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Determination of systemic inflammatory markers and determination of possible risk factors in post-term pregnancies

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Abstract

This study aims to examine systemic inflammatory markers and the influence of feto-maternal factors in post-term pregnancies, assessing their ability to predict the course of these pregnancies. The findings seek to contribute to the existing literature on post-term pregnancy outcomes. The study retrospectively analyzed data from 250 pregnant women, aged 16 to 45, with a known last menstrual period (LMP) and no active trauma, who were admitted to the Obstetrics and Gynecology, Tepecik Training and Research Hospital between 2018 and 2023. The parameters examined included age, parity, systolic arterial tension (SAT), white blood cell (WBC) count, neutrophil count, lymphocyte count, platelet count, mean platelet volume (MPV), red blood cell distribution width (RDW), and neonatal outcomes. The case group consisted of 125 pregnant women who were at or beyond 42 weeks (≥42+0) according to LMP, while the control group included 125 women between 37 and 40+6 weeks of gestation. Comparisons were made between the groups based on the neutrop- hil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and other demographic characteristics. When comparing post-term and term pregnancies, the post-term pregnancy group showed significantly higher values for age, gestation period, height, RDW, and PDW. In contrast, WBC, PLT, MPV, and PLR were significantly higher in the term pregnancy group. No significant differences were found between the two groups in terms of live birth rate, birth weight, birth height, neutrophil count, lymphocyte count, or NLR. In the post-term group, WBC, neutrophil, lymphocyte, MPV, and NLR levels were lower, while PDW and RDW levels were higher compared to the term group. No differences were observed in PLR and PLT levels. Studies with larger sample sizes are recommended to enhance the predictive value of these markers for post-term pregnancies.

Keywords: Pregnancy, Post-term, NLR, PLR, MPV, Inflammation

Introduction

In 2013, the American College of Obstetricians and Gynecologists (ACOG) redefined term pregnancy. It categorized early-term pregnancy as occurring between 37+0 and 38+6 weeks, full-term pregnancy between 39+0 and 40+6 weeks, late-term pregnancy between 41+0 and 41+6 weeks, and post-term pregnancy at 42+0 weeks and beyond.[1] Studies have shown that late-term and post- term pregnancies are associated with increased risks of perinatal morbidity and mortality.[2] The primary risks identified in these studies include gestational hypertension, prolonged labor with cephalopelvic disproportion, birth injuries, and hypoxic-ischemic encephalopathy due to prolonged labor.[3] The incidence of post-term pregnancy can vary based on pregnancy-related factors, such as the rate of first-time (primiparous) pregnancies, multiple pregnancies, preterm deliveries, elective cesarean sections, and differing physician practices, such as the routine induction of labor.[4] To prevent incorrect post- term diagnoses, fetal ultrasonography (USG) in the first trimester is considered effective for accurately determining gestational age. This approach helps identify any discrepancies between the last menstrual period (LMP) and gestational age, reducing the risk of false post-term pregnancy diagnoses.[5] The identification of a correlation between hemogram parameters and preterm birth in the existing literature prompted an inquiry into whether similar hematological patterns might be

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observed in post- term pregnancies, and whether these parameters could potentially serve as predictive biomarkers for the likelihood of a pregnancy progressing to post-term status. We aim to predict whether pregnancy will progress to a post-term stage by examining certain parameters that can be obtained solely through a hemogram, in light of recent advancements in the field of medicine. This study aims to contribute to the literature on systemic inflammatory markers and fetomaternal factors involved in the progression of pregnancies to the post-term period.

Methods

This retrospective study was conducted at the Obstetrics and Gynecology, Tepecik Training and Research Hospital and the Obstetrics and Gynecology, Izmir City Hospi- tal between November 2023 and June 2024. It was approved by the Non-Interventional Clinical Research Ethics Committee of the Ministry of Health University (S.B.U) Tepecik Training and Research Hospital on December 21, 2023, with decision number 2023/11-07 (Annex 1). The study was conducted in accordance with the principles of the 2013 Declaration of Helsinki. As part of the study, records of patients aged 16 to 45 diagnosed with post-term pregnancy and admitted to the Tepecik Training and Research Hospital Gynecology Clinic between December 15, 2018, and May 15, 2024, were reviewed. The data collected included demographic characteristics, hemogram and immunohistochemical results, diagnoses, treatment protocols, treatment responses, and maternal and fetal morbidities.

The post-term diagnosis for each pregnant patient was confirmed using both last menstrual period (LMP) data and early pregnancy USG scans. If there was any doubt or discrepancy, the pregnancy duration was calculated based on the gestational weeks determined through ear- ly ultrasound measurements for the determination of the pregnancy week. All patients were confirmed to be free of chronic or autoimmune diseases and not in the window period for any other illness. Exclusion criteria included a history of malignancy, chronic or autoimmune diseases, acute infections, trauma, rupture of membranes at admission, and fetal anomalies.

Blood parameters were analyzed for 125 patients who met the criterias, had hemogram counts taken at their initial admission, and were at or beyond 42 weeks' gestation. These data were compared with those of a control group of 125 patients who met the same criterias and delivered at term based on LMP and first-trimester USG data.

The data were analyzed using IBM SPSS Statistics Stan- dard Concurrent User V24 (IBM Corp., Armonk, New York, USA). Descriptive statistics are presented as per- centages and means (with standard deviations). To assess normality for the 250 patients, we analyzed histograms, coefficients of variation, skewness-kurtosis, detrended normal Q-Q plots, and Kolmogorov-Smirnov test values. Categorical variables between groups were compared using the chi-square test, with a significance level set at $p<0.05$ for all analyses. Power analysis was conducted using the G*Power statistical program (version 3.1.9.4; Faul and Erdfelder, 1998), with a Type I error rate of 5%, an effect size of 0.5, and a test power of 99% for 86 patients.

Results

A total of 250 pregnant women were included in the study: 125 who gave birth at term and 125 who gave birth post-term. Analysis of demographic data for all participants showed a mean age of 27.64 years and a mean parity of 2.01. A comparison of gestation periods and parity is provided in Table 1, where gestation periods were found to be statistically significantly different, while parity showed no statistically significant difference. Analysis of obstetric outcomes for both groups showed a mean newborn weight of 3236±457.2 g, a mean length of 49.63±1.79 cm, with 57.6% of the newborns being male and 42.4% female. When examined by group, post-term deliveries had a mean newborn weight of 3267.34±448.76 g, a mean length of 49.63±1.67 cm, with 56.0% of the newborns being male and 44.0% female. In term deliveries, the mean newborn weight was 3205.15 ± 465.20 g, the mean length was 49.63±1.92 cm, with 59.2% male and 40.8% female (Table 1).

Table 1. Comparison of Post-Term and Term Pregnancies

Post-term	**Term**					
Variable		Mini - mum	Maxi - mum			p
Minimum	Maximum	SD		SD		
Gestation Period (week)	42.4	0.58	37	1.07		**<0.001**
Number of Live Births (n)	1	2	0	2		0.286
Newborn's Birth Weight (gr)	1830		2080			0.836

Overall, the delivery modes were 30.4% vaginal and 69.6% cesarean. In the post-term group, 31.2% of deliveries were vaginal, and 68.8% were cesarean, while in the term group, 29.6% were vaginal and 70.4% were cesarean. Analysis of birth outcomes, delivery modes, and neonatal sex between term and post-term pregnancies revealed no statistically significant differences between the groups (p<0.05) (Table 1).

Comparison of laboratory results between the two groups revealed that white blood cell count (WBC), neutrophils (NEU), lymphocytes (LYM), mean platelet volume (MPV), and neutrophil-to-lymphocyte ratio (NLR) values were significantly higher in the term group compared to the post-term group (All p values being: p<0.05). Conversely, red cell distribution width (RDW) and platelet distribution width (PDW) values were significantly higher in the post-term group than in the term group. When analyzing NLR values specifically, these were significantly higher in the term group compared to the post-term group (p<0.001).

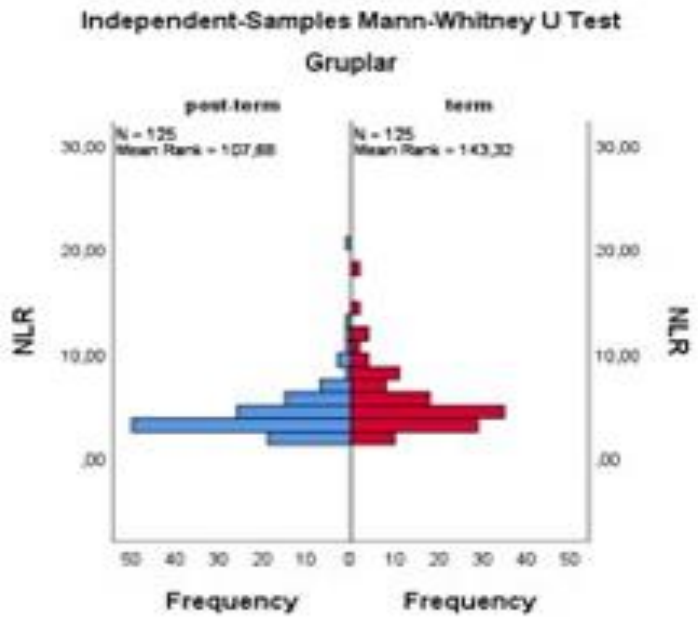

Figure 1. NRL distributions of term and post-term groups

Although the platelet-to-lympho- cyte ratio (PLR) was higher in the term group than in the post-term group, this difference was not sta- tistically significant (p=0.675) (Table 2). The dist- ribution of NLR values for both groups is summa- rized in Figure 1. The comparison of the term and post-term groups regarding age, gestational period, number of live births, weight, height, and laboratory values (WBC, NEU, LYM, PLT, MPV, RDW, PDW, NLR, PLR), as well as birth outcomes, modes of

delivery, and gender, is presented in Table 2.
Based on these results, we have obtained a sample and statistically significant outcomes for the identification of blood parameters that could be used to predict which pregnancies may progress to a post-term stage.

Table 2. Comparison of Laboratory Results of Patients

	Post-term Mini-mum	**Maxi-mum**	**Mean**	**SD**	**Term Mini-mum**	**Maxi-mum**	**Mean**	**SD**	**P**
WBC (x10³uL)	4.7	21.6	11.17	3.43	5.6	31.85	12.52	4.16	**0.006**
NEU (x10³uL)	2.6	19.3	8.06	2.98	3.77	27.08	9.60	3.89	**<0.001**
LYM (x10³uL)	0.2	4.4	2.15	0.74	0.8	3.68	1.97	0.56	**0.03**
PLT (x10³uL)	72	801	246.49	91.21	114	493	242.6	76.70	0.721
MPV (fL)	7	13.5	9.33	1.26	8.8	13.2	10.79	1.07	**<0.001**
RDW (%)	12.8	31.7	15.49	2.56	12.3	21.2	14.33	1.79	**<0.001**
PDW (%)	16	19.6	17.51	0.67	8.7	19.6	12.81	2.65	**<0.001**
NLR	1.5	20	4.19	2.42	1.76	17.85	5.36	3.02	**<0.001**
PLR	46.77	985	126.75	88.57	59.51	290	130.56	48.89	0.675

Discussion

Post-term pregnancy poses obstetric risks for both the mother and the fetus. While certain risk factors, such as genetic predisposition, obesity, nulliparity, anencephaly, and fetal adrenal insufficiency, have been identified in its etiology, the underlying causes of most true post-term pregnancies remain undetermined.[6] Therefore, recogni- zing and monitoring post-term pregnancies is crucial for improving obstetric and perinatal outcomes. This study aimed to examine systemic inflammatory markers in post- term pregnancies and to contribute to the literature on the feto-maternal factors that lead to the progression of post-term pregnancy

The hematologic system plays a crucial role in maintai- ning the integrity and health of the placental system, whi- ch connects the fetus, placenta, and maternal circulation. Various changes associated with post-term pregnancies can lead to decreased nutrient and oxygen transport to the fetus within the uterus. [7] Markers such as the NLR and PLR are strong indicators of an acute inflammatory state and are commonly used as diagnostic and prognostic mar- kers in cardiovascular events and myocardial infarction. Recent evidence supports the use of these hematologic in- dices as valuable biomarkers in obstetrics and gynecology. [8,9, 10] Studies have shown that neutrophil levels increase while lymphocyte levels decrease as gestation advances, resulting in an elevated NLR. However, the interpreta- tion of NLR in the context of fetal hypoxia remains unc- lear.[11] The present study aims to investigate the natural progression of serum inflammatory markers as predictors of post-term pregnancies.

Caughey et al. identified advanced maternal age as a risk factor for post-maturity in their study on the risk fac- tors for post-term pregnancy.[12] Similarly, Kortekaas et al. found that post-maturity was more prevalent among women who gave birth at age 35 and older, with poorer pregnancy outcomes associated with increasing age.[13] Consistent with these findings, our study also identified advanced maternal age as a risk factor for post-term preg- nancies. In a study conducted by Galal et al. that exami- ned risk factors for post-term pregnancies, it was found that first pregnancies are a significant risk factor for post- term delivery.[2] Similarly, Aaron et al. investigated the risk factors for post-term pregnancies (defined as gesta- tional week ≥42) and long-term pregnancies (gestational week ≥41) and also identified first pregnancies as a risk factor for both post-term and over-term deliveries.[14] In contrast to the existing literature, our study found that the incidence of post-term pregnancy was statistically insigni- ficant as the live birth rate increased.

In a study examining neonatal outcomes in post-term pregnancies, Sharma et al. reported no significant dif- ferences in birth weight and newborn height between

post-term and term pregnancies.[14] Similarly, in the study conducted by Kortekaas et al., which evaluated the risk fa- ctors and prenatal outcomes of post-term pregnancies, no differences were found in birth weight and length betwe- en the two groups. Consistent with these findings, in our study, no significant difference was found in the newborn weights, however, it did observe a significant increase in neonatal length among post-term infants.[15]

Interest in the NLR and PLR has increased in recent years, leading to numerous studies on these markers. Elevated NLR and PLR have been associated with poor pregnancy outcomes, including premature rupture of membranes, preterm labor, gestational diabetes, and cho- rioamnionitis.[16,17] In our findings, NLR was significantly lower in the post-term group, while the association with PLR was not significant. On the other hand, to date, the literature predominantly comprises studies focused solely on preterm births, within which the followings have been reported: that these serum inflammatory markers may serve as predictors of labor timing. In a study involving 78 pregnant women diagnosed with threatened preterm labor, Yuce et al. reported that elevated NLR and PLR could indicate an increased risk of preterm delivery.[18] Additionally, Ayşegül Özel et al. demonstrated that NLR levels were significantly higher in patients with prema- ture rupture of membranes and suggested that NLR might also predict the occurrence of neonatal sepsis.[19] Studies have shown that the neutrophil-to-lymphocyte ratio (NLR) is an inflammatory biochemical marker, and its elevation is associated with poor obstetric outcomes during pregnancy.[20] While Akgün et al. found an inverse correlation between increased NLR and preterm delivery and low birth weight, they did not report a statistically significant difference.[21] Yüce et al., in their study of 78 pregnant women, divided participants at risk for preterm delivery into two groups: those who delivered within one week and those who did not. They found that NLR was significantly higher in the group that delivered within one week.[18] In our study, we observed that NLR increased significantly in third trimesters among women who deli- vered post-term ($p<0.001$). In light of this information, it can be hypothesized that post-term pregnancies may re- sult from a suppressed or dysregulated immune response; however, further evidence and further research required to substantiate this assumption in various centers with lar- ger patient populations to explore this topic more comp- rehensively.

Elevated WBC counts are commonly associated with acute infections and inflammation. WBC levels tend to increase more significantly in pregnancies complicated by conditions such as appendicitis, cholecystitis, cystitis, and other inflammatory processes, often accompanied by physiological leukocytosis during pregnancy.[18] Our study found that WBC values were significantly lower in post-term pregnancies compared to preterm pregnan- cies. Since no study has been conducted so far regarding the relationship between post-term pregnancies and the- se markers, a comparison with the literature cannot be made. Here, we might assume that a diminished immune response could have played a role. On the other hand in a study conducted by Liyin et al. involving 400 pregnant women, high WBC levels were identified as a potential marker for predicting preterm delivery, with results cor- related to histologic chorioamnionitis.[22] Similarly, Karen et al. found that elevated WBC levels in symptomatic pregnant women could predict preterm delivery in their study of 218 participants (p:0.001).[23] Their results indi- cated that deliveries occurring before 28 weeks of gesta- tion were linked to subclinical infections, while outcomes after 28 weeks were associated with the maternal and/or fetal hypothalamic-pituitary-adrenal axis. In contrast,. This highlights the need for further research in diverse clinical settings with larger patient populations.

Research has shown that platelet activation and inflam- mation-related processes may contribute to decreased MPV levels in preterm pregnancies. In our study, we ob- served that MPV levels were significantly lower in post- term pregnant women compared to those who delivered at term. Various conditions, including ectopic pregnancy, preeclampsia, and cholestasis, have been studied in this context.[24,25] In a similar study conducted by Yurtçu et al. with 1,049 pregnant women, no statistically significant difference was observed between MPV values in the first trimester and those in the third trimester. Conversely, a study by Ma et al. reported that MPV is a reliable marker for predicting preterm delivery, with a cut-off value set at 10 f/L.[26] In contrast, the mean MPV for all groups in

our study was found to be less than 10 f/L. Additionally, a study by Aktün et al. involving 270 pregnant women found a statistically significant decrease in MPV levels among those who delivered preterm.[27] In summary, MPV values were found to be significantly lower in both preterm laborers, as reported by Ma et al. and Aktün et al., and in post-term laborers in our study. However, the- re are currently no studies in literature examining MPV levels specifically in post-term pregnancies. Further rese- arch on this topic is needed.

Elevated neutrophil levels are commonly used as markers of acute infection and inflammation, along with WBC counts.[28] Neutrophil evaluations have also been con- ducted in studies examining inflammation, where other hemogram parameters were assessed during pregnancy. [24,25,29] In our current study, we found that neutrophil values were significantly lower in post-term pregnant women compared to those in term labor. While existing studies in the literature examining hemogram parame- ters and pregnancy have associated elevated inflamma- tory responses with preterm birth, our study suggests that a reduced inflammatory response may be associated with post-term pregnancies. For instance, Tolunay et al. evaluated 92 pregnant women at risk of preterm deli- very between 24 and 34 weeks of gestation. Their results showed that neutrophil counts were significantly higher in those who delivered within one week compared to tho- se who delivered after one week.[30] Additionally, Zhang et al. compared hemogram parameters between 175 preg- nant women with preterm labor and healthy pregnant women.[31] Several studies in the literature have demons- trated a relationship between RDW and preeclampsia. [32] It has been observed that erythropoietic stimulation increases in cases of preeclampsia due to placental hy- poxia. While RDWx values are known to be higher in individuals with prehypertension and hypertension, no significant differences have been found between women with preeclampsia and a control group regarding RDW values.[33] In our present study, we found that RDW va- lues were significantly lower. However, there is currently limited research on this topic in literature. Further stu- dies are needed to determine whether RDW can serve as a predictive marker in post-term pregnancies. Aside from the parameters discussed above, there are no existing stu- dies in the literature that examine PDW and lymphocyte values in post-term pregnancies. In the present study, we found that both PDW and lymphocyte values were signi- ficantly higher in post-term pregnant women compared to those in the control group.

Conclusion

This study is significant as it is the first to examine the relationship between post-term pregnancy and inflam- mation. The aim was to identify parameters that could serve as simple and accessible markers- specifically, vari- ous hemogram parameters- for predicting the progressi- on of pregnancy to a post-term state. The evaluated para- meters included WBC counts, lymphocytes, neutrophils, NLR, RDW, PDW, and MPV.

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