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Original Article

The association between in vitro fertilization outcome and the inflammatory markers of complete blood count among nonobese unexplained infertile couples

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ABSTRACT

Objective(s): The purpose of our study was to evaluate whether the inflammatory parameters of complete blood count (CBC), including white blood cell (WBC), neutrophil-to-lymphocyte-ratio (NLR), platelet-to-lymphocyte-ratio (PLR), and mean platelet volume (MPV), had potential roles in the etiopathogenesis of unexplained infertility (UI) among nonobese women. We also aimed to investigate whether there could be an association between these markers and in vitro fertilization (IVF) success among nonobese women with UI.

Materials and methods: This was a retrospective clinical trial, including a total of 246 nonobese patients undergoing IVF procedures, 121 diagnosed as UI and 125 were age and body mass index (BMI) matched infertile controls who received IVF for tubal factor and male factor. Only normoweight (BMI<25 kg/m^2) participants were recruited to our study to rule out the effect of obesity on inflammation. CBC parameters were evaluated before ovarian stimulation protocol.

Results: All of the inflammatory parameters of CBC were distributed homogenously between groups. Platelet and lymphocyte count were positively correlated with fertilization rate (FR) among UI patients. Embryo count was positively correlated with platelet and negatively correlated with MPV. PLR was also positively correlated with luteinizing hormone on day 3 of cycle. After adjustment for age and BMI, there was a positive association between lymphocyte count and FR and a negative association between PLR and implantation among UI patients. None of the inflammatory markers of CBC were predictive for clinical pregnancy, take home baby, and clinical and biochemical abortion rates among nonobese UI patients.

Conclusion: Increased levels of CBC inflammation markers may have a negative impact on IVF outcomes among nonobese women with UI.

Introduction

Unexplained infertility (UI) refers to the condition of infertility in which the results of standard investigations, including ovulation tests (midluteal serum progesteron level), tubal and uterine patency (hysterosalpingogram), and semen analysis (spermiogram), are all normal [1]. The prevalence of UI ranges from 15 to 25% among infertile couples after their diagnostic procedures [2]. Although the etiopathogenetic mechanisms underlying UI are unclear, several mechanisms have been proposed, such as abnormalities related to oocyte, tubal, or sperm function, which cannot be diagnosed by standard diagnostic procedures [3–5].

In vitro fertilization (IVF) is an effective and successful therapeutic option for UI patients when other infertility treatments have failed to achieve a pregnancy. Moreover, IVF may provide additional diagnostic information regarding gamete function [6]. However, studies have shown lower success rates of IVF in women with UI than in other infertile women [6]. Higher failure rates of IVF in UI couples suggest that there may be other key factors which play essential roles in the absence of known infertility.

Low-grade chronic inflammation is defined as an elevation of several inflammatory markers, such as C-reactive protein (CRP), tumour necrosis factor-α (TNF-α), and interleukins (IL) [7–10]. Low-grade chronic inflammation is commonly blamed for the etiopathogenetic mechanisms of infertility due to the altered levels of inflammatory markers in unexplained infertile patients [11,12]. Studies have demonstrated an association between IL and proinflammatory

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factors and higher failure rates of IVF, especially in the implantation stage, among UI women [13]. Some complete blood count (CBC) parameters, such as white blood cell (WBC), neutrophil, and neutrophil-to-lymphocyte ratio (NLR), are thought to be inflammatory markers [14–17]. In recent years, the platelet-to-lymphocyte ratio (PLR) and mean platelet volume (MPV) are also increasingly used as markers of chronic inflammation [17–19]. It has been found that PLR could serve as a biological marker of both thrombosis and inflammation [20]. It is believed that increased proliferation of platelets is the result of an ongoing proinflammatory state [20]. MPV is also a marker of platelet activation because there is a close relationship between platelet size and platelet activation [20].

Although it has been documented that infertility involves chronic inflammation, it remains to be seen whether an increased inflammatory response affects IVF success rates. There are some reports about NLR, MPV, and PLR in infertile women with PCOS [20]; however, there is no report regarding CBC parameters in women with UI. Concerning the possible role of inflammation in infertility and IVF success, we aimed to investigate whether CBC inflammation markers are one of the etiopathogenetic mechanisms of UI and whether there is an association between these markers and IVF success among women with UI.

Material-method

This was a retrospective case control study performed in the IVF Unit of Suleyman Demirel University Faculty of Medicine, between January 2012 and December 2016. The study was approved by the Local Ethics Committee with the protocol number 72867572- 050-5026. Data were collected from the hospital files of infertile women who administered to our clinic for an IVF cycle.

Patients selection

We scanned all the files of patients undergoing IVF treatment. A total of 246 infertile patients were randomly selected for the study. *The unexplained group* was comprised of 121 women, and *the control group* was comprised of 125 infertile women, who were matched by age and body mass index (BMI). All the women in the sample were between the ages of 21 and 44 years old. Only normoweight (BMI<25 kg/m^2) participants were recruited to our study to rule out the effect of obesity on inflammation. All participants had normal ovarian morphology, demonstrated normal ultrasonographic examinations, and had regular ovulatory cycles.

Patients were diagnosed with UI after being evaluated based on standard infertility tests, according to the guidelines of the Practice Committee of the American Society for Reproductive Medicine [2]. These tests included assessments of spermiogram, ovulation, hysterosalpingogram, and, if indicated, ovarian reserve tests and laparoscopy. If the results of all these tests were normal, patients were accepted as UI. The inclusion criteria for the study group were a minimum of one-year infertility duration, a regular menstrual cycle of 21–35 days, evidence of ovulation (midluteal serum progesterone (PG) level >5 ng/ml), levels of the day 2 follicle stimulating hormone (FSH) being <10 IU/L, normal tubal patency confirmed with hysterosalpingogram, and normal sperm parameters (sperm density >15 million/mL; progressive motility >40%; and normal forms >4%; or total progressive motile sperm count >5 million according to World Health Organization criteria) [21].

The control group included women who underwent IVF for male or tubal factor related infertility. However, patients with hydrosalpinx, severe pelvic adhesions, endometriosis or pelvic inflammatory disease, severe male factor (azoospermia and severe oligoasthenospermia), and diminished ovarian reserve were not included as controls.

Exclusion criteria for all participants were systemic diseases (hypertension, diabetes, asthma, liver/kidney disease, etc), endocrinological abnormalities (hyper/hypothyroidism, hyperprolactinemia, etc), evidence of postmenopausal FSH levels, ovarian disease (endometrioma, etc), hematologic disorders (haemophilia, etc), malignancy, presence of infectious disease, autoimmune diseases, history of splenectomy, use of anti-inflammatory drugs or glucocorticoids, and other chronic inflammatory conditions (arthritis, etc). Patients who had a BMI of >25 kg/m^2 and demonstrated smoking and alcohol use were also excluded.

Data collection

We recorded the demographic features of patients, including age; partner's age; BMI; cycle count (if performed); duration of infertility; and day 3 basal hormone levels, including FSH, LH, and estradiol (E_2) levels. Moreover, thyroid stimulating hormone (TSH) and prolactin (PRL) levels that had been measured on a random day were recorded from the patients' files.

Stimulation protocol (agonist/antagonist), type of gonadotropin (recombinant/urinary), type of human chorionic gonadotropin (hCG) (recombinant/urinary), and starting dose of gonadotropin were also recorded from the patients' files.

Oocyte retrieval parameters, including the number of total retrieved oocytes, methaphase II (MII), MI, germinal vesicle (GV), oocytes with anomaly, and oocytes with empty zona (EZ), were noted from embryologic data. “An oocyte with anomaly” was defined on the basis of cytoplasmic (such as presence of abnormal cytoplasmic granulation, dark cytoplasm, vacuolization, inclusion body, refractile body and smooth endoplasmic reticulum) and extracytoplasmic (such as differences in size, anomaly in shape, thickness of zona pellucida, wideness of perivitelline space, presence of debris in perivitelline space, fragmented polar body) features of an oocyte. Fertilization (defined as the presence of two pronuclei one day after intracytoplasmic sperm injection), embryo number, and embryo quality were also recorded. In our IVF unit, the quality of embryos was evaluated on day 3 when the embryos were at least at the 8-cell stage, according to their morphological characteristics. The embryos were classified from Grade 1 (best quality) to Grade 3 (poor quality). Embryos with even-sized blastomeres and/or <5% fragments were classified as Grade 1; embryos with slightly-moderate size differences in blastomeres and/or 5–50% fragments were classified as Grade 2 (moderate quality); and embryos with markedly different-sized blastomeres and/or >50% fragments were classified as Grade 3.

We calculated the *fertilization rate (FR)* as the ratio of fertilized oocytes to MII oocytes. The results were classified as ‘*low FR*’ and ‘*normal FR*’, if the FR was <60% and ≥60%, respectively.

IVF outcomes, including implantation, clinical pregnancy (CP), take-home baby, biochemical abortion (BA), and clinical abortion (CA), were noted from the patient's file. *Implantation* was determined as positive hCG 14 days following embryo transfer. *CP* was established as the identification of an intrauterine gestational sac via transvaginal ultrasonographic examination. The *take-home baby* rate was determined by identifying whether the patients delivered or not. *BA* referred to a pregnancy that was diagnosed only by the detection of hCG in serum or urine and that did not develop into a clinical pregnancy. *CA* was defined as the disappearance of an initially proven gestational sac according to a transvaginal ultrasound.

Laboratory evaluation

We also scanned the CBC parameters of all the patients in the sample. In our IVF unit, we routinely scanned the CBC of all the