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Evaluation of inflammation markers and pregnancy outcomes of patients undergoing intrauterin insemination (IUI) for unexplained infertility

Açıklanamayan infertilite nedeniyle intrauterin inseminasyon (IUI) yapılan hastaların inflamasyon belirteçleri ve gebelik sonuçlarının değerlendirilmesi

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ABSTRACT

Aim: This study aimed to compare the inflammatory markers in patients who had ovu-lation induction with clomiphene citrate (CC) and who underwent intrauterine insemi-nation (IUI) due to unexplained infertility in patients who could get pregnant and who could not.

Materials and Methods: The study included 125 females with unexplained infertility who underwent ovulation induction with CC and who underwent IUI at the Health Sciences University Ankara Etlik Zübeyde HanımGynecology Training and Research Hospital Assisted-Reproduction Therapy Clinic between July 2019 and December 2019. Of the patients, 104 (83.2%) of them could not get pregnant as a result of IUI, and 21 (16.8%) females got pregnant. Hemogram parameters collected from patients on the day of IUI were recorded.

Results: In terms of age, infertility duration, BMI, gravida, parity, number of living children, abortion and stillbirth numbers, no statistically significant difference was found between the two patient groups which were created based on getting pregnant or not ($p>0.05$). No significant difference was found between the groups in terms of se-rum estrogen, progesterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), prolactin, and anti-mullerian hormone (AMH) levels, hemoglobin, white blood cell count, neutrophil count, lymphocyte count, platelet count, MPV, CRP, and P/ ($p>0.05$). A statistically significant difference was found in terms of N/L ($p<0.05$). The N/L ratio was found to be higher in the group whose members could not get pregnant after IUI compared to the group whose members could get pregnant after IUI.

Conclusion: We found that increased N/L is a marker that may negatively affect IUI success. According to these results, we believe that increased inflammation and throm-bosis may negatively impact pregnancy rates. When beginning treatment with assisted reproductive technology, hemogram parameters can be used as a guide as a simple and routine examination to predict pregnancy success, and it is a cost-effective method. However, larger series of studies and other inflammatory markers are needed.

Keywords: Unexplained infertility, intrauterine insemination, inflammation marker

ÖZ

Amaç: Bu çalışmada açıklanamayan infertilite nedeniyle klomifen sitrat (CC) ile ovülasyon indüksiyonu uygulanan ve intrauterin inseminasyon (IUI) yapılan hastalarda inflamasyon belirteçlerinin gebelik elde edilebilen ve gebelik elde edilemeyen hastalarda karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya Temmuz 2019 ile Aralık 2019 tarihleri arasında Sağlık Bilimleri Üniversitesi Ankara Etlik Zübeyde Hanım Kadın Hastalıkları Eğitim Araştırma Hastanesi Üremeye Yardımcı Tedavi Kliniği'nde açıklanamayan infertilite tanısı ile CC ile ovulasyon indüksiyonu uygulanan ve IUI yapılan 125 kadın dahil edil-di.Bunların 104 (%83.2)'ünde IUI sonucu gebelik elde edilemedi, 21 kadında (%16.8) gebelik elde edildi. Hastalardan IUI günü alınan hemogram parametreleri kaydedildi.

Bulgular: IUI sonucunda gebelik elde edilen ve elde edilemeyen her iki hasta grubu arasında; yaş, infertilite süresi, VKİ, gravida, parite, yaşayan çocuk sayısı, abortus ve ölü doğum sayıları açısından istatistiksel anlamlı farklılık saptanmadı ($p>0.05$). Her iki grup arasında; serum östrojen, progesteron, folikül uyarıcı hormon (FSH),lüteinleştirici hormon(LH), tiroid uyarıcı hormon (TSH), prolaktin ve anti müllerian hormon (AMH) düzeyleri, hemoglobin, beyaz küre sayısı, nötrofil sayısı, lenfosit sayısı, platelet sayısı, MPV, CRP ve P/L açısından istatistiksel anlamlı farklılık saptanmadı ($p>0.05$). N/L oranı açısından istatistiksel anlamlı farklılık saptandı ($p<0.05$). IUI sonrasında gebelik elde edilemeyen grupta, IUI sonrasında gebelik elde edilen gruba kıyasla N/L'nin daha yüksek olduğu belirlendi.

Sonuç: Çalışmamız sonucunda artmışN/L'ninIUI başarısını olumsuz yönde etkileyen bir belirteç olarak ortaya çıkmıştır. Bu sonuca göre artmış inflamasyonun ve trombozun gebelik oranlarını olumsuz etkileyebileceğini düşünüyoruz. Yardımcı üreme teknikleri ile tedaviye başlarken hemogram parametreleri, gebelik başarısını tahmin etmek için basit ve rutin bir muayene olarak yol gösterici olarak kullanılabilir ve uygun maliyetli bir yöntemdir. Bununla birlikte, daha büyük serilerde ve diğer inflamatuar belirteçlerin de incelendiği çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Açıklanamayan infertilite, intrauterin inseminasyon, inflamasyon markerleri

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INTRODUCTION

Infertility is defined as a couple's inability to have a baby despite having regular sexual intercourse for at least a year without using any form of contraception (1). Infertility affects 10-15% of the population and should be considered a couple's disease. When the World Health Organization (WHO) diagnosis protocols are examined, infertile couples are classified as having 40-45% female-related causes, 30-40% male-related causes, and the etiology of the infertility of the remaining 10-15% cannot be clarified or explained by diagnostic methods (2). Unexplained infertility refers to infertility condition in which the results of standard investigations, such as ovulation tests, tubal patency and uterine cavity compliance, and spermiogram, are normal, and while the underlying etiopathogenetic mechanisms are unknown, they are thought to be related to causes such as oocyte, tubal, or sperm function abnormalities that are not diagnosed by standard diagnostic procedures (3-6).

In patients with unexplained infertility due to altered levels of inflammatory markers, low-grade chronic inflammation is frequently blamed for the etiopathogenetic mechanisms of infertility (7, 8). Low-grade chronic inflammation is defined as an increase in inflammatory markers such as tumor necrosis factor-a (TNF-a), interleukin-1 (IL-1), interleukin-6 (IL-6) and C-reactive protein (CRP) (9, 10). Some studies suggest that some CBC parameters, such as white blood cell (WBC), neutrophil, and neutrophil-to-lymphocyte ratio (N/L), are also markers of inflammatory response (11-14). It has been shown that patients with endometriosis and polycystic ovary syndrome (PCOS) with infertility have a high N/L (15). Platelet-to-lymphocyte ratio (P/L) and mean platelet volume (MPV) have recently been identified as chronic inflammation markers (13, 16, 17). It has been demonstrated that the P/L is a biomarker of both thrombosis and inflammation, and platelet proliferation is thought to be the result of an ongoing pro-inflammatory process (18, 19). Furthermore, in patients with pancreatic or colorectal cancer, the P/L was found to be an independent risk factor for decreased survival (20, 21). Since platelet volume and platelet activation are closely related, MPV is an indicator of platelet activation (22).

It was determined that chronic inflammation can cause infertility. There are some studies on N/L, MPV and P/L in infertile women with PCOS (22). However, no studies have been conducted to examine the relationship between CBC inflammation markers and IUI outcomes in women with unexplained infertility. This study aimed to investigate whether CBC inflammation markers related to the possible role of chronic inflammation in infertility and IUI success are one of the etiopathogenetic mechanisms of unexplained infertility and whether there is a relationship between these markers and IUI success of women with unexplained infertility.

MATERIAL AND METHODS

The data of patients who received ovulation induction with clomiphene citrate (CC) or with CC and IUI treatment in the Reproductive Endocrinology and Infertility Clinic of University of Health Sciences Ankara Etlik Zübeyde Hanım Gynecology Training and Research Hospital between July 2019 and December 2019 were reviewed retrospectively. In line with the relevant university the permission by TUEK (Medical Specialty Education Board) and institutional permissions, the files of the patients included in the study were retrospectively reviewed from the patient files and electronic database and evaluated within the scope of the study.

Couples who could not conceive despite unprotected sexual intercourse for more than 1 year for couples whose female age was <35 years and more than 6 months for couples whose female age ≥35 were considered infertility. Patients aged between 18-42 years who were diagnosed with unexplained infertility and underwent IUI at the Infertility Clinic. Among the for the diagnosis of unexplained infertility who had normal ovarian morphology, no gynecologic pelvic pathology was detected on ultrasonographic examination, regular ovulatory cycles, normal spermiogram, normal hysterosalpingogram, no evidence of decreased ovarian reserve according to ovarian reserve tests.If any, and no pathology was detected in diagnostic laparoscopy, and patients with a BMI level of <30 kg/m2 were included in the study. Those with systemic diseases (hypertension, diabetes, asthma, etc.), endocrinologic abnormalities (hyper/hypothyroidism, hyperprolactinemia, etc.), proven by postmenopausal FSH levels, ovarian disease (endometrioma, etc.), hematologic disorders, malignancy, infectious disease or autoimmune disease, history of splenectomy, those who use anti-inflammatory drugs or glucocorticoids, patients with other chronic infections, hematologic disorders, malignancy, infectious disease or autoimmune disease, history of splenectomy, and other chronic inflammatory conditions (arthritis, etc.), patients which are smokers, and patients with a BMI≥30 kg/m² were excluded.

The study retrieved and reviewed file records of patients diagnosed with unexplained infertility and who underwent CC+IUI from the database. The study included 125 patients with unexplained infertility, and all patients received CC+IUI. The patients' age, BMI, duration of infertility, number of cycles, serum basal E2, basal FSH, basal LH, TSH, PRL, AMH, endometrial thickness on the day of HCG, follicle number and diameter on the day of HCG, on the day of IUI, WBC, neutrophils, lymphocytes, platelets, N/L, P/L, MPV, CRP, progesterone level (21th day of menstruation),pregnancy results were recorded and the results of the patients who achieved pregnancy post-treatment and those who did not were compared.

The statistical analysis was conducted in a computer environment using the SPSS Statistics 22 package program. Descriptive statistics and continuous variables are represented as mean, standard deviation, largest and smallest, respectively, whereas categorical variables are represented as number of cases (n) and percentage (%). The Kolmogorov-Smirnov test was used to assess variable distribution and normality analyses. When comparing the significant differences between study groups, Mann-Whitney U test and Independent Sample T-Test were used. The quantitative data was evaluated using Pearson's and Spearman's correlation tests. The 95% confidence interval was calculated for each variable, and the results were considered statistically significant for $p<0.05$.

RESULTS

In this study, 125 female patients aged between 18 and 42 with unexplained infertility underwent IUI after ovulation induction with CC. Demographic data of the females participated in the study are shown in Table 1.

Table 1. Distribution of demographic data of females who underwent IUI treatment

	Lowest - Highest	Mean
Age (years)	18-42	28.3±5.1
Duration of Infertility (month)	6-120	32.4±19.4
BMI (kg/m2)**	17-29	24±3.2
Gravida (n)	0-5	0.5±0.8
Parity (n)	0-3	0.28±0.6
Surviving Child (n)	0-3	0.28±0.6
Abortion (n)	0-3	0.21±0.54
Stillbirth (n)	0	0

*The results are given as mean (n). **BMI: Body Mass Index

In the follow-up of CC+IUI treatment applied to 125 female patients with unexplained infertility, it was found that CC+IUI treatment was unsuccessful in 104 (83.2%) of them and pregnancy did not occur. Of 21 (16.8%) females of whom CC+IUI treatment were successful, clinical pregnancy was detected in 20 (16%) of them and ectopic pregnancy in 1 (0.8%).

In terms of age, infertility duration, BMI, gravida, parity, number of living children, abortions, and stillbirths, no statistically significant difference was found between the groups ($p>0.05$). Table 2 shows the distribution of demographic data in terms of pregnancy status as a result of IUI in patients with unexplained infertility.

In 125 (100%) of the patients with unexplained infertility, ovulation induction with CC was performed. The meantreatment cycle for CC+IUI was 1.67±0.73 days, and the meanendometrial thickness was 8.62.4 mm. The mean number of follicles measuring 14-16 mm was determined as 0, while the mean number of follicles measuring 16-18 mm was 0.01±0.12 and the mean number of follicles measuring 18-20 mm was 1±0.36 (Table 3).

In terms of CC dose used for ovulation induction, number of cycles which pregnancy occur, endometrial thickness, and follicle sizes ($p>0.05$), no statistically significant difference was found between the group that did not achieve pregnancy with CC+IUI treatment and the group that did achieve pregnancy with CC+IUI treatment (Table 4).

In patients with unexplained infertility, a weak positive correlation between BMI measurements and CBC, lymphocyte count and platelet count (Figure 1) and a moderate positive correlation between BMI measurements and CRP were found (Figure 2) (WBC: $p<0.05$; r:0.231 and Lymphocyte count: $p<0.05$; r:0.299 and Platelet count: $p<0.05$; r:0.178 and CRP: $p<0.05$; r:0.439).

Table 2. Demographic Data Distribution in Terms of Pregnancy Occurred as a Result of IUI Treatment

	Pregnancy (-) n=104 (83.2%)	Pregnancy (+) n=20 (16%)	p
Age (years)	28.5±5.2	27.6±4.9	0.454[t]
Duration of Infertility (month)	32.5±19.7	32.1±18.8	0.842[m]
BMI (kg/m2)**	24±3.2	23.9±3.4	0.827[m]
Gravida (n)	0.5±0.95	0.4±0.5	0.742[m]
Parity (n)	0.2±0.6	0.3±0.4	0.284[m]
Surviving Child (n)	0.2±0.6	0.3±0.4	0.284[m]
Abortion (n)	0.2±0.5	0.04±0.2	0.119[m]
Stillbirth (n)	0	0	1[m]
BMI: Body Mass Index			

* The results are given as mean (n). **t: Independent Sample T-Test ***m: Mann Whitney-U Test

Table 3. Ultrasonographic and Gynecological Data Distribution in Terms of Pregnancy Occurred as a Result of IUI Treatment

	Pregnancy (-) n=104 (83.2%)	Pregnancy (+) n=20 (16%)	P
Clomiphene Citrate Dosage (mg/day)	55.7±17.4	54.7±15.03	0.876[m]
Number of Cycleswhich the pregnancy occur (n)	1.68±0.71	1.61±0.74	0.506[m]
Endometrial Thickness (mm)	8.5±2.4	9.1±2.6	0,337[t]
Dominant Follicle Sizes (HCG Day)			
14-16 mm	0	0	1 [m]
16-18 mm	0.001±0.09	0.04±0.2	0.207[m]
18-20 mm	1.1±0.3	1.04±0.5	0.217[m]

* The results are given as mean (n). **t: Independent Sample T-Test ***m: Mann Whitney-U Test

Table 4. Distribution of Early Follicular Phase Hormonal Data of Patients with Unexplained Infertility in terms of Pregnancy Status

	Pregnancy (-) n=104 (83.2%)	Pregnancy (+) n=20 (16%)	p
Estradiol (pg/ml)	45.7±20.7	41.6±16.8	0.392 [m]
Progesterone (ng/ml)	8.4±3.7	9±3.2	0.986[m]
FSH (mIU/ml)	7±1.8	7.2±1.7	0.646 [t]
LH (mIU/ml)	5.4±3.5	5.2±1.8	0.422[m]
TSH (mIU/l)	2±0.95	2±0.68	0.352[m]
Prolactin (ng/ml)	14.4±6.7	14.4±7.3	0.848 [m]
AMH (ng/ml)	3.9±2.5	4.1±2.2	0.632 [m]
FSH: Follicle Stimulating Hormone LH: Luteinizing Hormone TSH: Thyroid Stimulating Hormone AMH: Anti-Mullerian Hormone			

* The results are given as mean (n). **t: Independent Sample T-Test ***m: Mann Whitney-U Test

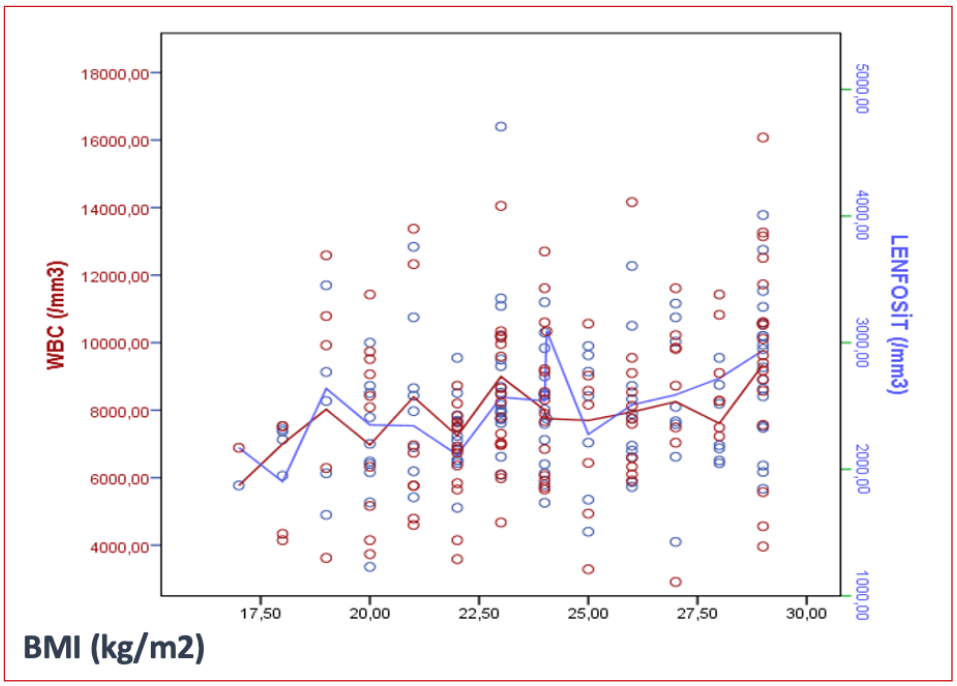

Figure 1. Correlation graph between BMI and WBC and lymphocyte counts in com-plete blood count

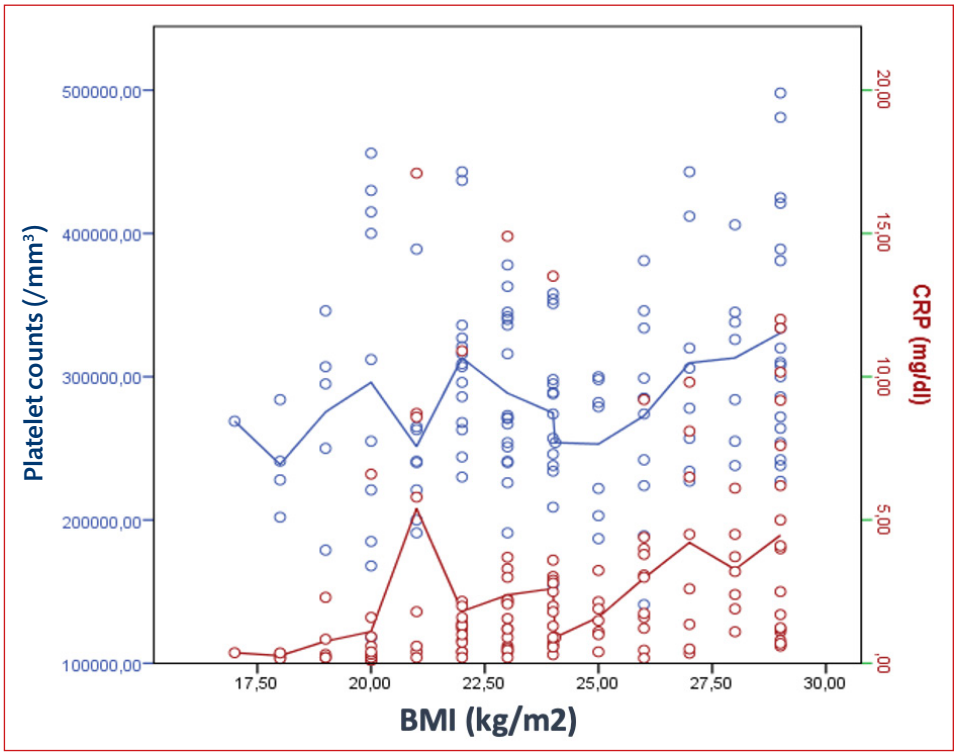

Figure 2. The graph demonstrating the correlation between BMI, platelet counts in complete blood count, and CRP

Table 5. Pregnancy Status Distribution of Complete Blood Count Parameters and Inflammatory Markers in Patients with Unexplained Infertility

	Pregnancy (-) n=104 (83.2%)	Pregnancy (+) n=20 (16%)	p
Hb (g/dl)	12.9±1.4	13.08±1.4	0.795[t]
WBC (/mm³)	8120±2017	8048±2295	0.883[t]
Neutrophil Count (/mm³)	4997±1589	4688±1802	0.428[t]
Lymphocyte Count (/mm³)	2455±673	2759±709	0.06[t]
Number of Platelets (/mm³)	289711±72182	296142±77022	0.713[t]
MPV (fl)	9.8±1.6	9.6±1.06	0.33[t]
N/L	2.1±0.77	1.74±0.61	0.028[m]
P/L	125.3±42.07	111.2±32.86	0.15[t]
CRP (mg/l)	2.91±3.54	1.94±2.06	0.394[m]

HB: Hemoglobin WBC: White Blood Cell N/L: Neutrophil/Lymphocyte Ratio P/L: Platelet Lymphocyte Ratio; CRP: C-Reactive Protein
* The results are given as mean (n). **t: Independent Sample T-Test ***m: Mann Whitney-U Test

The mean serum E2 level of patients with unexplained infertility was 45.02±20.1 pg/ml, while the mean serum progesterone level was 8.53±3.6 ng/ml. Their mean serum FSH level and mean serum LH level were respectively found to be 7.05±1.8 mIU/ml, and 5.42±3.35 mIU/ml. And the mean serum TSH level, the mean serum prolactin level and the mean serum AMH level were found to be 2±0.91 mIU/l, 14.4±6.8 ng/ml and 3.9±2.4 ng/ml, respectively. No statistically significant difference was found between the two groups in terms of serum E2, progesterone, FSH, LH, TSH, prolactin and AMH levels (p>0.05).

The mean hemoglobin level in the complete blood count of patients with unexplained infertility was detected as 13±1.41 g/dl. In the patients, the mean WBC was found to be 8108±2056 /mm³, mean neutrophil count to be 4945±1623 /mm³. While the mean lymphocyte count was 2506±686 /mm³, the mean platelet count was 290792±72736 /mm³. The mean platelet volume (MPV) was found to be 9.84±1.52 fl while the mean neutrophil/lymphocyte ratio (N/L) was found to be 2.07±0.76. While the mean platelet/lymphocyte ratio (P/L) was calculated as 122.9±40.8, the mean CRP level was calculated as 2.75±3.35 mg/dl. It was found that there

was no statistically significant difference in terms of hemoglobin, WBC, neutrophil count, lymphocyte count, platelet count, MPV, CRP and platelet/lymphocyte ratio (P/L) between the two groups which received CC+IUI treatment and divided based on the occurrence of pregnancy (p>0.05). Table 5 depicts the distribution of complete blood count parameters and inflammatory markers in terms of pregnancy status in patients with unexplained infertility.

A statistically significant difference was found between the groups who received CC+IUI treatment which was divided based on achieving pregnancy in terms of neutrophil/lymphocyte ratio (N/L) (p<0.05). The N/L ratio was found to be higher in the group in which pregnancy could not be achieved with CC+IUI treatment compared to the group in which pregnancy could be achieved with the aforementioned treatment (Figure 3).

A positive and weak statistically significant correlation was found between the infertility period of the patients and the neutrophil counts and N/L (Figure 4) (N/L: p<0.05; r:0.028 and neutrophil count: p<0.05).

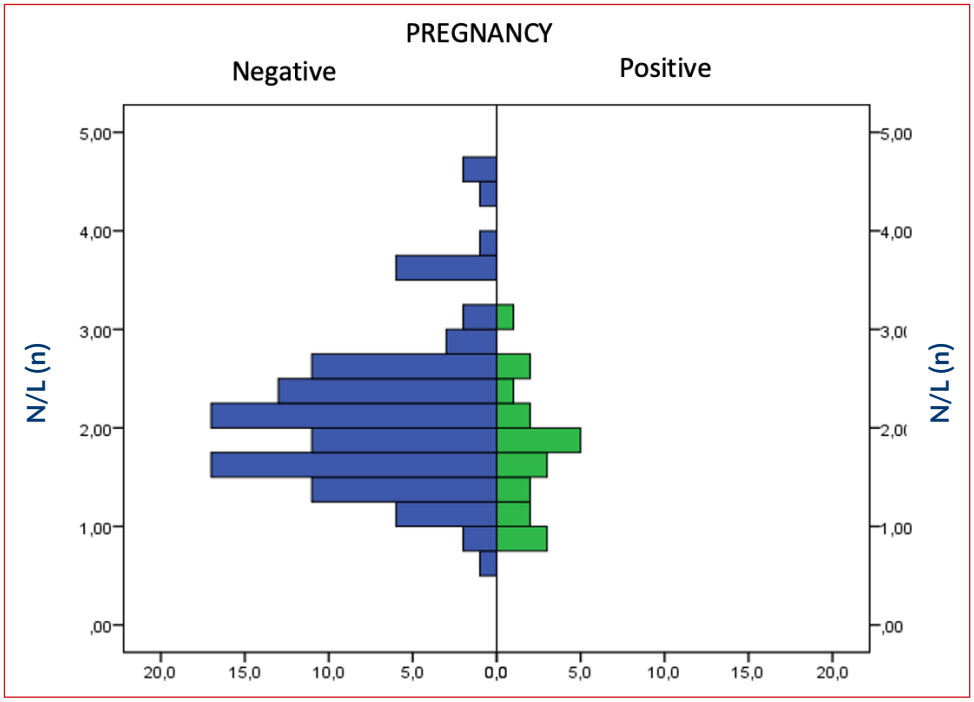

Figure 3. The graph showing the correlation between the pregnancy status and the N/L post-IUI-treatment

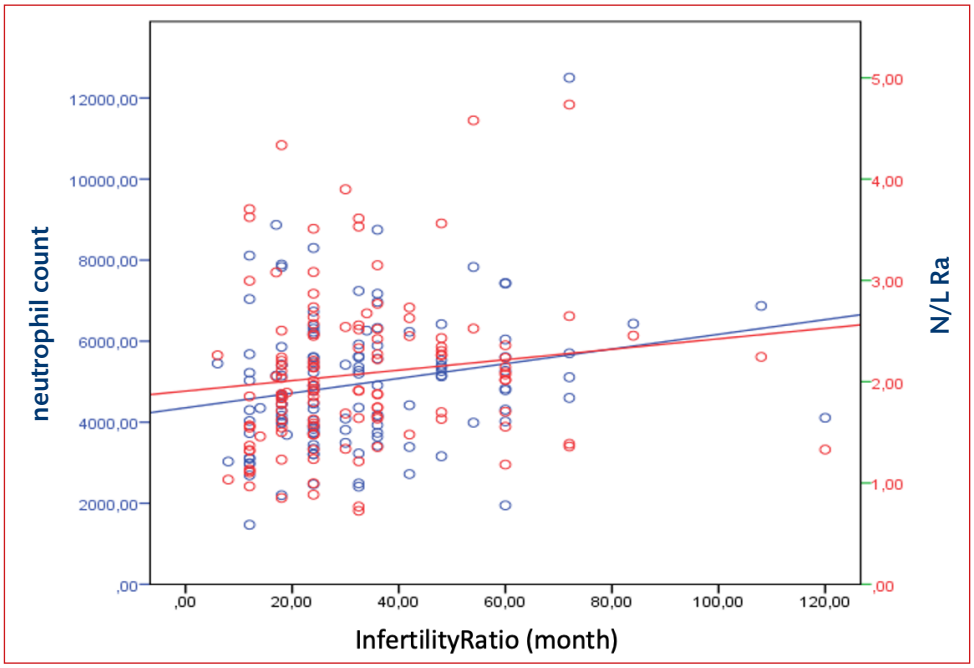

Figure 4. The graph showing the correlation between the duration of infertility and neu-trophil count and N/L in complete blood count

DISCUSSION

A negative statistically significant difference was found between the N/L and pregnancy between the group in whom pregnancy could not be achieved with CC+IUI treatment and in the group in whom pregnancy was achieved with CC+IUI treatment. It was found that there was no statistically significant difference between the groups in terms of WBC, neutrophil count, lymphocyte count, platelet count, MPV, P/L, and CRP. There was a statistically significant weak positive correlation between BMI measurements of the patients and WBC, lymphocyte count and platelet count, and a statistically significant moderate positive correlation between BMI measurements and CRP. A weak statistically significant positive correlation between the duration of infertility and neutrophil counts and N/L was observed.

Unexplained infertility is an infertility condition in which etiopathogenesis cannot be determined, although results of standard examinations including ovulation tests, tubal and uterine patency, and semen analysis are normal. Although the etiopathogenetic mechanisms are unclear, several mechanisms have been blamed, such as abnormalities related to ovarian, tubal or sperm function that cannot be diagnosed by standard diagnostic procedures. Recently, low-grade chronic inflammation has been blamed for altered levels of inflammatory markers (7). Studies have shown that ILs and pro-inflammatory factors are effective at the implantation stage in patients undergoing IVF(23). Studies have found elevated levels of interferon-γ (IFN-γ) and IL-2 and decreased TGF-β in the plasma of patients with unexplained infertility compared to fertile controls in the luteal phase (23). In addition, it has been shown that patients with unexplained infertility have higher serum levels of IL-2, IL-4, IL-6, IL-21, TNF-α and IFN-γ compared to fertile individuals (7). However, it is not cost-effective to measure these markers in all patients with unexplained infertility. IUI is one of the first preferred treatment options for infertile women who cannot get pregnant. Inflammation has been studied concerning assisted reproductive techniques (24). This study aimed to investigate whether whole blood parameters can be a guide in determining IUI success.

N/L hasbeen used as a marker of inflammation and predicting prognosis in malignancy, cardiovascular disease, autoimmune disease, endometriosis and PCOS in many studies. The N/L is an inexpensive and easily available marker that can be of practical use in the evaluation of chronic inflammatory conditions (25). According to a growing body of evidence, endometriosis may be a localized inflammatory disease with subclinical systemic manifestations (26, 27). Endometriosis has been linked to increased neutrophils and decreased lymphocytes, as well as systemic inflammation that shifts the differential WBC count (15). In a study of 745 patients (662 patients with endometriosis and 83 patients with benign ovarian tumor), Jing et al. found that the N/L was significantly higher in endometriosis compared to the control group and they suggested that it could be used as a marker (28). In contrast, they divided all endometriosis patients into groups based on their fertility status (fertile or infertile) and found that the N/L was significantly higher in the fertile group compared to the infertile group (15). In their study conducted with 153 patients (42 pregnant patients, and 111 infertile patients), Karlı et al. showed that although there was no statistical difference in patients who underwent IVF for unexplained infertility, the N/L tended to be higher in those who could not conceive compared to those who remained pregnant when median values were analyzed (29). Tola et al. discovered no significant difference in N/L between the two groups in a study of 246 patients (125 with unexplained infertility and 121 control subjects) (30). In addition, it was found that there was no significant difference between pregnancy status and N/L in patients treated for unexplained infertility (22). In their study, Çakıroğlu et al. evaluated the relationship between inflammation markers and pregnancy outcomes by regression analysis in 146 patients with PCOS undergoing IVF. It was found that there was no significant difference in the N/L (18). In our study, a statistically significant difference was found in terms of the N/L between the two groups in which pregnancy could not be achieved and in which pregnancy was achieved. We found that the N/L was higher in the group in which CC+IUI treatment was unsuccessful (pregnancy could not be achieved) when compared to the group in which CC+IUI treatment was successful.

Studies and meta-analyses have shown that obesity has negative effects on assisted reproductive techniques. It has been shown that adipose tissue can secrete hormones, adipokines, and cytokines and cause inflammation (31). Similar to our study, Heishanu et al. discovered a positive correlation between BMI and WBC, neutrophils, platelets, and CRP in 327 patients in their study (32). Madan et al. also found a positive correlation between CRP and BMI in their cross-sectional study of 80 patients (33). In order to objectively determine the effect of obesity in this direction, studies with a sufficient number of cases allowing comparison by grouping based on different BMI values must be designed. In the study, we discovered a statistically significant positive correlation between patients' BMI measurements and WBC, lymphocyte count, and platelet count at a positive and weak level, as well as a positive moderate correlation between BMI measurements and CRP.

We also found a weak statistically significant positive correlation between the duration of infertility and neutrophil counts and N/L. This may indicate that the duration of infertility is prolonged due to the deterioration of endometrial receptivity, fertilization and/or implantation due to chronic inflammation. Studies with a larger

sample size can be planned to delve deeper into the presence of weak positive correlations.

The P/L has recently emerged as a biomarker of the balance between thrombosis and inflammation. The ongoing pro-inflammatory state results in megakaryocytic lineage proliferation and relative thrombocytosis. High platelet counts and low lymphocyte counts have been proposed as risk indicators. They reflect both aggregation and the inflammatory pathway (18, 34). In their study conducted on 153 patients (42 pregnant patients and 111 infertile patients), Karlı et al. compared pregnancy and inflammation markers in patients who underwent IVF for unexplained infertility. In terms of MPV value, it was found that there was no significant difference between the two groups, but there was a significant difference in the P/L (29). In their study conducted with 292 patients (146 patients with PCOS, n:146), Çakıroğlu et al. reported that the P/L and MPV increased in patients with PCOS compared to the control group due to chronic inflammation. Furthermore, among 146 PCOS patients, MPV values were found to be significantly correlated with implantation and clinical pregnancy rates, and the P/L was found to be positively associated with miscarriages. In addition, a negative correlation was observed between WBC and neutrophil count, and oocyte count and oocyte quality (18). Tola et al. conducted a study with 246 patients (125 patients with unexplained infertility, and a control group consisting of 121 females) and found no significant difference between the two groups in terms of MPV and P/L (30). However, among patients with unexplained infertility, lymphocyte count was the only positive predictor for fertilization, and the P/L for implantation was the only negative predictor (22). In our study, although not statistically significant, we discovered that the median value of lymphocytes was lower and the median value of the P/L was higher in the group that could not conceive compared to those who did not become pregnant. In 129 patients who underwent IVF for unexplained infertility, Horikawa et al. discovered no correlation between pregnancy outcomes and CRP (35). Similarly, Taşdemir et al. found no difference in CRP levels between patients who had IUI and those who could not conceive in their study conducted on 42 patients (36). In our study, we found no statistically significant difference in terms of WBC, neutrophil count, lymphocyte count, platelet count, MPV, or P/L between the two groups that did not achieve pregnancy and those that did. Studies have shown that MPV and the P/L can be used as a marker of chronic inflammation. In our study, we did not find a significant difference in CRP values between both groups in accordance with the literature.

CONCLUSION

In our study, we found a statistically significant difference in terms of the N/L between the two groups in whom pregnancy was not achieved with CC+IUI treatment and pregnancy was achieved with CC+IUI treatment. We discovered that the N/L was higher in the group that received failed CC+IUI treatment versus the group that received successful CC+IUI treatment. Some studies show that chronic inflammation may be a factor in unexplained infertility. When beginning assisted reproductive techniques treatment, hemogram parameters can be used as a simple and routine guide to predicting pregnancy success rates and can be a guide for the evaluation of treatment options. Prospective studies with larger patient populations, as well as other assisted reproductive techniques, are needed.

Limitations

The sample size is small, there is no power calculation, and other ovulation induction treatments are not included. Another limitation is that the study was retrospective and data were obtained from a single center. In addition, one patient experienced an ectopic pregnancy thus she could not be included in the groups. Our study's strength is that it is the first to examine the relationship between WBC inflammation parameters, IUI treatment, and pregnancy outcome.

Conflict of Interest
No conflict of interest was declared by the authors.

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Authors' contributions
The authors contributed to the article as follows: Conceptualisation (HEK, MÇK), data collection (HEK, TE), data curation and analysis (HEK, TE), supervision and project administration (HEK, TE), writing original draft (MFK, HEK), review and editing (MFK, TE). All authors approved of the final version of the article prior to submission.

REFERENCES

1. Farquhar CM, Liu E, Armstrong S, Arroll N, Lensen S, Brown J. Intrauterine insemination with ovarian stimulation versus expectant management for unexplained infertility (TUI): a pragmatic, open-label, randomised, controlled, two-centre trial. Lancet. 2018;391(10119):441-50. Epub 2017/11/28.
2. L S, NH G, RG K. Clinical Gynecologic Endocrinology and Infertility2007.
3. Tafvizi F, Masomi M. Comparison of Serum Leptin Level in Women with Unexplained Infertility and Fertile Women in Iran. J Obstet Gynaecol India. 2016;66(Suppl 1):466-70. Epub 2016/09/22.
4. Blacker CM, Ginsburg KA, Leach RE, Randolph J, Moghissi KS. Unexplained infertility: evaluation of the luteal phase; results of the National Center for Infertility Research at Michigan. Fertil Steril. 1997;67(3):437-42. Epub 1997/03/01.
5. Guvenc G, Bektas Pardes B, Kinci MF, Karasahin KE. Effect of education and counselling on reducing pain and anxiety in women undergoing hysterosalpingography: A randomised controlled trial. Journal of Clinical Nursing. 2020;29(9-10):1653-61.
6. Kinci MF, Kinci OS. The opinions and thoughts of the women who had undergone hysterosalpingography for the first time: a qualitative study. International Journal of Caring Sciences. 2020;13(1):683-91.

7. An LF, Zhang XH, Sun XT, Zhao LH, Li S, Wang WH. Unexplained infertility patients have increased serum IL-2, IL-4, IL-6, IL-8, IL-21, TNFα, IFNγ and increased Tfh/CD4 T cell ratio: increased Tfh and IL-21 strongly correlate with presence of autoantibodies. Immunol Invest. 2015;44(2):164-73. Epub 2014/07/18.
8. Gong Q, Zhu Y, Pang N, Ai H, Gong X, La X, et al. Increased levels of CCR7(lo) PD-1(hi) CXCR5(+) CD4(+) T cells, and associated factors Bcl-6, CXCR5, IL-21 and IL-6 contribute to repeated implantation failure. Exp Ther Med. 2017;14(6):5931-41. Epub 2017/12/30.
9. Repaci A, Gambineri A, Pasquali R. The role of low-grade inflammation in the polycystic ovary syndrome. Mol Cell Endocrinol. 2011;335(1):30-41. Epub 2010/08/17.
10. Orio F, Jr., Palomba S, Cascella T, Di Biase S, Manguso F, Tauchmanovà L, et al. The increase of leukocytes as a new putative marker of low-grade chronic inflammation and early cardiovascular risk in polycystic ovary syndrome. J Clin Endocrinol Metab. 2005;90(1):2-5. Epub 2004/10/16.
11. Lee CD, Folsom AR, Nieto FJ, Chambless LE, Shahar E, Wolfe DA. White blood cell count and incidence of coronary heart disease and ischemic stroke and mortality from cardiovascular disease in African-American and White men and women: atherosclerosis risk in communities study. Am J Epidemiol. 2001;154(8):758-64. Epub 2001/10/09.
12. Brown DW, Giles WH, Croft JB. White blood cell count: an independent predictor of coronary heart disease mortality among a national cohort. J Clin Epidemiol. 2001;54(3):316-22. Epub 2001/02/27.
13. Templeton AJ, Ace O, McNamara MG, Al-Mubarak M, Vera-Badillo FE, Hermanns T, et al. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2014;23(7):1204-12. Epub 2014/05/06.
14. Elmas B, Kinci MF, Gök İE, Alkan A, Toğrul C, Sarikaya E. Is higher IgE levels in preeclamptic pregnancies suggest autoimmune pathophysiology? Çukurova Medical Journal. 2019;44:547-54.
15. Jing X, Li C, Sun J, Peng J, Dou Y, Xu X, et al. Systemic Inflammatory Response Markers Associated with Infertility and Endometrioma or Uterine Leiomyoma in Endometriosis. Ther Clin Risk Manag. 2020;16:403-12. Epub 2020/06/05.
16. Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: a link between thrombosis and inflammation? Curr Pharm Des. 2011;17(1):47-58. Epub 2011/01/21.
17. Akboga MK, Canpolat U, Yuksel M, Yayla C, Yilmaz S, Turak O, et al. Platelet to lymphocyte ratio as a novel indicator of inflammation is correlated with the severity of metabolic syndrome: A single center large-scale study. Platelets. 2016;27(2):178-83. Epub 2015/07/22.
18. Çakıroğlu Y, Vural F, Vural B. The inflammatory markers in polycystic ovary syndrome: association with obesity and IVF outcomes. J Endocrinol Invest. 2016;39(8):899-907. Epub 2016/03/17.
19. Sezgin B, Kinci MF, Pirinççi F, Camuzcuoğlu A, Erel Ö, Neşelioğlu S, et al. Thiol-disulfide status of patients with cervical cancer. Journal of Obstetrics and Gynaecology Research. 2020;46(11):2423-9.
20. Kwon HC, Kim SH, Oh SY, Lee S, Lee JH, Choi HJ, et al. Clinical significance of preoperative neutrophil-lymphocyte versus platelet-lymphocyte ratio in patients with operable colorectal cancer. Biomarkers. 2012;17(3):216-22. Epub 2012/03/20.
21. Smith RA, Bosonnet L, Raraty M, Sutton R, Neoptolemos JP, Campbell F, et al. Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. Am J Surg. 2009;197(4):466-72. Epub 2008/07/22.
22. Tola EN. The association between in vitro fertilization outcome and the inflammatory markers of complete blood count among nonobese unexplained infertile couples. Taiwan J Obstet Gynecol. 2018;57(2):289-94. Epub 2018/04/21.
23. Fornari MC, Sarto A, Berardi VE, Martínez MA, Rocha MG, Pasqualini S, et al. Effect of ovaric hyper-stimulation on blood lymphocyte subpopulations, cytokines, leptin and nitrite among patients with unexplained infertility. Am J Reprod Immunol. 2002;48(6):394-403. Epub 2003/02/28.
24. Spritzer PM, Lecke SB, Satler F, Morsch DM. Adipose tissue dysfunction, adipokines, and low-grade chronic inflammation in polycystic ovary syndrome. Reproduction. 2015;149(5):R219-R27.
25. Keskin Kurt R, Okyay AG, Hakverdi AU, Gungoren A, Dolapcioglu KS, Karateke A, et al. The effect of obesity on inflammatory markers in patients with PCOS: a BMI-matched case-control study. Arch Gynecol Obstet. 2014;290(2):315-9. Epub 2014/03/20.
26. Berbic M, Fraser IS. Regulatory T cells and other leukocytes in the pathogenesis of endometriosis. J Reprod Immunol. 2011;88(2):149-55. Epub 2011/01/29.
27. Tikhonchuk EY, Asaturova A, Adamyan L. Research Center of Obstetrics, Gynecology, and Perinatology, Ministry of Health of Russia, Moscow 117997, Ac. Oparina str. 4, Russia.
28. Jing X, Li C, Sun J, Peng J, Dou Y, Xu X, et al. Systemic inflammatory response markers associated with infertility and endometrioma or uterine leiomyoma in endometriosis. Therapeutics and Clinical Risk Management. 2020:403-12.
29. Karli P, Ozdemir AZ, Gulumser C. Do inflammation and hormone parameters have effects on IVF results in patients with unexplained infertility? Annals of Medical Research. 2019;26(7):1363-8.
30. Tola EN. The association between in vitro fertilization outcome and the inflammatory markers of complete blood count among nonobese unexplained infertile couples. Taiwanese Journal of Obstetrics and Gynecology. 2018;57(2):289-94.
31. Spritzer PM, Lecke SB, Satler F, Morsch DM. Adipose tissue dysfunction, adipokines, and low-grade chronic inflammation in polycystic ovary syndrome. Reproduction. 2015;149(5):R219-27. Epub 2015/01/30.
32. Herishanu Y, Rogowski O, Polliack A, Marilus R. Leukocytosis in obese individuals: possible link in patients with unexplained persistent neutrophilia. Eur J Haematol. 2006;76(6):516-20. Epub 2006/05/16.
33. Madan JC, Davis JM, Craig WY, Collins M, Allan W, Quinn R, et al. Maternal obesity and markers of inflammation in pregnancy. Cytokine. 2009;47(1):61-4. Epub 2009/06/10.
34. Balta S, Ozturk C. The platelet-lymphocyte ratio: A simple, inexpensive and rapid prognostic marker for cardiovascular events. Platelets. 2015;26(7):680-1. Epub 2014/12/31.
35. Horikawa T, Nakagawa K, Nakashima A, Ohgi S, Saito T, Saito H. Is high-sensitivity CRP useful as a predictor of fecundity? Fertility and Sterility. 2008;90:S226.
36. Tasdemir N, Sahin A, Celik C, Abali R, Guzel S, Uzunlar O, et al. Evaluation of human chaperonin 10 and high-sensitivity C-reactive protein levels of infertile women who underwent ovulation induction and intra-uterine insemination. J Obstet Gynaecol. 2015;35(7):707-10. Epub 2014/12/30.