RESEARCH ARTICLE

# White blood cell Indices to predict first trimester missed miscarriage

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## Abstract

**Objective:** To identify the relationship between white blood cell indices in missed miscarriage compared to ongoing pregnancy in the first trimester.

**Method:** The diagnostic accuracy study was conducted at the Department of Maternity, Al-Yarmouk Hospital, Baghdad, Iraq, from January to October 2021,and comprised healthy first-trimester pregnant women in group A and those with missed miscarriage after 7-13 weeks of gestation in group B. Ultrasound findings and the last menstrual period were noted for all the subjects. Total and differential leukocyte counts, neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio were compared between the groups. Data was analysed using SPSS 22.

**Results:** Of the 167 women, 81(48.5%) were in group A and 86(51.5%) were in group B. Demographic and obstetrics data was not significantly different between the groups ($p>0.05$). Mean white blood cell, neutrophil and monocyte counts showed no significant difference between the groups ($p>0.05$), while lymphocyte count, neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio were significantly different between the groups ($p<0.05$). With respect to gestational age, neutrophil-to-lymphocyte ratio and monocyte-to-lymphocyte ratio had a fair ability to predict missed miscarriage at various time points within the first trimester ($p<0.05$).

**Conclusion:** There was no significant correlation between WBC count and gestational age. Reduced MLR and NLR levels can be utilised to forecast miscarriages in a cost-effective manner.

**Key Words:** Pregnancy, Abortion, Spontaneous, Neutrophils, Monocytes, Gestational, Lymphocytes, Miscarriage.

(JPMA 74: S156 (Supple-8); 2024) **DOI:https://doi.org/10.47391/JPMA-BAGH-16-34**

## Introduction

Miscarriage is spontaneous pregnancy loss before foetal viability. Missed miscarriage is a term used when the foetus/embryo has died, but is retained in the uterus for a variable period of time. The woman presents with receding symptoms of pregnancy with or without vaginal bleeding or brown-coloured discharge. Missed miscarriage can be classified into anembryonic and embryonic types[1].

Approximately, half of first-trimester miscarriages are anembryonic that can replace blighted ovum, which is an empty gestational sac >20mm in diameter without a foetal pole, or there is no growth noted on a repeat sonogram at 7 days when the sac diameter is <20mm. The remaining cases are embryonic[2].

Diagnosis of missed miscarriage by ultrasound scan of the pelvis is done in multiple ways, like mean sac diameter ≥25mm and no foetal pole, or crown rump length ≥7mm without heartbeat or foetal pole, or crown rump length <7mm and no foetal heart activity and no change on repeat ultrasound examination performed a week later, or mean gestational sac diameter <25mm with no foetal pole evident and no change in scan findings after a week[1,3,4]. Complete blood count (CBC) is a widely used test during the first trimester of pregnancy aimed at excluding complications[5]. The total white blood cell (WBC) count increases as a result of increase in polymorph nuclear leucocytes. The neutrophil count rises with increased oestrogen concentrations and reach its peak at about 33 weeks when it maintains the same level till labour and early puerperium, after which it increases sharply. Their phagocytic ability also increases during gestation[6]. Neutrophils and lymphocytes represent the first-line defence cells in both acute and chronic inflammation[7]. Studies have reported that blood indices and ratios, such as neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR), can be used as markers for inflammatory response in different pathological conditions during pregnancy[8-10]. An association was observed between these CBC indices and miscarriage, and with recurrent pregnancy loss[11, 12], with increased neutrophils, lymphocytes and NLR in spontaneous miscarriages, suggesting their utility as markers for risk assessment of spontaneous miscarriage[1]. However, the role of NLR, MLR and CBC components in missed miscarriage remain ambiguous[14].

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## Patients and Methods

The diagnostic accuracy study was conducted at the Department of Maternity, Al-Yarmouk Hospital, Baghdad, Iraq, from January to October 2021, in line with Standards for reporting diagnostic accuracy studies (STARD) 2015[15]. Ongoing pregnancy was taken as the reference standard, and missed miscarriage was the index test.

After approval from the Scientific Council of Iraqi Board for Medical Specialisations, and the ethics review committee of the College of Medicine, Mustansiriyah University, the sample was raised using consecutive non-probability sampling technique, those included on the basis of ultrasound findings and the date of last menstrual period were healthy first-trimester pregnant women with 7-13 weeks of gestation in group A and those with missed miscarriage in group B.

Pregnant women with a history of recurrent miscarriage, or had cervical incompetence, hydatidiform mole, multiple pregnancy, thrombophilia or antiphospholipid syndrome, chronic diseases, like diabetes mellitus and heart disease, threatened miscarriage, febrile illnesses, like urinary tract infection (UTI), were excluded, and so were the smokers.

After taking written informed consent, the participants were subjected to general and systemic examination along with measurement of vital signs. The body mass index (BMI) was calculated:[16]

$$BMI = \frac{Weight\ (kg)}{Height\ (m)^2}$$

Maternal blood samples were collected and sent to a laboratory where they were tested using an automated haematology (XN-20, Sysmex, 3 diff. made in Japan). CBC and automated differential leukocyte count was assessed along with NLR and MLR.

The sample size was calculated using MedCalc 14.8.1 based on an earlier study[17]. The area under curve (AUC) of NLR was 0.792, with 95% confidence interval (CI) 0.721-0.864, while assuming as null hypothesis the target AUC to be 0.9. With type I alpha error 0.05, and type II beta error 0.05, the sample was inflated by >10%.

Data was analysed using SPSS 22 and Graph Pad Prism 8.0.0. Data wsa expresses as frequencies ad percentages, mean +/- standard deviation or median and interquartile range (IQR) (25-75% percentile), as appropriate. Two samples t-test and Mann Whitney U test were used, as appropriate, to examine intergroup differences. P<0.05 was considered significant.

## Results

Of the 167 women, 81(48.5%) were in group A and 86(51.5%) were in group B. Demographic and obstetrics data was not significantly different between the groups (p>0.05).

Mean WBC, neutrophil and monocyte counts showed no significant difference between the groups (p>0.05), while lymphocyte count, NLR and MLR in group B were significantly different between groups (Table 1).

NLR (0.700) and lymphocyte count (0.736) had the highest AUC, compared to MLR, while MLR and lymphocyte count showed the highest sensitivity (75.6%) to predict missed miscarriage. Monocyte, neutrophil and NLR respectively showed 88.9%, 99% and 88.9 specificity to predict missed miscarriage.

In terms of probability, neutrophil count and NLR showed the best positive predictive value (PPV) 99% and 83%,

**Table-1:** Assessment of diagnostic validity of various markers in predicting missed miscarriage.

| Variable | AUC | p-value | Cut-off value |
|---|---|---|---|
| WBC | 0.540 | 0.386 | 9300 |
| Neutrophil | 0.518 | 0.697 | 4600 |
| Lymphocyte | 0.736 | <0.001 | 1600 |
| Monocyte | 0.545 | 0.316 | 700 |
| NLR | 0.700 | <0.001 | 2.56 |
| MLR | 0.629 | 0.004 | 0.39 |

AUC: Area under curve, WBC; White blood cell, MLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio. p≤0.05 was significant.

**Table-2:** NLR diagnostic validity in relation to gestational age.

| Variable | AUC | p-value | Cut-off | SN | Sp | PPV | NPV |
|---|---|---|---|---|---|---|---|
| **8th week** | 0.556 | 0.569 | 2.48 | 55.6 | 99 | 99 | 42.9 |
| **9th week** | 0.600 | 0.445 | 2.47 | 60 | 99 | 99 | 60 |
| **11th week** | 0.999 | <0.001 | 3.2 | 99 | 99 | 99 | 99 |
| **12th week** | 0.999 | <0.001 | 7.14 | 99 | 99 | 99 | 99 |
| **13th week** | 0.778 | 0.006 | 77.8 | 77.8 | 99 | 99 | 69.2 |

AUC: Area under curve, WBC; White blood cell, MLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio. p≤0.05 was significant.

**Table-3:** MLR diagnostic validity in relation to gestational age.

| Variable | AUC | p-value | Cut-off | SN | Sp | PPV | NPV |
|---|---|---|---|---|---|---|---|
| **8th week** | 0.926 | <0.001 | 0.19 | 85.2 | 99 | 75 | 99 |
| **9th week** | 0.800 | 0.005 | 0.21 | 80 | 100 | 100 | 75 |
| **11th week** | 0.667 | 0.071 | 0.28 | 99 | 66.7 | 43.7 | 99 |
| **12th week** | 0.999 | <0.001 | 0.56 | 99 | 99 | 99 | 99 |
| **13th week** | 0.611 | 0.347 | 61.1 | 61.1 | 99 | 99 | 56.3 |

AUC: Area under curve, MLR: Monocyte-to-lymphocyte ratio, SN: Sensitivity, SP: Specificity, PPV: Positive predictive value, NPV: Negative predictive value. P<0.05 was significant.

respectively, while lymphocyte count and MLR showed the best negative predictive value (NPV),72% and 68.2%, respectively. Overall, lymphocyte count and NLR showed the best predictive values for predicting and excluding missed miscarriage 72%, 63.2%, respectively. There was no significant correlation between gestational age and WBC for both groups ($p>0.05$).

The diagnostic validity of NLR with respect to gestational age was the highest in weeks 11 and 12, and there was a trend towards increased sensitivity as gestational age increased (Table 2).

The diagnostic validity of MLR with respect to gestational age was the highest in weeks 8, 9 and 12, and sensitivity was high from all weeks except week 13 when it was the lowest (Table 3).

## Discussion

Higher WBC counts have been reportedly found in women with spontaneous miscarriage which has a pathology similar to that in missed miscarriage, indicating a possible relationship between WBC parameters and missed miscarriage case[18]. In a study, WBC was significantly higher in spontaneous miscarriage compared to normal pregnancy[19]. In another study, the WBC count was significantly lower in spontaneous miscarriage compared to ongoing pregnancy[20].

In the present study, lymphocyte was significantly higher in missed miscarriage compared to ongoing pregnancy. This was in agreement with some studies[19], and in contrast to some other findings[14].

In the present study, neutrophil count did not show significant difference between the groups, which was in agreement with earlier findings[19,21], while others found that neutrophil was lower in the missed miscarriage group[14].

The variability in findings may reflect a possible inflammatory response. That is why the current study preferred the use of markers like NLR or MLR that are adjusted, and have more consistency.

NLR was considerably lower in missed miscarriage cases compared to controls in the current study. Ata et al. found no significant difference in NLR values between the groups[22]. Wang et al. found that NLR was higher in healthy pregnancies compared to missed miscarriage[14]. Bas et al. reported results that were contrary to the current findings[13]. Biyik et al. reported NLR was significantly higher in missed miscarriage compared to an ongoing pregnancy[21]. There is no clear theory regarding variability of finings in this regard, which could be related to the differences in study design.

MLR was significantly lower in missed miscarriages compared to controls, which could be explained by the fact that macrophages and monocytes play an important role in placental development, and extra villous trophoblast invasion and deregulation of these cells can be linked to pregnancy-related problems, such as miscarriage[23]. In one study, it was also lower in missed miscarriages compared to controls[14]. A study did not show any significant difference in terms of first-trimester MLR between the groups[24]. Regarding diagnostic accuracy, both NLR and MLR showed a fair ability to diagnose missed miscarriage, while NLR having slightly better capacity. The finding was in disagreement with an earlier study which reported NLR as not having a fair diagnostic value[24]. Multiple blood ratios are present[25], but choosing the right one with the highest accuracy among missed abortion cases is the key to introducing a diagnostic and prognostic avenue in management.

The diagnostic validity in the current study was the highest in weeks 11 and 12 for NLR, and in weeks 8, 9 and 12 for MLR. This can be explained by the fact that macrophages and monocytes play an important role in extra villous trophoblast invasion which is usually completed at 12th of gestation.

## Conclusion

There was no significant correlation between WBC count and gestational age. Reduced MLR and NLR levels can be utilised to forecast miscarriages in a cost-effective manner.

**Acknowledgement:** We are grateful to Mustansiriyah University, Baghdad, Iraq, and to obstetricians and gynaecologists of Al-Yarmouk Teaching Hospital for facilitating the study.

**Disclaimer:** None.

**Conflict of Interest:** None.

**Source of Funding:** None.

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