-value at a definite level of significance, e.g., 3.90 at 0.01% level of significance, Zβ=Z-value at a definite power, e.g., 2.33 at 99% power (when β=0.01). Putting the values therefore we get, n=762, but, due to time constraints, 200 cases were enrolled in the study (100 in case and 100 in control).

Sampling methods

Purposive sampling was the method of choice to select the sample from the women attending the Gynecology & Obstetrics department of SSMC&MH during the earlier mentioned study period to evaluate NLR impact to diagnose preterm PROM.

Inclusion criteria

Inclusion criteria were preterm PROM patients (cases), age-matched non-PROM pregnant women at term (control), and mothers who agreed to participate in the study.

Exclusion criteria

Exclusion criteria were multiple gestations, hematologic disorders, malignancies, hepatic disease, history of autoimmune disease, any inflammatory disease of pregnancy such as gestational diabetes mellitus and preeclampsia, any acute or chronic infectious or inflammatory diseases, pregnancies with fetal chromosomal anomalies, intrauterine growth restriction, fetal infection, and women who will undergo any invasive procedures such as amniocentesis.

Operational definitions

PROM: Spontaneous rupture of the membrane after the age of viability but before the onset of labour is called PROM. Preterm-PROM: Spontaneous rupture of the membrane after the age of viability but before 37 completed weeks is called Preterm-PROM.

Table 1: Considerable variables for the study.

Parameters		
Independent variables		
Socio-demographic profile	**Obstetric profile**	**Hematological profile**
Age	Parity	Platelet count
Income status	Duration of amenorrhea	Lymphocyte count
Occupation	Gravida	PLR
Dependent variables		
Platelet to lymphocyte ratio as a marker of preterm PROM		
Confounding variable		
(NA); Selection bias may be act as a confounding factor		

Study procedure

It was a prospective case-control study in which 100 pregnant women with preterm PROM and 100 age-matched pregnant women at term were enrolled by purposive sampling. A pre-structured data collection sheet was prepared. The detailed history and physical examination, including per speculum examination, was done to scrutinize cases and control. Patients were those with preterm PROM, and controls were those with term pregnancy. Data regarding socio-demographic, obstetrics, and hematological profile was recorded. Age, gestational week, gravida, parity, delivery mode, birth weight, APGAR score, neonatal intensive care unit (NICU) admission rate, presence of neonatal sepsis, and development of respiratory distress syndrome (RDS) was recorded. In addition, the results of a complete series of routine laboratory investigations, including complete blood cell counts, were recorded. Complete blood counts

were analyzed using a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland INC, Mervue, Galway, Ireland). The platelet-to-lymphocyte ratio (PLR) was calculated by dividing the platelet count by the lymphocyte count. Randomization and blinding methods were not applicable. The equipment used in the study were clinical records, observation, investigation reports, and questionnaires. We collected data by interviewing through preformed structured questionnaires. Direct students, children, and prisoners acutely ill patients were excluded from the study. The procedure was explained to the sample unit, and they were informed that if they did not wish to be included in the study, that would not hamper the treatment. At any point in the study, if they wanted, they could withdraw themselves from the study at any moment. Informed written consent of the patient was taken. Written permission has also been taken from the concerned department where the study was undertaken.

Procedures of data analysis and interpretation

All data were checked and edited after collection. Then we made charts by a spreadsheet of Windows 7. After that, the frequency distribution and normal distribution of all continuous variables were calculated. Next, cross-tabulation was prepared. We used SPSS version 23, $p<0.5$ were considered significant.

RESULTS

The (Table 2) shows that in terms of the mean age and parity, case and control matched with each other and p value is not significant.

Table 2: Baseline characteristics of respondents (n=200).

Variables	Case (N=100)	Control (N=100)	P value
Age (years) (Mean±SD)	24.39±2.81	24.31±2.34	0.49^{NS}
Range (years)	18-36	19-35	
Parity	2.1±0.9	1.98±0.2	0.35^{NS}
Range	0-5	0-3	
Occupation	**%**	**%**	
Housewife	67	72	-
Service holder	29	25	
Students	3	3	
Farmer	1	0	

P value was calculated by student's t test (continuous variables) and Chi square test (categorical variable), NS: Not significant, p value was significant at <0.05.

Besides, maximum patients were housewives (67%), and 29% was service holder. The (Table 3) shows that 51%, 35% and 14% in cases and 52%, 38% and 20% in control come from lower middle income, low income and upper middle-income group respectively.

Table 3: Distribution of the study subjects by socioeconomic status according to world bank data team (n=200).

Socioeconomic status	Case (N=100) (%)	Control (N=100) (%)
Low income (BDT 6821.14-26851.99 TK/month)	35	38
Lower middle income (BDT 6827.79-26851.99 TK/month)	51	52
Upper middle income (BDT 26858.64-83018 TK/month)	14	20
High income (BDT≥83024.87 TK/month)	0	0

Table 4: Obstetric profile of the respondents (n=200).

Obstetric profile	Case (N=100)	Control (N=100)	P value
Gravida	3.1±1.2	3.4±1.4	0.53^{NS}
Para	2±1.3	1.9±1.4	0.16^{NS}
Gestational age (week)	33.6±2.5	37.3±0.29	0.86^{NS}

P value was calculated by student's t test, NS: Not significant, p value was significant at <0.05.

The (Table 4) shows that there was no statistically significant difference between case and control regarding mean gravida (3.1±1.2 vs. 3.4±1.4), mean para (2±1.3 vs. 1.9±1.4) and mean gestational age (33.6±2.5 vs. 34.7±1.2) ($p\geq0.05$). The (Table 5) expresses that the platelet count was significant higher in patients with preterm PROM as compared to controls (9936.5±3385.2 vs. 7311.1± 1593.5/mm^3 of blood, $p<0.001$) and PLR is higher in cases ($p\leq0.001$).

Table 5: Hematological profile of the respondents (n=200).

Hematological profile	Case (N=100)	Control (N=100)	P value
WBC count (/mm^3)	9.1 (6.31-10.7)	8.8 (6.1-9.9)	0.85^{NS}
Platelet count (/mm^3)	241.6±58.7	201.7±65.9	$<0.001^{S}$
PLR	125.8±67.1	105.2±48.6	$<0.001^{S}$

P value was calculated by student's t test, S: significant NS: Not significant, p value was significant at <0.05.

DISCUSSION

Preterm PROM is one of the major pregnancy complications. Recent studies demonstrated that the major etiologic mechanism of preterm PROM was inflammation.[9] A case-control study was conducted in the

obstetrics & gynecology department of Sir Salimullah medical college and Mitford Hospital, Bangladesh, with 200 patients. Among them, 100 were cases with preterm PROM & 100 were control who were term pregnancy without any complication. The role of platelet - lymphocyte ratio (NLR) was determined to understand its impact on predicting preterm PROM in this study.

In our study, the cases and controls were matched. None of the sociodemographic variables between case and control showed a statistically significant difference ($p \geq 0.05$). The mean age of cases was 24.39±2.81 years, and that of the controls was 24.31±2.34 years (Table 2). These findings were similar to those found by Endale et al.[10] The mean parity of case and control were 2.1±0.9 (range: 0-5) and 1.98±0.2 (range: 0-3), respectively. No statistically significant difference ($p \geq 0.05$) in the mean of gravida, para, and gestational age between cases and controls. These findings were consistent with the Turkish study done by Jaffar et al.[11] The socio-economic status of cases and controls were matched each other (Table 3). Most of the patients were in the lower middle-income group. Endale et al found the same findings in their study.[10] In this study Platelet count was found to be significantly higher in preterm PROM group (case) than control (241.6±58.7×1000/mm³ vs. 201.7±65.9 ×1000/mm³), p value is <0.001 which is statistically significant. This is supported by the studies done by Satar et al and Flídrová et al.[13-16] Satar et al reported that interleukin (IL)-8 levels were increased in preterm PROM in maternal serum and in the umbilical cord blood. Similarly, IL-6 was found elevated only in the umbilical cord blood, especially in preterm PROM with microbial invasion and histologic chorioamnionitis.[15] In the study of Krejsek et al cytokines such as tumor necrosis factor (TNF)-α, IL-8, IL-6, and IL-1, were reported to be increased in preterm birth and preterm labour.[16]

In this study, WBC count in cases and controls did not differ significantly. The p value was 0.85, which is not significant. But neutrophil count was significantly higher in patients with preterm PROM (9936.5±3385.2/mm^3) compared to control (7311.1±1593.5/mm^3). The p value is less than 0,001, which is significant. These findings are consistent with the studies done by Toprak et al and Klement et al.[8,13]

Lymphocyte count in the case and control group was 1896.7±651.8/mm³ and 2144±673.2/mm³, respectively. P value was 0.5, which was not statistically significant. This finding is supported by the study done by Toprak et al and Klement et al.[8,13] PLR plays a vital role in inflammatory processes. It is a good indicator of platelet activation, lymphocyte function and immune response. In chronic inflammatory process, platelet count proliferates increasingly and lymphocyte counts tend to decrease due to apoptosis. As a result, PLR (platelet to lymphocyte ratio) value is affected in inflammatory process. It has been demonstrated that PLR (platelet to lymphocyte ratio) predicts thrombotic events, inflammatory diseases, and malignancies and preterm PROM. In pregnant women, PLR was investigated in gestational diabetes, acute pancreatitis, preeclampsia, and preterm PROM.[17] This study found PLR higher in the preterm PROM group (cases) than in the control. The p value was statistically significant (<0.001). These findings were strongly supported by the study done by Toprah et al and Ekin et al.[8,17]

Limitations

Limitations of the study were the duration of the study period was short. It would be better if the study could have been found if the study period was longer and the sample size was small, and it was a single-centered study.

CONCLUSION

This study reveals that the PLR significantly affects preterm premature membrane rupture. It can help to predict who is at risk of having early preterm PROM. This allows for taking appropriate measures to manage preterm labour and to avoid the poor feto-maternal outcome of Preterm PROM.

Recommendations

A multi-centered study in Bangladesh's divisional/ tertiary hospitals can be conducted. A long-term study is recommended. A comparative study involving the different inflammatory biomarkers like NLR (neutrophil to lymphocyte ratio), PLR (platelet to lymphocyte ratio) and CRP (C Reactive Protein) will clearly reveal the most effective marker for preterm PROM.

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