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Evaluation of hemogram parameters in the diagnosis of ectopic pregnancy, early pregnancy loss and threatened miscarriage

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ABSTRACT

Aims: In present study, it aimed to analyse the importance and potential use of inflammatory blood parameters in the prediction of threatened miscarriage (TM), early pregnancy loss (EPL) and ectopic pregnancy (EP).

Methods: Between October 2021 and 2023, the demographic data and obstetric histories of a total of 300 patients (n=100 for each group) diagnosed with TM, EPL, and EP at a single center, as well as 100 healthy women with a first-trimester intrauterine pregnancy, were analyzed. Complete blood count data obtained from these participants included. In statistical analyses, the significance level was set at $p<0.05$.

Results: Although there was no notable discrepancy between the groups with regard to age, gravidity, and gestational week, the EPL cohort exhibited a markedly elevated parity rate (p=0.003). Additionally, notable disparities in platelet-lymphocyte ratio (PLR) were observed between the EPL and TM groups (p=0.021) and between the EP and TM groups (p=0.030). Additionally, monocyte-lymphocyte ratio (MLR) and neutrophil-lymphocyte ratio (NLR) were found to be higher in the EP group compared to the TM and EPL groups (p=0.004 and p=0.001 for MLR; p=0.000 in both comparisons for NLR).

Conclusion: Inflammatory blood parameters namely PLR, MLR, and NLR appear to be significant biomarkers for the diagnosis and management of TM, EPL, and EP. These findings suggest that integrating PLR, MLR, and NLR into obstetric practice could facilitate the early diagnosis and treatment of these complications.

Keywords: Early pregnancy loss, ectopic pregnancy, hematologic markers, inflammation, threatened miscarriage

INTRODUCTION

Early pregnancy loss (EPL) is defined as the absence of an embryo or the lack of detectable heart activity in the gestational sac within the first three months of pregnancy, occurring in approximately 10% of all pregnancies.[1,2] The contributing factors include genetic, infectious, endocrinological, anatomical, and immunological implantation abnormalities; however, in some cases, the exact cause remains unknown.[3,4] Ectopic pregnancy (EP) is characterized by the implantation of a fertilized egg outside the uterine cavity, with 98% of cases occurring in the fallopian tubes. It is primarily associated with impaired tubal embryo transfer due to ciliary dysfunction resulting from microenvironmental changes.[5,6] The overall incidence of EP is estimated to be approximately 2% of reported pregnancies.[7] Threatened miscarriage (TM) is defined by painless vaginal bleeding in the presence of a viable intrauterine pregnancy and occurs in approximately 20% of pregnancies.[8,9] Among these cases, the rate of missed abortion (pregnancy loss) ranges from 5.5% to 17%.[10,11] The literature suggests that immunological, endocrinological, and hematological factors may contribute to TM.[12]

TM may present with symptoms similar to those of EPL and EP, making differential diagnosis challenging. The presence of severe pain and heavy bleeding further increases the risk of miscarriage.[13] Blood parameters have been widely utilized to assess the prognosis of inflammatory diseases.[14] Inflammatory conditions lead to an increase in neutrophils and a decrease in lymphocytes due to platelet activation and the release of arachidonic acid metabolites. Consequently, neutrophil-to-lymphocyte ratio (NLR) is considered a reliable marker of underlying inflammatory processes.[15] Recent research has demonstrated that platelets and platelet-derived substances play a crucial role in various biological processes.[16] Furthermore, in EP, specific inflammatory cytokines have been observed to increase both at the implantation site and in the systemic circulation.[17]

The diagnosis and management of EPL, EP, and TM require the development of rapid, reliable, and cost-effective methods. Hematological inflammatory parameters represent easily accessible and inexpensive tests that may aid in differentiating these conditions.

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This study aims to analyze hematological inflammatory markers, including platelet count (PLT), mean platelet volume (MPV), mean platelet volume-to-platelet ratio (MPV/PLT), NLR, monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR), by comparing their levels in EPL, EP, TM, and normal intrauterine pregnancies. These markers will be evaluated using routine hemogram parameters obtained during pregnancy. This analysis seeks to enhance the diagnostic process and explore the potential clinical applications of these markers in disease diagnosis and management.

METHODS

Ethics

This study was approved by the Non-interventional Ethics Committee of Niğde Ömer Halisdemir University Faculty of Medicine (Date: 22.12.2022, Decision No: 2022/109). The study was conducted in accordance with all versions of the Helsinki Declaration.

Study Design and Participant Groups

Between October 2021 and October 2023, a retrospective case analysis was performed on patients diagnosed with EP, EPL, and TM at the Department of Obstetrics and Gynecology, Niğde Ömer Halisdemir University Faculty of Medicine Research and Practice Hospital. Demographic data and obstetric histories of the patients were collected.

Diagnosis and Criteria

The diagnoses of EP, TM, and EPL were established based on clinical examination, transvaginal ultrasonography, and hCG testing, considering gestational age. The study groups were defined as follows:

- **Threatened miscarriage (TM) group**: Patients presenting with vaginal bleeding and cramping, a detected fetal heartbeat, but no cervical dilation.
- **Early pregnancy loss (EPL) group**: Patients who experienced spontaneous miscarriage after being diagnosed with TM.
- **Ectopic pregnancy (EP) group**: Patients diagnosed with EP requiring surgical intervention.
- **Control group**: Healthy pregnant women up to 20 weeks of gestation without any signs of TM, selected randomly.

Exclusion Criteria

Patients meeting any of the following criteria were excluded from the study:

- Multiple pregnancies
- Conception through in vitro fertilization (IVF)
- History of cervical insufficiency
- History of cervical loop electrosurgical excision procedure (LEEP) or conization
- Presence of uterine pathologies
- Diagnosed thrombophilia or use of oral/parenteral anticoagulants
- Pregnancy while using an intrauterine device (IUD)
- Presence of pregnancy-related complications

Hematologic Parameters

The study evaluated the following hematologic inflammatory markers:

- Platelet count (PLT)
- Mean platelet volume (MPV)
- MPV/PLT ratio
- Neutrophil-to-lymphocyte ratio (NLR)
- Platelet-to-lymphocyte ratio (PLR)
- Monocyte-to-lymphocyte ratio (MLR)

These parameters were compared among the EPL, EP, TM, and normal intrauterine pregnancy groups to assess their diagnostic utility in early pregnancy complications.

RESULTS

A total of 400 patients were included in the study and categorized into four groups: healthy intrauterine pregnancies, TM, EPL, and EP. The control group comprised 100 healthy intrauterine pregnancies, while the study group consisted of 100 patients with TM, 100 with EPL, and 100 with EP. Demographic and hemogram data of the study and control groups are presented in Table 1. No significant differences were observed between the groups in terms of age, gravidity, or gestational week (Table 1). However, parity was significantly higher in the EPL group compared to the control and TM groups (p=0.02, p=0.048, respectively) (Table 2, Table 3). Additionally, MPV, MPV/PLT, and PLT values did not differ significantly between the groups (p=0.909, p=0.557, and p=0.135, respectively) (Table 1).

A statistically significant difference in PLR values was observed between the EPL and EP groups compared to the control group (p=0.02, p=0.03, respectively) (Table 2). Furthermore, when comparing PLR values among the groups, significant differences were noted between EPL and TM, as well as between EP and TM (p=0.021, p=0.03, respectively) (Table 3).

The NLR value was significantly higher in the EP group compared to the control group (p<0.001) (Table 2). Additionally, NLR was significantly elevated in the EP group compared to the TM and EPL groups (p<0.001 for both) (Table 3).

Similarly, the MLR value was significantly higher in the EP group compared to the control group (p<0.001) (Table 2). Moreover, MLR was significantly elevated in the EP group compared to the TM and EPL groups, with statistically significant differences (p<0.001 for both) (Table 3).

Table 1. Distribution of blood parameters and demographic characteristics of the groups

	Control	Threatened miscarriage	Early pregnancy lose	Ectopic pregnancy	p-value
Age (years, mean±SD)	27.2±4.8	27.6±5.6	29±6.5	28±5.6	0.132
Gestational age (weeks, mean±SD)	10.1±2	10.9±3.4	9.8±3.6	8.9±1.8	0.145
Gravidity	2.3±1.1	2.6±1.6	3±1.5	2.6±1.1	0.09
Parity	1±0.9	1.1±1.1	1.5±1.1	1.3±0.9	0.03
PLT (103/µL) (mean±SD)	249.5±71.8	259.5±63.1	277.2±248.8	232.4±63.7	0.135
MPV/PLT (mean±SD)	428.7±182.9	499.6±531.4	452.5±441.6	437.9±244.5	0.557
PLR (mean±SD)	9408.1±4735.3	9996±5670	12444±5215.4	12348.1±7556.4	0.000
MLR (mean±SD)	2495.1±1324.6	2711.2±2751.1	2609.5±2094.8	3718.5±1932	0.000
NLR (mean±SD)	25465.9±13267.6	277719.5±1550	30927±32920.9	44631.1±28514.3	0.000
MPV (fl) (mean±SD)	99.5±28.6	96.9±26.9	97.3±27.3	97.1±30.8	0.909

* The mean difference is significant at the 0.05 level. NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte, MPV: Mean platelet volume, PLT: Platelet, MLR: Monocyte-lymphocyte ratio, Data are mean±SD. Statistically significant p values are shown in boldface. p-values were calculated with the One-Way ANOVA

Table 2. Comparison of demographic characteristics and blood parameters

Parameters	Groups		
	Control group-threatened miscarriage	Control group-early pregnancy lose	Control group-ectopic pregnancy
PLT (×10³/µL)	10 p=1.000	27.6 p=0.927	17.1 p=1.000
MPV/PLT	70.8 p=1.000	23.8 p=1.000	9.17 p=1.000
PLR	587.9 p=1.000	3035.9 p=0.02	2940 p=0.03
MLR	216.1 p=1.000	114.3 p=1.000	1223.4 p=<0.001
NLR	2253.6 p=1.000	5461.1 p=0.655	19165.2 p=0.<001
MPV (fL)	2.6 p=1.000	2.2 p=1.000	2.4 p=1.000
Parity	0.14 p=1.000	0.54 p=0.02	0.28 p=0.379

NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte, MPV: Mean platelet volume, PLT: Platelet, MLR: Monocyte-lymphocyte ratio, †Bonferroni correction was made for post-hoc analyses.

Table 3. Comparison of demographic characteristics and blood parameters between groups

Parameters	Groups		
	Threatened miscarriage-early pregnancy lose	Threatened miscarriage-ectopic pregnancy	Early pregnancy lose-ectopic pregnancy
PLT (×10³/µL)	17.6 p=1.000	27.1 p=0.975	44.7 p=0.129
MPV/PLT	47 p=1.000	61.6 p=1.000	14.6 p=1.000
PLR	2448 p=0.021	2352.1 p=0.03	95.8 p=1.000
MLR	101.7 p=1.000	1007.2 p=0.004	1109 p=<0.001
NLR	3207.5 p=1.000	16911.6 p=<0.001	13704.1 p=0.<001
MPV (fL)	0.4 p=1.000	0.2 p=1.000	0.2 p=1.000
Parite	0.40 p=0.048	0.14 p=1.000	0.26 p=0.506

NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte, MPV: Mean platelet volume, PLT: Platelet, MLR: Monocyte-lymphocyte ratio, †Bonferroni correction was made for post-hoc analyses.

DISCUSSION

This study aimed to evaluate the role of inflammatory biomarkers in predicting EP, TM, and EPL. Our key findings indicate that NLR, PLR, and MLR were significantly higher in the EP group compared to the control group. Additionally, MLR and NLR levels were significantly higher in the EP group than in the EPL group. Furthermore, PLR values were significantly elevated in the EP group compared to the TM group.

These findings suggest that NLR, PLR, and MLR may serve as potential biomarkers for the diagnosis of EP and EPL. Therefore, integrating these parameters into the early diagnostic process could enhance clinical decision-making and facilitate patient management.

Lurie et al.[18] evaluated changes in leukocyte count and leukocyte differentials across trimesters in a large cohort of women with healthy and uncomplicated singleton pregnancies. Their study demonstrated that leukocyte and neutrophil counts increased gradually and significantly from the first to the third trimester, whereas lymphocyte counts decreased from the first to the second trimester. Overall, these findings suggest that neutrophil counts are relatively low, while lymphocyte counts are higher in the first trimester.

However, studies investigating the relationship between NLR and PLR and pregnancy loss have reported conflicting results. For instance, one study found no significant difference in NLR between women who experienced pregnancy loss and those who had a healthy birth in the first trimester.[19] In contrast, another study reported an association between low NLR and PLR values and EPL, whereas a different study found a link between high PLR and NLR values and EPL.[20,21]

Specifically, in cases of TM diagnosed in the first trimester, one study found that NLR values were significantly higher in women who experienced pregnancy loss compared to those whose pregnancies continued beyond the 24th week (p<0.001).[22] Similarly, Bas et al.[23] reported that NLR levels in women who experienced pregnancy loss during the first and second trimesters were significantly higher compared to those who had live births (p<0.0001). Additionally, Onat et al.[24] demonstrated that PLR values were significantly higher in the pregnancy loss group compared to the control group

(p=0.032). Furthermore, a study conducted in 2020 found that PLR was significantly higher in the EPL compared to both TM and healthy control groups (p<0.001).[25] Additionally, a study comparing hemogram parameters between 112 women with a healthy intrauterine pregnancy (6–8 weeks) and 97 women with EPL reported that NLR was significantly higher in the EPL group.[26]

Regarding EP, studies suggest that NLR and PLR may serve as important biomarkers. For instance, Yılmaz et al.[27] found that NLR levels were higher in ruptured EP cases compared to non-ruptured EP cases. Similarly, Dönmez et al.[28] reported significantly elevated NLR and PLR levels in patients with ruptured EP. These differences can be explained by the varying degrees of inflammation observed in ruptured and non-ruptured EP, as well as the progression and severity of the inflammatory response. Therefore, these findings suggest that inflammatory markers may play a crucial role in the diagnosis of EP and EPL.

Since platelets function as acute-phase reactants, an increase in PLT and changes in platelet-related markers may serve as indicators of inflammation.[29] MPV is a parameter that directly reflects platelet function, as larger platelets exhibit greater pro-inflammatory and pro-thrombotic activity. In pregnancy loss cases, it has been suggested that larger platelets migrate to the damaged site, leading to a decrease in MPV as part of the inflammatory response.[30]

On the other hand, some studies suggest that platelet indices, including MPV and platelet distribution width (PDW), differ between ectopic and intrauterine pregnancies due to inflammation at the implantation site and microenvironmental changes in the fallopian tube.[31] In this context, Ülkümen et al.[31] analyzed 153 EP cases and reported a significant decrease in MPV and an increase in PDW, particularly in ruptured EP cases. However, Turgut et al.[32] examined 138 EP cases and found an increase in MPV values. This discrepancy suggests that MPV may vary across different stages of inflammation. Additionally, some studies have shown that MPV decreases in mild inflammation but increases in severe inflammatory disorders.[33]

However, in our study, MPV, PLT, and MPV/PLT values did not show significant differences among the TM, EPL, and EP groups. Similarly, Kara et al.[34] compared spontaneous abortion cases with healthy pregnancies and found similar MPV values, but reported that PLTs were significantly higher in abortion cases. In contrast, Kaplanoğlu et al.[35] reported significantly lower MPV levels in the pregnancy loss group compared to the control group (p<0.001). These discrepancies may be attributed to variations in patient populations or methodological differences.

In recent years, there has been a growing number of studies evaluating hematological inflammatory markers in terms of diagnosis and prognosis in conditions such as EPL, TM, and tubal EP. For instance, Çallıoğlu et al.[36] reported elevated systemic immune-inflammation index (SII) and decreased platelet PDW in women experiencing EPL. Similarly, Huang et al.[37] emphasized significantly reduced lymphocyte levels in patients diagnosed with missed abortion. In cases of tubal EP, Dereli et al.[38] found that patients who responded to medical treatment had lower NLR and SII values, along with higher lymphocyte and PLTs. Erten and Soysal[39] reported a significantly lower MLR in cases of ruptured EP. Furthermore, in patients with TM, Topkara Sucu et al.[40] suggested that systemic and pan-immune-inflammation indices could serve as potential risk markers, while Yang et al.[41] demonstrated that NLR, MLR, and IL-1β levels may also be used as predictive indicators.

In line with these findings, a multicenter study conducted in Iran reported that women who experienced miscarriage had elevated levels of PLR, NLR, PDW, and lymphocytes, while their MPV was found to be decreased.[42] In a multicenter retrospective study conducted in Greece, mean NLR levels were not found to be associated with miscarriage; however, an NLR value greater than 5.8, observed only in the miscarriage group, was reported to be statistically significant.[19] On the other hand, a prospective study by Görkem et al.[43] found no significant differences in complete blood count parameters and serum kisspeptin levels among groups with healthy pregnancies, TM, and spontaneous miscarriage. Similarly, in a prospective study by Amedy et al.,[44] elevated NLR and decreased LMR were shown to be useful in distinguishing ectopic pregnancies from other types of gestation.

Nevertheless, the literature reveals inconsistencies in the findings related to inflammatory parameters. These discrepancies may be attributed to various factors, including heterogeneity in patient populations, variability in gestational age, individual differences in the inflammatory response, the timing of parameter measurement, and differences in laboratory methodologies. Despite these variations, inflammatory blood parameters are believed to have potential as supportive biomarkers in the diagnosis of early pregnancy complications and may contribute to the clinical decision-making process.

Limitations

In this context, certain methodological limitations of our study should be acknowledged. Its retrospective and single-center design may limit the generalizability of the findings. Therefore, future research should aim to overcome these limitations by incorporating a broader range of hematological and biochemical parameters and including long-term follow-up data. In particular, prospective, multicenter validation studies involving diverse populations are needed to enhance the reliability of current findings and to better clarify the clinical utility of inflammatory biomarkers.

CONCLUSION

As a result, the hematologic inflammatory markers PLR, MLR, and NLR were found to have clinical significance, particularly in the diagnosis of EP and EPL. These findings suggest that blood parameters could serve as valuable diagnostic tools for early pregnancy complications, enabling faster and more effective treatment approaches.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Non-interventional Ethics Committee of Niğde Ömer Halisdemir University Faculty of Medicine (Date: 22.12.2022, Decision No: 2022/109).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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