RESEARCH PAPER.

IDENTIFYING THE ROLE OF MEAN PLATELET VOLUME AND PLATELET COUNT AT BOOKING VISIT AS A PREDICTOR OF PRE-LABOUR RUPTURE OF MEMBRANES

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ABSTRACT

Prelabour rupture of membrane (PROM) comprises prelabour rupture of membrane at term (TPROM) or preterm (PPROM). Prelabour rupture of membrane after 37 weeks of gestation is defined as TPROM. Rupture of membrane before 37 weeks of gestation with leakage of amniotic fluid prior to the onset of labour is defined as PPROM. A descriptive cross-sectional study was conducted among 346 participants. All pregnant women presented to the study setting during the study period were included. Interviewer administered structured questionnaire was used for data collection. Data were analysed by SPSS 21.0. Receiver operating curve was used for diagnostic test accuracy and 95% confidence interval was applied for statistical significant. Predominantly primigravidae represented the study sample and the mean age was 26.67 years. Mean platelet count was 250 × 109/L and mean platelet volume was 8.54fl. Probability of predicting PPROM by the platelet count was 69.2%, and platelet volume was 85.9%. When the platelet count at the booking visit was 248 ×109/L or more it helped to predict PPROM with a probability of 80% sensitivity and 57% specificity. When the MPV at the booking visit was 8.15fl or less it helped to predict PPROM with a probability of 80% sensitivity and 75% specificity. When 237 × 109/L or more platelet count was considered as the cut off value it was possible to achieve a 76% sensitivity and 33.7% of specificity for predicting TPROM. When 9.6fl or less MPV was considered as the cut off value it was possible to achieve a 79% sensitivity and 22 % of specificity to predict TPROM. ***Conclusions:*** There is a possibility of predicting PPROM during the third trimester, by using the platelet count and the mean platelet volume measured during the first trimester. PPROM could be predicted when the platelet count is 248 × 109/L or more and the MPV is less than 8.15fl. It is not possible to use above mentioned parameters, to predict PROM during term. Possibility of predicting PPROM by using the platelet count and the MPV value of the first trimester could be considered in obstetric practice.

Key words: Platelet count, Mean platelet volume, Prelabour rupture of the membranes,

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Introduction

Prelabour rupture of membrane (PROM) comprises prelabour rupture of membrane at term (TPROM) and preterm prelabour rupture of membrane (PPROM). The term TPROM refers to spontaneous rupture of the membrane prior to the onset of labour in women after 37 completed weeks of gestation[1]. PPROM is defined as spontaneous rupture of the fetal membrane before 37 completed weeks of gestation prior to the onset of labour[1-2].

Prelabour rupture of membranes occurs in 6-19% of term pregnancies. PROM at term is associated with both neonatal and maternal sepsis, as well as cord prolapse. The possibilities of neonatal and maternal sepsis are positively correlated with the time between the rupture of membrane and the onset of labour[4]. Despite the rarity of major complications, TPROM is associated with increased maternal and neonatal morbidity[5]. The risk of serious neonatal infection doubles, with TPROM alone, is 1% rather than 0.5% for women with no risk factors and intact membrane[3].

PPROM complicates approximately 2% of pregnancies but accounts for 40% of preterm births and causes significant neonatal morbidity and mortality. Prematurity, pulmonary hypoplasia, and sepsis are the three primary causes of neonatal death in PPROM[3]. It is linked to higher neonatal morbidity and perinatal mortality[3].

PROM has a multifactorial etiology. The reduced collagen content of membrane, placental vascular pathologies, intraamniotic infections, overextended membranes and decidual bleeding are among the possible mechanisms for PROM[7,8]. Chronic subclinical infection of the fetal membrane plays a clear role in initiating and propagating molecular actions that lead to PROM[9]. An amniotic fluid culture is positive in 35% of pregnancies with PPROM.

Even though many PROM patients have no obvious risk factors. Early prediction of patients at risk will be facilitated by existing knowledge and experience of health care providers. The presence of fetal fibronectin in vaginal secretions is an important predictor of PPROM[7]. Furthermore, C-reactive protein level enhancement and low pregnancy related plasma protein-A can predict PPROM. There is some evidence suggesting that lead and selenium levels in maternal blood can be used to predict PPROM. However, the implications of those techniques were not established in existing clinical practice[10-13].

Intrauterine infection increases inflammatory cytokines in amniotic fluid and maternal plasma[14-16]. The body's inflammatory response is closely tied to cytokines. So hypothetically, PPROM may be correlated with changes of pathological inflammatory markers in maternal plasma especially at the early stage of pregnancy. Number of white blood cells and levels of C reactive proteins are shown to be elevated in the blood of pregnant women preceding preterm PROM[10,17].

Platelet activation and functions are reflected by platelet size. The mean platelet volume (MPV) accurately indicates platelet size. Platelet activation is contributing to the pathophysiology of infection, inflammation, and malignancy. Available study findings published the interrelationship of MPV with both pro-thrombosis and pro-inflammation[18]. Based on all this evidence, detecting, and preventing PROM at an early stage reduces the risk of maternal and neonatal morbidity and mortality.

Therefore, the objective of this study is to investigate whether any changes in platelet volume and number detectable by simple full blood count (FBC) in booking visit (first antenatal appointment, usually happen between

eight and twelve weeks of gestation) precede PPROM and also to determine the diagnostic value of these markers for prediction of PPROM.

Methods

A descriptive longitudinal cross-sectional study was conducted between October 2015 and November 2016 among 346 participants (172 pregnant women with PROM and 174 healthy pregnant controls) in a single tertiary care center. In this study, all singleton pregnant women who presented with a confirmed diagnosis of PROM without active labour between 28 and 41 weeks of gestation were included. The control group comprised uncomplicated pregnant women who met the inclusion criteria between 37 and 41 weeks. Study controls were selected using a simple random sampling technique. A fetus with major structural anomalies; an estimated fetal birth weight below the 10th centile; multiple gestations; history of chorionic villus sampling, amniocentesis, cerclage or other cervical surgery; previous preterm labor or preterm prelabour rupture of membranes; and systemic diseases including malignancies, infectious diseases and inflammatory diseases were excluded.

Interviewer administered structured questionnaire was used for data collection. Ethical clearance was obtained, and statistical analysis was performed using SPSS 21.0. The platelet volume and the platelet count were considered as exposure variables. The outcome was the presence of PROM. The data were described using descriptive and analytical statistics. Continuous data were expressed as mean and SD, while categorical data were presented as a proportion. A $\chi 2$ test was used to analyze categorical variables. The odds ratio with 95% confidence interval (CI) was calculated and a P-value of 0.05 was used to assess statistical significance. The sensitivity and specificity were calculated. The accuracy of diagnostic tests was assessed using ROC curves and statistical significance was determined using 95% confidence intervals.

Results

Age of the study participants ranged between 16 years to 42 years (Mean 26.67: SD=3.29). Majority was in the 26-30 years group (N=137:39.6%). There was a significant difference in the distribution of study participants between age groups (X2=87.27: p<0.001). BMI of the study participants ranged between 16.8 kg/m^2 to 34.6 kg/m^2 (Mean 24.50:SD5.14). Majority was in the 19.1-24.9 kg/m^2 group (N=182:52.6%). Among the study participants, there was a significant difference between BMI groups (X2=250.1: p<0.001). Pregnant women from $para_1$ to $para_5$ were distributed in the study sample. Distribution of the study participants according to parity appeared significant (X^2=358.3: p<0.001) and the majority were primigravidae (N=193:55.8%).

TABLE 1: Distribution of age, BMI and parity of the study participants

Characteristic	Number(N)	Percentage (%)	Significance

Age(years)	≤20	18	5.2	X^2=87.27 P<0.001
	21-25	104	30.1	
	26-30	137	39.6	
	31-35	76	21.9	
	36-40	9	2.6	
	≥41	2	0.58	
BMI	<20	11	3.2	X^2=250.1 P<0.001
	20-24.9	182	52.6	
	25-29.9	134	38.7	
	≥30	19	5.5	
Parity	1	193	55.8	X^2=358.3 P<0.001
	2	98	28.3	
	3	42	12.1	
	≥4	13	3.8	
Total		**346**	**100**	

The majority of pregnant women in the PROM group experienced PPROM (N=101:29.2%) while 20.5% (N=71) experienced PROM at term. The platelet count ranged from 149 × 103 to 355 × 103 and (mean 250.21 × 103: SD=22.93) the majority was included in the group with platelet count between 201 × 103 to 250 × 103. The platelet volume ranged from 6.3 to 10.8 (8.54: SD 1.12) and the majority were included in the 7.1 to 8.0 group (N=99:28.6%).

TABLE: 2 Distribution of the platelet volume, platelet count and the incidence of prelabour rupture of membrane among study participants

Parameter	Number (N)	Percentage (%)	Significance
PROM			
Preterm	101	29.2	X^2=48.66 P<0.001
Term	71	20.5	
No-PROM	174	50.3	
Platelet Count/ml			
<200 × 10^3	2	0.6	Mean=250.21 SD=22.93
201-250 × 10^3	170	49.1	
251-300 × 10^3	166	48.0	
>300 × 10^3	8	2.3	
Platelet Volume (fl)			

<7	35	10.1	
7.1-8	99	28.6	
8.1-9	89	25.7	Mean=8.54 SD=1.12
9.1-10	84	24.3	
>10.1	39	11.3	
Total	**346**	**100**	

FIGURE 1: ROC Curve for prediction of Prelabour rupture of the membranes. (A) ROC Curve - Platelet count for predicting PROM. (B) ROC Curve - Platelet volume for predicting PROM.

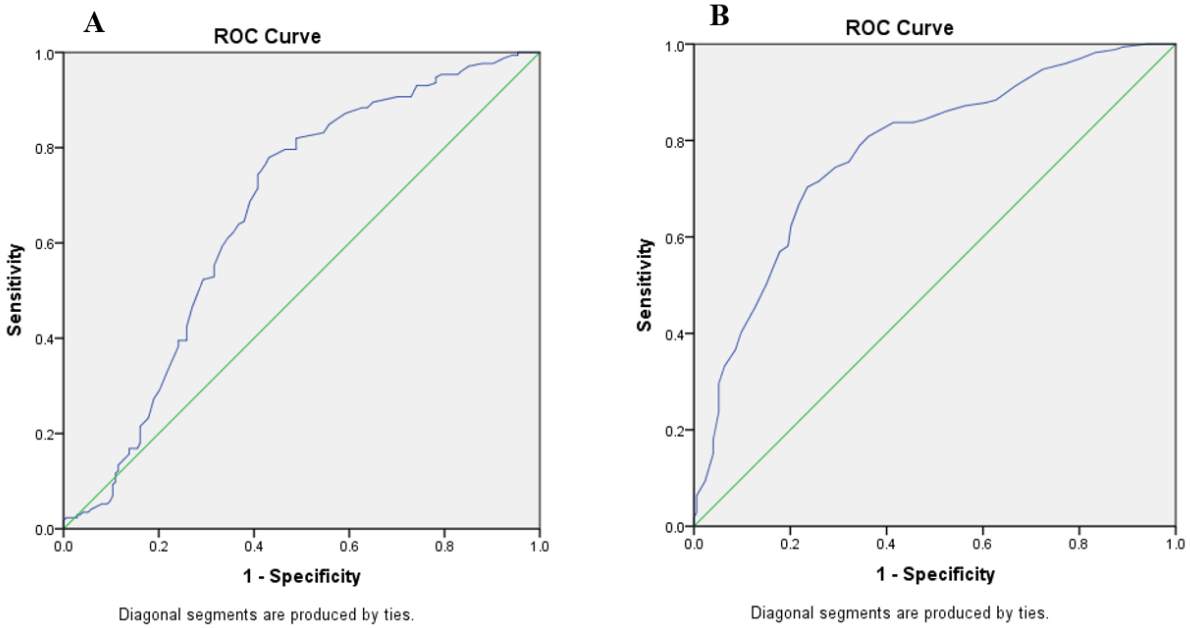
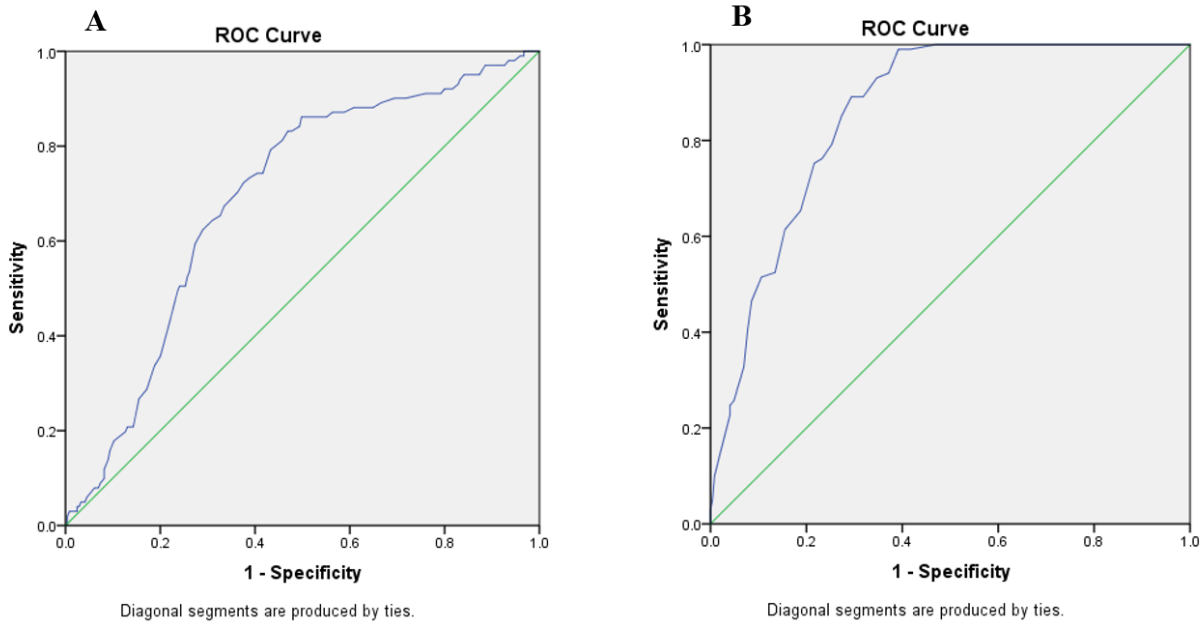


Figure 1 (A) describes the method of using platelet count to predict PROM. More positive curve was observed for the platelet count. Therefore, platelet count seems to be the most suitable method to predict PROM (AUC=0.664: SE=0.030: 95%CI=0.606-0.722). Probability of predicting PROM by the platelet count is 66.4%. False negatives are undesirable when considering PROM. Hence, a diagnostic cut-off value with a low specificity would be ideal. The diagnostic cut-off value should be on the right side of the ROC curve. When the platelet count at the booking visit is 240x103 or more it helps to predict PROM with a probability of 80% sensitivity and 52% specificity.

Figure 1 (B) illustrates how mean platelet volume can be used to predict PROM. The mean platelet volume showed a more positive curve. Hence, mean platelet volume appears to be a more useful method for predicting PROM (AUC=0.777: SE=0.025:95%, CI=0.728-0.826). Probability of predicting PROM by the mean platelet volume is 77.7%. PROM can be predicted with an 80% sensitivity and 64% specificity when the mean platelet volume at the booking visit is 8.8 fl or less.

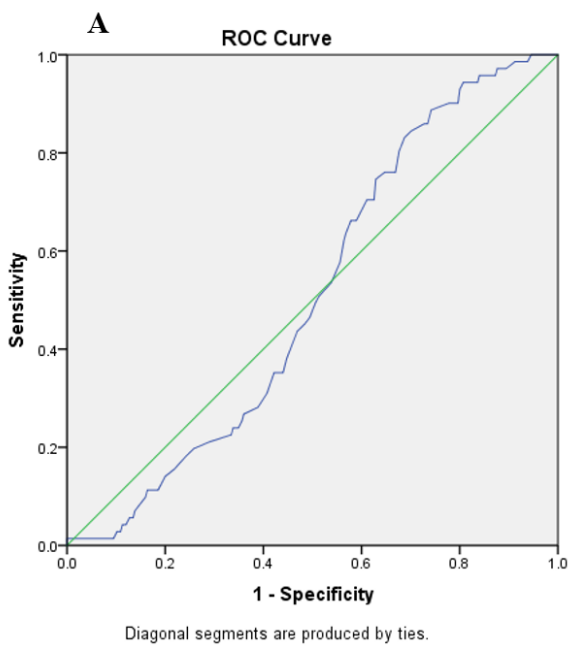
FIGURE 2: ROC Curve for prediction of Preterm prelabour rupture of the membranes. (A) ROC Curve- Platelet count for predicting PPROM. (B) ROC Curve-Platelet volume for predicting PPROM.

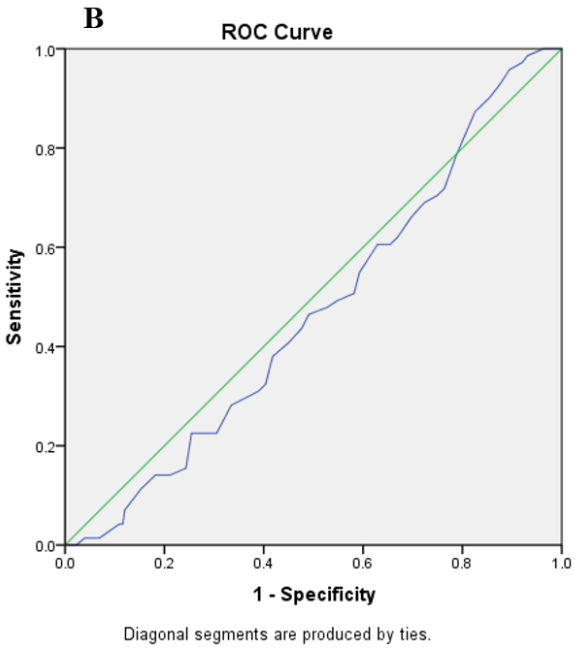


The method of predicting PPROM using platelet count is shown in Figure 2 (A). A more positive curve was observed for platelet count as a predictor of PPROM. Thus, platelet count appears to be a better predictor of PPROM (AUC=0.692: SE=0.034:95%, CI=0.632-0.751). Probability of predicting PPROM by the platelet count is 69.2%. When the platelet count at the booking visit is $248x10^9$/L or more it helps to predict PPROM with a probability of 80% sensitivity and 57% specificity.

As shown in Figure 2 (B), mean platelet volume can be used to predict preterm prelabour rupture of membranes. Mean platelet volume displayed a more positive curve. Therefore, mean platelet volume appears to be a more suitable method to predict preterm PROM (AUC=0.859: SE=0.019:95%, CI=0.821-0.896). There is a probability of 85.9% in predicting preterm PROM based on the mean platelet volume. A mean platelet volume of 8.15 fl or less at the booking visit helps predict PROM with 80% sensitivity and 75% specificity.

Figure 3: ROC Curve for prediction of Prelabour rupture of the membranes at term. (A) ROC Curve- Platelet count for predicting term PROM. (B) ROC Curve- Platelet volume for predicting term PROM.





The method of predicting term PROM using platelet count is shown in Figure 3 (A). The ROC curve crosses the referral line in the above figure. The area under the curve is 50.9%. That is when platelet count is used to predict PROM at term, incidents are not detected with a significant probability. When 237 x 109/L or more platelet count is considered as the cut off value it is possible to achieve a 76% sensitivity and 33.7% of specificity.

Figure 3 (B) illustrates how mean platelet volume can be used to predict term PROM. The ROC curve crosses the referral line in the above figure. The area under the curve is 47%. As a result, incidents are not detected with a significant probability when MPV is used to predict PROM at term. When 9.6 fl or less MPV is considered as the cut off value it is possible to achieve 79% sensitivity and 22 % of specificity.

DISCUSSION

PROM can be predicted by platelet count with a probability of 66.4%, and by platelet volume with a probability of 77.7%. When the platelet count at the booking visit is 240x109 or more it helps to predict PROM with a probability of 80% sensitivity and 52% specificity. A MPV of 8.8 fl or less at the booking visit can help predict PROM with 80% sensitivity and 64% specificity.

Probability of predicting PPROM by the platelet count is 69.2%, and from MPV is 85.9%. A platelet count of 248x109/L or more helps predict PPROM with 80% sensitivity and 57% specificity. When the MPV at the booking visit is 8.15 fl or less it helps to predict PPROM with a probability of 80% sensitivity and 75% specificity.

A platelet count of 237 x 109/L or more can predict PROM at term with 76% sensitivity and 33.7% specificity. When 9.6 fl or less MPV is considered as the cut off value, it is possible to achieve a 79% sensitivity and 22 % of specificity to predict term PROM. In the research conducted by Atalay et al in 2015, the same study parameters which were used in the present study were tested[19]. Only PPROM cases were included in that study, and the number of study participants was twice as high as in the present study. The area under the ROC curve for predicting PPROM using the platelet count was

0.579. In this study, the value was 0.692. In both studies, the predictability of using the platelet count was recognized as significant. Cut off value of the platelet count in the mentioned study was identified as being more than 216×103/L and in the present study, the cut off value is 248×103/L.

Neonatal morbidity and mortality will be significantly increased by PPROM and subsequent preterm birth. It negatively impacts the psychological state of the mother and her family members, as well as the utilization of resources within the health care system. The cause of PROM can be multifactorial, or it can be idiopathic. Thus, it is practically impossible to predict the occurrence of PROM earlier and to develop a diagnostic test to identify it. Because PROM can be caused without a precise aetiology, it is important to consider parameters that are not directly related to obstetrics when predicting it. This study examines platelet-related parameters, for instance.

Sri Lanka has a high attendance rate at routine antenatal clinics, greater than 90%[20]. This is known as the booking visit, during which routine investigations are carried out, such as FBC and UFR, as well as testing for diabetes mellitus. A FBC is used to measure haemoglobin levels. During the first trimester, information about platelet count and platelet volume is available. Thus, no additional resources were used in making predictions, and the parameters available were used.

If risk assessment of the occurrence of PROM can be done in the first trimester, the risk factors that lead to PROM and thus occurrence of PROM, immediate complications due to PROM and consequences of preterm delivery can be minimized. As a result, perinatal complications due to PROM can be reduced and it helps to achieve a healthy and a satisfactory outcome.

The findings of this study should be modified accordingly, and the external validity should be improved. Afterwards, it could be incorporated into regular obstetric practice. Pregnant women at high risk for PROM can be closely observed during the antenatal period. Furthermore, health care staff can raise awareness of high-risk pregnant women during clinic and home visits. The present study indicates that it is feasible to implement policy changes into the current system in a satisfactory way.

There are many other parameters that can be used to assess the risk factors for PROM. There are several indices in FBC that can be helpful in the prediction of the above. There may be a higher predictability in those parameters than in the variables used in the present study. A pregnant woman's anthropometric data is also available after the booking visit. The categorized information such as family history, parity, and socio demographic factors, which are mentioned in the antenatal records can also be analysed. To calculate the predictive ability, these parameters can be considered separately. The most relevant clinical parameter or parameters can be decided by comparing with the calculated predictive abilities of each of those parameters. Management strategies should take into account cost effectiveness and practical feasibility.

Also, according to the biological parameters in the first trimester, it may be effective to implement follow-up studies for pregnant women who were predicted and for those who were not predicted. A cohort study design can be planned and the other two trimesters which are nearly six to eight months can be used as the study period. As a consequence, it provides an opportunity to identify the pathological incidences related to the study variables. It is also possible to design and apply interventions to mothers who are detected as having a high risk of PROM. A new strategy for preventing PROM can be proven scientifically by comparing it with a group of participants who were predicted not to have PROM. In order to achieve the above mentioned objectives, a randomized clinical trial can be designed and executed in such a way.

The limitation of our study is the relatively long follow-up period. Even though some significant findings were generated during the study, there was also a possibility of unidentified confounding factors. The study sample was taken only from a single tertiary centre and a convenient sampling technique was used and there was a minimum practical feasibility for randomization. Due to this, the representativeness of the sample was reduced. It will create drawbacks when the study findings are applied to the general population. This can be reduced by using a large study sample which is collected over an extended period of time. The MPV and platelet count were considered as variables and the predictive ability was analysed by using a ROC methodology. Number of study participants in the study sample were not enough to obtain a smooth ROC curve. This leads to a difficulty in detecting the left uppermost value and the high sensitivity level with a low specificity level. This limitation could have been avoided to some extent by using each cut off level separately and analysing them categorically with likelihood ratio. The use of study variables with low existing knowledge in categorical analysis is practically impossible.

CONCLUSION

There is a possibility of predicting PROM during the third trimester, by using the platelet count and the mean platelet volume measured during the first trimester. It is possible to predict a risk of developing PROM when the platelet count is more than 240 x 10 9 /L and when the Mean Platelet Volume is below 8.8fl. Preterm PROM could be predicted when the platelet count is 248 x 109/L or more and the platelet volume is less than 8.15 fl. It is not possible to use above mentioned parameters, to predict PROM during term. Possibility of predicting PROM by using the platelet count and the mean platelet volume value of the first trimester could be considered in obstetric practice. Further studies should be conducted to determine the feasibility of predicting PROM by other haematological parameters.

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