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The Role of Complete Blood Count Derived Inflammatory Markers in Gestational Trophoblastic Diseases

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Abstract

Background: Gestational trophoblastic disease (GTD) originates from the placenta, which can show local invasion and metastasis.

Aims: To investigate the value of the parameters of the complete blood count in our GTD patients and their usage as an inflammatory marker.

Study Design: Between January 1, 2016 and December 31, 2019, the records of patients who were followed up with the diagnosis of Gestational Trophoblastic Disease and underwent curettages at the Okmeydani Training and Research Hospital Obstetrics and Gynecology Department, were analyzed retrospectively.

Methods: A total of 52 cases were included, including 27 partial and 25 complete mole cases. (Group 1). 62 pregnant women under 12 weeks of age (Group2) and 66 non-pregnant gynecology patients (Group3) were determined as the control group. All values in the complete blood count and Neutrophil / Lymphocyte Ratio (NLR), Platelet / Lymphocyte Ratio (PLR) values were recorded.

Results: Mean Corpuscular Hemoglobin (MCH) and Mean Corpuscular Hemoglobin Concentration (MCHC) values were statistically different between the 3 groups (p.0.02 and p <0.001 respectively). RDW-CV values were statistically lower in the group 2 compared to the group 3 (p: 0.039). When RDW-SD values were compared, both group 1 and group 2 were found statistically significantly lower than the group 3 (p.0.019 and p: 0.028 respectively). There was a significant difference between the 3 groups in

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NLR values. (P = 0.006).

Conclusions: The neutrophil / lymphocyte Ratio can be evaluated as an important parameter in gestational trophoblastic patients. However, multicentered and prospective studies with a large number of patients are needed to be conducted for the routine use of these parameters.

Keywords: Blood count parameters ,Gestational trophoblastic disease, Neutrophil / Lymphocyte Ratio (NLR), Platelet / Lymphocyte Ratio (PLR)

INTRODUCTION

Gestational trophoblastic disease (GTD) forms the gynecological malignant group that originates from the placenta, which can show local invasion and metastasis, but can be provided the most cure. Within this disease group, complete hydatiform mole (CHM), partial hydatiform mole (PHM), exaggerated placental site (EPS) and placental-site nodule (PSN) are defined as premalignant disorders. Invasive mole, choriocarcinoma (CC), placenta -site trophoblastic tumor (PSTT) and epitheloid trophoblastic tumor (ETT) are malignant disorders and are also referred to as gestational trophoblastic neoplasia (GTN). The incidence of GTD differs in various parts of the world. While CHM and PHM appear 1-3 in 1000 pregnant women in North America and Europe, this rate increases in Asia and Latin America. CC, PSTT and ETT are very rare tumors and are seen in 1 in 50000 pregnant women (1,2).

Maternal age, menarche age, previous history of molar pregnancy, genetic factors, parity, socioeconomic status, malnutrition, infections, and oral contraceptive usage are all defined as possible risk factors (3,4).

In recent years, MPV (Mean Platelet Volume), Platelet Distribution Width (PDW), Platelet Count (PC) and Platelet Crit (PCT) Neutrophil / Lymphocyte Ratio (NLR), Platelet / Lymphocyte Ratio (PLR), Red Cell Distribution Width (RDW) have been used as diagnostic markers in many inflammatory diseases (5,6).

The aim of our study is to investigate the value of the accessible parameters of the complete blood count in our GTD patients and their usage as inflammatory markers.

MATERIAL AND METHODS

Between January 1, 2016 and December 31, 2019, the records of patients who were followed up with the diagnosis of Gestational Trophoblastic Disease and underwent curettages at the Okmeydani Training and Research Hospital Obstetrics and Gynecology Department, were analyzed retrospectively. During this 4-year period, 30 partial moles, 26 complete moles and 1 choriocarcinoma cases were followed up and treated in our clinic. However, a total of 52 cases, including 27 partial and 25 complete mole cases of whose records can all be accessed completely, were included in our study (Group 1). In addition, the choriocarcinoma case was excluded because it may affect the results since it was a malignant case. Age, gravidity, parity and abortus numbers, gestational weeks, demographic information and complete blood count at the time of diagnosis were recorded. 62 pregnant women under 12 weeks of age (Group 2) and 66 non-pregnant gynecology patients (Group 3) who applied to our outpatient clinic on the same dates were determined as the control group and complete blood count values of these patients were also examined.

Patients with any systemic disorder, acute or chronic inflammatory disease, any previous history of hematopoietic system disease, history of malignancy or drug use that may affect the blood count were excluded from the study.

The diagnosis of GTD was confirmed with pathological results. The blood test was taken into EDTA (potassium ethylenediaminetetraacetic acid) tubes and examined within two hours. In GTD patients, blood was collected before any therapeutic intervention was made after hospitalization.

Neutrophil / Lymphocyte Ratio (NLR) was calculated by dividing absolute neutrophil count to absolute lymphocyte count, and Platelet / Lymphocyte Ratio (PLR) was calculated by dividing absolute platelet count to absolute lymphocyte count.

All information obtained was entered into a statistical package for the social sciences, version 25.0, SPSS Inc, Chicago, Illinois, USA (SPSS). Descriptive statistics were used to calculate the frequency (n), percentage (%), central tendency (mean, median&mode) and dispersion (range, variance, SD, maximum & minimum) for each variable when appropriate. Continuous data was evaluated by the Kolmogorov-Smirnov test for normal distribution. According to the result of the Kolmogorov Smirnov test, the difference between the groups were investigated by Student t test or Mann Whitney U test. In the triple comparison we used the Kruskal Wallis test with pairwise comparisons after Bonferroni corrections if statistically significant. A p-value<0.05 has been considered statistically significant.

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University of Health Sciences, Okmeydanı Training and Research Hospital Prof.Dr. Cemil Tascıoglu (Date 23/06/2020/No 48670771-514.10-243).

RESULTS

Between January 1, 2016 and December 31, 2019, 11873 deliveries took place in our clinic and the incidence of molar pregnancy was found to be 4.37 / 1000. Of the total 52 molar pregnancy cases, 27 were partial (51.9%) and 25 (48.1%) were complete hydatiform moles.

When the age distribution of the group 1 (the mole group) included in the study was examined; mean age was found as 29.52 ± 8.603. The parity of 11.5% of the patients was 4 and above (Table 1).

In the study, the mean age of the patients who were diagnosed with partial moles was 29.59 ± 7.732, and the mean age of the patients who were diagnosed with complete moles was 29.44 ± 9.618 (P = 0.595 There was no significant difference in the number of gravidity, parity and abortus (Table 2).

Table 1: Demographic characteristics of gestational trophoblastic disease

		n	%
Age (Year)	15-19	6	11,5
	20-24	9	17,3
	25-29	16	30,8
	30-34	9	17,3
	35-39	5	9,6
	40-44	2	3,8
	45-49	5	9,6
Gravida	1	16	30,8
	2	11	21,2
	3	13	25
	4 and above	12	23
Parity	0	18	34,6
	1	16	30,8
	2	11	21,2
	3	1	1,9
	4 and above	6	11,5
Abortion	0	40	76,9
	1	6	11,5
	2	1	1,9
	3	3	5,8
	4 and above	2	3,9
O Rh	+	15	28,8
	-	0	0
A Rh	+	17	32,7
	-	6	11,5
B Rh	+	7	13,5
	-	1	1,9
AB Rh	+	6	11,5
	-	0	0
Pathology Report	Complete	25	48,1
	Partial	27	51,9

Table 2: Comparisons of partial and complete molar pregnancies

	Partial	Complete	*p*
Age	29,59 ± 7,732	29,44 ± 7,618	0,595
Gravida	2 (1-14)	2 (1-10)	0,706
Parity	1 (0-5)	1 (0-8)	0,142
Abortion	0 (0-12)	0 (0-6)	0,264
Week of pregnancy	8,83 ± 2,335	8,7 ± 2,259	0,57

The mean age was 28.73 ± 5.926 in the healthy pregnant group (group 2), and the mean age was 35.41 ± 9.79 in the gynecology patient group (group 3). When the demographic characteristics of molar pregnancy (group 1) and healthy pregnancy under 12 weeks (group 2) were compared, there was no statistically significant difference in the mean age (p: 0.882). Gravidity mean was 2 (1-6) (min-max), parity mean was 1 (0-3) (min-max), abortus mean was 0 (0-3) (min-max), pregnancy week mean was 8.44 ± 2.199 in healthy pregnant group. There was no significant difference between group 1 and group 2 on gravidity, parity, abortus and gestational weeks. (p.0.179, p: 0.209, p.0.751, p: 0.694 respectively)

Complete blood count results of 180 patients with inclusion criteria are shown in table-3 as "mean ± SD" values.

Pairwise comparisons of the variables after the Bonferroni correction in statistically significant triplet comparisons are shown in table 4.

There was no statistically significant difference between the 3 groups in White Blood Cell (WBC), Red Blood Cell (RBC), Hemoglobin, Hematocrit, Mean Corpuscular Volume (MCV), Platelet Count (PLT), Mean Platelet Volume (MPV), Platelet Crit (PCT), Platelet Distribution Width (PDW) values. In contrast, Mean Corpuscular Hemoglobin (MCH) and Mean Corpuscular Hemoglobin Concentration (MCHC) values were statistically different (p.0.02 and p <0.001 respectively). While P.0.034 was detected between Group 1 and Group 3 in MCH; the values were found as p <0.001 between Group 1 and Group 3, and p <0.001 between Group 2 and Group 3 in MCHC.

There were statistically significant differences between 3 groups in Red Cell Distribution Width Coefficient of Variation (RDW-CV) and Standard Deviation (RDW-SD) values. (P: 0.028, p: 0.008 respectively). When the subgroups were examined, RDW-CV values were statistically lower ingroup 2 patients compared to the group 3 (p: 0.039). When RDW-SD values were compared, both group 1 and group 2 were found to be statistically significantly lower than the group 3 (p.0:019 and p: 0.028 respectively).

Table 3: Comparisons of blood count parameters among mole hydatidiform, non-mole pregnancy and gynecology groups

	Group 1	Group 2	Group 3	*p*
	n=52	*n=62*	*n=66*	
WBC (10^3/µl)	9,09 ± 3,15	8,49 ± 2,32	7,94 ± 2,29	0,051
RBC (10^6/µl)	4,36 ± 0,47	4,36 ± 0,33	4,45 ± 0,33	0,343
HGB	12,45 ± 1,307	12,25 ± 1,098	11,97 ± 1,56	0,243
HCT (%)	36,93 ± 3,61	41,47 ± 38,89	36,62 ± 3,95	0,852
MCV	84,805 ± 5,23	83,73 ± 5,96	82,55 ± 7,81	0,553
MCH (pg)	28,58 ± 2,01	36,89 ± 48,42	27,139 ± 3,56	0,02*
MCHC (g/dL)	33,69 ± 1,008	33,57 ± 1,05	32,68 ± 1,69	<0,00
PLT (10^3/µl)	244,15 ± 53,72	257,26 ± 57,79	273,12 ± 77,806	0,138
MPV	11,46 ± 10,74	9,6 ± 2,004	10,075 ± 1,02	0,357
PCT	0,244 ± 0,506	0,39 ± 1,16	0,2715 ± 0,706	0,111
PDW	15,22 ± 1,801	17,99 ± 19,01	15,06 ± 1,92	0,44
RDW-CV (%)	13,68 ± 1,08	13,79 ± 1,6	14,49 ± 1,87	0,028
RDW-SD	40,703 ± 3,46	41,08 ± 4,02	42,85 ± 4,17	0,008
NEU (%)	67,13 ± 8,38	65,92 ± 8,07	60,77 ± 11,68	0,001
NEU (10^3/µl)	7,0019 ± 5,62	5,78 ± 1,87	5,03 ± 2,09	0,001
LYM (%)	25,18 ± 7,24	26,38 ± 7,33	29,47 ± 9,34	0,014
LYM (10^3/µl)	2,18 ± 0,63	2,19 ± 0,59	2,25 ± 0,76	0,964
NLR	3,0637 ± 1,64	2,8115 ± 1,204	2,52 ± 1,601	0,006
PLR	122,32 ± 42,29	122,96 ± 36,82	133,44 ± 55,38	0,696

**: statistically significant*

Table 4: Pairwise comparisons of the variable after Bonferroni correction in statistically significant triplet comparisons

					Group 3				
		MCH(pg)	MCHC(g/dL)	RDW-CV(%)	RDW-SD	NEU(%)	NEU(10^3/µl)	LYM(%)	NLR
Group 1	MCH(pg)	0,034							
	MCHC(g/dL)		<0,001						
	RDW-CV(%)								
	RDW-SD				0,019				
	NEU(%)					0,002			
	NEU(10^3/µl)						0,001		
	LYM(%)							0,015	
	NLR								0,007
Group 2	MCH(pg)								
	MCHC(g/dL)		<0,001						
	RDW-CV(%)			0,039					
	RDW-SD				0,028				
	NEU(%)					0,017			
	NEU(10^3/µl)						0,03		
	LYM(%)								
	NLR								

A statistically significant difference was found between neutrophil numbers and percentages among the 3 groups (p <0.001). When group 1 and group 3 were compared, the number and percentage of the neutrophils were significantly higher in group 1 than group 3 (p.0.001 and p: 0.002 respectively). Likewise, the number and percentage values were higher in group 2 compared to group 3. (p: 0.03 and p: 0.017 respectively). When we look at the lymphocyte percentages, there was a significant difference between the 3 groups. (P = 0.014). Group 1 lymphocyte percentage values were statistically significantly lower than group 3. (P = 0.015). While there was no statistically significant difference in platelet / lymphocyte ratio (PLR) values, there was a significant difference between the 3 groups in Neutrophil / lymphocyte ratio (NLR) values. (P = 0.006). NLR values in group 1 were significantly higher than the group 3. (P = 0.007).

DISCUSSION

The incidence of molar pregnancy differs between countries. In a comprehensive study by Matsui et al., they reported that the incidence decreased in Japan over the years and was 1.65 per 1000 live births in 2000 (7).

In our study, this rate was found to be 4.37 / 1000. Although complete moles are seen more frequently in many studies, the ratio of CHM in a British study was found to be 1 / 1423 and the

ratio of PHM was found to be 1 / 1058 (8). In our cases, the PHM rate was 2.27 per 1000 live births, and the CHM rate was 2.1 per 1000 live births.

When the average age range of the patients in the mole group in our study was examined; it was determined that the highest rate was 30.8% with the age range of 25-29, 11.5% were below 19 years old and 13.4% were above 40 years old. Compared to the other age groups, gestational trophoblastic diseases were more common in the reproductive age group. In the study of Lurain et al., it has been reported that the risk of gestational trophoblastic diseases increases 1.5 times under the age of 20 and 5.2 times over the age of 40 (9).

The incidence of hydatiform moles increased in early and late fertile pregnancies. The number of parities has no place among the risk factors of molar pregnancy (2,10). In the study of Bagshwe et al., they reported that blood typeA was more common in molar pregnancy (11).

In our study, in accordance with the literature, blood type A was found to be significantly higher, at 44.2%.

A complete mole may present with vaginal bleeding, larger uterus for the gestational age, hypertension and hyperemesis. In our cases, vaginal bleeding and larger than expected uterus were the most important findings. In partial moles, as in our cases, missed or incomplete abortus findings are more common and it can be diagnosed with the curettage material. In all cases, considering the risk of recurrence, weekly follow-ups were performed until serum ß-HCG values decreased to normal, and three times weekly follow-up after normalization, and then serum ß-HCG levels were followed for one year by monthly checks. Patients were offered contraception for approximately a year.

Leukocytosis is an expected finding in a healthy pregnancy. In our study, the number of leukocytes was significantly higher in molar and healthy pregnancies compared to the gynecological patient group. But there was no statistically significant difference. (P: 0.051). Mean Corpuscular Hemoglobin (MCH) and Mean Corpuscular Hemoglobin Concentration (MCHC) in our study were also significantly higher in molar and healthy pregnancies than in the gynecological patient group. However, this increase may be secondary to the changes in pregnancy-related blood parameters and may not be clinically relevant.

Another indicator of platelet activation is the Mean Platelet Volume (MPV), Platelet Distribution Width (PDW) and Platelet Crit (PCT) in the complete blood count. The increase in these values is associated with ongoing inflammation (12,13,14).

Compared to healthy pregnancies, an increase in leukocyte, MPV and PDV values is observed in cases of preeclampsia with increased inflammatory response and abnormal placental invasion. Preeclampsia and hyperemesis gravidarum are also expected findings in GTD. Dilutional thrombocytopenia due to increased intravascular volume is observed in

healthy pregnant women, and a compensatory increase in MPV can be observed (15).

In our study, MPV values were found to be higher in molar pregnancy compared to healthy pregnancy and gynecology patient group, but no statistically significant difference was found. In the study of Eskicioglu et al., Leukocyte count and PDW values were found to be significantly lower in molarpregnancy than in the healthy control pregnancy group. There was no difference in PLT and MPV values (16).

Especially due to the lack of cytotrophoblast invasion which is usually seen in complete molar pregnancy; the relationship between leukocyte values and GTD can be observed. There are very few studies on this subject, and most of the studies have examined platelet counts more than CBC (complete blood count) parameters (17,18). RDW (Red Cell Distribution Width), another marker used in the clinic, is a parameter that shows the distribution of erythrocyte volume in hemogram examinations. There are many conditions in which the width of the distribution of erythrocytes is clinically related, apart from anemia. RDW values increase as a result of defective erythropoiesis, increased inflammation or hemolysis. In pregnant women, RDW does not change much between 16-34 weeks and remains stable (19,20).

In our study, the gestational week was the first trimester in both molar and healthy pregnancy groups. The RDW values were found to be statistically low in these two groups compared to the gynecological patient group.

Recently, studies with markers that show systemic inflammation in the peripheral blood such as Neutrophil / lymphocyte ratio (NLR), Platelet / lymphocyte ratio (PLR) and are easily obtained by simple complete blood count (hemogram) tests attract attention. The high value of Neutrophil / lymphocyte ratio (NLR) is related to the increased neutrophil count in value because of increased inflammation; on the other hand, the low lymphocyte count is related to a defect in a patient's general health condition, increased cortisol levels because of physiological stress and increased apoptosis (21).

NLR and PLR values, which are thought to reflect systemic inflammation, are studied in many diseases. It has been reported that high NLR and PLR values show increased inflammation; and are associated with worsening renal function in diabetic patients, increased mortality in malignancy patients, and poor prognosis in cardiovascular disease patients (22). In our study when molar pregnancy, healthy pregnancy and gynecological patients were compared, NLR values were statistically significantly higher in molar pregnancies. This increase is also present in healthy pregnancies. However, especially when comparing molar pregnancy and gynecological patient groups, NLR value was found much higher (p: 0.007). There was no statistical difference in PLR values. In a study of Guzel et al., invasive and non-invasive GTDs were compared and it was found that the rate of NLR increased significantly in the invasive group (23).

Increased neutrophil levels inhibit lymphocyte activity and stimulate lymphopenia by increasing lymphocyte apoptosis (24).

In our study, although the neutrophil count and percentage were significantly higher in both the molar and healthy pregnancy groups, the percentage of lymphocytes was significantly lower compared to the gynecological patient group in the molar pregnancy patient group. (P: 0.015). In cases such as inflammation and malignancy, the immune response of circulating leukocytes causes an increase in the number of neutrophils and a decrease in the number of lymphocytes (25). In addition, the growth factor and interleukins cause neutrophil accumulation, and an increase in the number of neutrophils is also observed in solid tumors (26,27).

CONCLUSIONS

There are a small number of studies examining inflammatory markers in complete blood count parameters in relation to gestational trophoblastic patients. Although a significant difference was observed between the molar pregnancy group and the gynecological patient group in some parameters in our work, no statistical difference was found between the molar and the healthy pregnancy groups.

Easily accessible inflammation markers in the complete blood count are also important in Gestational Trophoblastic Diseases. Specifically, the neutrophil / lymphocyte ratio can be considered as an important parameter for diseases in which systemic inflammation is evident. However, multicentered and prospective studies with a large number of patients must be conducted to routinely use these parameters.

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Conflict of Interest Disclosure: These authors have no conflict of interest.

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