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Original Article

Do inflammation and hormone parameters have effects on IVF results in patients with unexplained infertility?

Pervin Karli[1], Ayse Zehra Ozdemir[2], Cagri Gulumser[3]

[1]Amasya University, Faculty of Medicine, Department of Obstetric and Gynecology, Amasya, Turkey
[2]Ondokuz Mayis University, Faculty of Medicine, Department of Obstetric and Gynecology, Samsun, Turkey
[3]Bilkent University, Faculty of Medicine, Department of Obstetric and Gynecology, Ankara, Turkey

Abstract

Aim: To invastigate the inflammatory process and hormone parameters as a result of underlying cause of unexplained infertility (UI)
Metarial and Methods: In total 153 patients with UI who underwent to intracytoplasmic sperm injection (ICSI) were included in the study. The blood hormones levels were obtained on the 2nd or 3rd day of the menstruation. Other blood count examinations were taken on the day of HCG administration. Relationship regarding embryo grade was also investigated.
Results: Of those 153 patients, only 42 of them got pregnant. Mean maternal age was 29.08±3.5 and mean duration of the infertility was 8.19±3.1 years, respectively. There was no statistically significant difference between pregnancy rate, embriyo grade, and FSH, progesterone, fT3, fT4, TSH levels (p>0.05). Also no significant difference was found between pregnancy rate, embriyo grade and hemoglobin, hemotocrit, platelet, mean platelet volume, neutrophil, lymphocyte counts, neutrophil lymphocyte ratio and platelet lymphocyte ratio (PLR) (p>0.05). However, a significant difference was found between embriyo grade and estradiol values (p<0.05). There was a negative correlation between hematocrit values and the oosit number collected with the number of embryos (p<0.05). PLR was found to be 110.9 (63.6 - 313.2) in pregnant women and 110.5 (51.8 - 390) in nonpregnant patients and the correlation between the PRL measured on HCG day and pregnancy rate.was significant (p=0.002). LH median values measured on HCG day were significantly lower in pregnant group (p<0.001).
Conclusion: We found that inflammation does not affect on IVF result and estradiol levels significantly effects on embriyo quality. Also there was an inverse correlation between hematocrit levels and the number of oocyte- and number of embryos.

Keywords: Infertility; blood cell count; inflammation; estrogen.

INTRODUCTION

Infertility is one of the primary health problem in many countries (1,2). Infertility is a condition in which pregnancy does not occur although no contraception method is used for a year (3). Whereas unexplained infertility (UI) is the condition that no reason found related to infertility despite the ovulation tests, semen analysis and tubal patency are evaluated as normal (4). UI prevalance varies between 22%-28% in World wide (4,5). In vitro fertilization (IVF) is an appropriate method to use in the UI women if other asissted repruductive technics were failed. IVF success in the UI group has been shown to be low despite many improvements (6). This is due to the fact that the reasons are not known and which has key role, are not yet explained (7). A number of possibilities have been proposed for the etiology of UI. But the exact cause is still unknown. Minor changes in ovulation, luteal phase and follicle development and sperm count at the lower limit of normal and motility disorders are those shown in patients with UI (8-11). It has been shown in several studies that there are markers such as tumour necrosis factor-a (TNF-a), C-reactive protein (CRP) and interleukins, which are thought to be within these key roles for UI and is proven to be increased in the case of mild chronic inflammation(12-15). But these markers are not cost-effective to be measured for all patients with UI. Desipite the fact that White Blood Cell (WBC) from Complete Blood Count (CBC) is the markers showing the inflammatory process in parameters such as neutrophil and neutrophil-to-lymphocyte ratio (NLR) (10,11,16,17). It is also stated to be a marker that can be used to demonstrate the inflammatory process and thrombosis in the platelet-to-lymphocyte ratio (PLR).

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Corresponding Author: Pervin Karli, Amasya University, Faculty of Medicine, Department of Obstetric and Gynecology, Amasya, Turkey, **E-mail:** parpi2300@hotmail.com

Increased platelet proliferation also indicates an ongoing inflammatory process. MPV (Mean Platelet Volume) is important because it provides the platelet activation and contributes to this inflammatory process by increasing the platelet volume (18). Considering that these parameters in the blood may have increased in the inflammatory process considered to be present in the infertility group that its cause is unknown such as UI and that the underlying cause may be useful in lighting and treatment process. The aim of this study was to investigate the effects of these cost-effective markers on the success of IVF in the UI infertile patients and on the rate of fertilization.

MATERIAL and METHODS

This is a retrospective chort study, which was conducted in UI patients who underwent to intracytoplasmic sperm injection (ICSI) between January 2017 and July 2018 at Ondokuz Mayıs University School of Medicine. Totally 153 patients was included in the study. Demographic details such as; the age, weight, age of the partner, the number of IVF trials, hormonal parameters at the beginning of the cycle, duration of infertility, protocol used in induction, the drug dose used in induction and the number of antral follicles detected on ultrasonography were recorded. This article was approved by the Ethics Committee of the Faculty of Medicine of Amasya University, Decision No 15386878-044.

Inclusion Criteria: Patients, who was at least one year of infertile, regular ovulation and menstruation, had normal spermiogram results and whose tubal patency was confirmed by HSG as normal were included in the study. The UI patients were selected according to the criteria of the American College of Obstetricians and Gynecologists (ACOG) guidelines. Spermiogram results according to ACOG criteria, whether ovulation, hysterosalpingogram, ovarian reserve tests and the patients diagnosed as infertility (according to the diagnostic laparoscopy results) were included in the study (18,19).

Exclusion Criteria: Patients with male factors, low ovarian reserve, present tubal factor and other explained causes of infertility among all patients who had ICSI were excluded from the study. In addition, patients with systemic chronic disease, endocrine disorders, chronic drug use, and patients with BMI> 25 were also excluded from the study.

All patients were evaluated in the early follicular phase. Recombinant FSH (Gonal F 450 IU; Merck Serono, Spain) was used from subcutaneous for stimulation. Ovarian stimulation was performed with antagonist protocol. A suitable dose of gonadotropin was applied based on the number of antral follicles, FSH level, patient age and body mass index. FSH, LH, E2, progesterone and serial ultrasonography measurements were performed during stimulation. When a follicle with a diameter of 12 mm or more was observed, its antagonist was given up to the day of oocyte aggregation (OPU). When two follicles with a diameter of 17 mm or more were observed in serial ultrasonography measurements, ovulation was stimulated subcutaneously by applying human chorionic gonadotropin (hCG) (Ovitrelle 250 mcg; Merck Serono, Switzerland). OPU was performed 36 hours after HCG injection. The embryo was then obtained by ICSI. One or two embryo transfers were performed according to the patient's age and the embryos' status. 100 mg progesterone (50 mg Progestin; Kocak, Turkey) were provided to each patient intramuscularly for luteal support. Venous blood samples was taken from all patients in the morning on the day of HCG after 12 hours fasting for pre-OPU.. CBC was performed using automatic blood counting device (Cell-Dyn 3700.Abbott®, USA). The levels of FSH, LH, E2 and progesterone were measured on the 2nd or 3rd day of menstruation and on the day of HCG in Roche Cobas device. The study protocol was approved by Amasya University Ethics Committee of Medical Faculty. To assess the success of IVF, the positive test of pregnancy in the blood, which is evidence of the presence of implantation, was used. On the 14th day following embryo transfer, b-HCG positivity was accepted as evidence of implantation. The primary outcome is the presence of implantation. The relationship between embryo count and embryo grade and CBC and hormone parameters were also investigated.

Statistical analysis: IBM SPSS (Statistical Package for Social Sciences) V23 was used for statistical analysis. The conformity of the data to the normal distribution was examined by Kolmogorov Smirnov test. Kruskal Wallis and Mann Whitney U tests were used to compare quantitative data that were not normally distributed. Qualitative data were examined by chi-square test. Quantitative data were presented as median (minimum-maximum) and qualitative data were presented as frequency (percentage). The significance level was taken as $p < 0.05$.

RESULTS

In total, 42 of 153 patients got pregnancy. The effects of hemogram parameters and follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), triiodothyronine (T3), thyroxin (sT4) and thyroid stimulating hormone (TSH) results on the outcome of pregnancy, embryo quality and embryo degree were statistically evaluated. Hemogram parameters hemoglobin (Hb) g/dl, Hematokrit (Htc)%, mean platelet volume MPV Fl, neutrophil, White blood cell (WBC), eosinophil and platelet (PLT) 103/uL were denominated in FSH and LH mU/ml, Estradiol pg/ml, sT3 pg /ml, sT4 ng/ml and TSH mIU/ ml. It was denominated in PRL (ng/ml).

The mean age of the women, mean partner's age, mean BMI (kg/m2) and duration of infertility (years) were 29.08±3.51, 33.82±6.23, 23.85±4.26 and 8.19±3.19; respectively. Mean cycle count was 1.86±0.91, and mean TSH (mIU/ml) value was 2.3±1.25. Mean PRL (ng/ml) values was 15.13±7.32 and mean day three basal hormone levels were E2 (pg/ml) 51.33±34.28. FSH (mIU/ml) and LH (mIU/ml) levels were 7.45±2.3, 4.56±3.19, respectively. Demografic details of the study population were demonsrated in Table 1.

The median value of E2 was obtained 42.8 pg/ml in non-pregnant and 41.7 pg/ml in pregnant. Estradiol median values measured at the beginning of the cycle did not significantly differ according to the pregnancy outcome (p=0,747). All parameters measured at the beginning of the cycle are shown in Table 2.

Table 1. Demografic details of the study population

Parameters	Non Pregnant n: 111	Pregnant n: 43	p
Age (years)	28.08±3.41	29.08±3.51	>0.05
Partner's age (years)	32.82±6.23	33.12±5.23	>0.05
BMI (kg/m^2)	22.82±4.26	23.47±4.26	>0.05
Duration of infertility (years)	8.19±3.18	7.79±2.19	>0.05
Cycle count	1.88±0.80	1.46±0.91	>0.05

Total number of patients 153
Serum samples were taken on the 2nd or 3rd day of menstruation

Table 2. Comparison of parameters according to pregnancy variable

	Non-Pregnant	Pregnant	p
Eosinophils*	0.1 (0 - 3.8)	0.1 (0 - 0.3)	0.576
WBC count*	6.7 (4.3 - 14.7)	6.6 (4.2 - 10.1)	0.94
Hematocrit*	40.2 (31.3 - 48.9)	39.7 (33.2 - 47.1)	0.853
Hemoglobin*	13.2 (9.6 - 16)	13 (10.2 - 15.3)	0.835
MPV*	7.8 (6 - 11.7)	7.8 (5.8 - 12.6)	0.727
Neutrophils*	4.1 (1.9 - 11.5)	4 (1.4 - 6.5)	0.892
PLT*	385.4 (173 - 434)	255.5 (158 - 439)	0.001*
RBC count*	4.6 (3.7 - 5.4)	4.6 (3.8 - 5.5)	0.746
NLR*	1.9 (0.5 - 6)	1.7 (0.8 - 5.2)	0.762
PLR*	110.5 (51.8 - 390)	151.9 (63.6 - 313.2)	0.002*
ST3*	3.3 (1.7 - 19.1)	3.4 (1.7 - 4.2)	0.905
ST4*	1.3 (0.5 - 4.1)	1.2 (0.5 - 1.7)	0.656
TSH*	2.2 (0 - 77.7)	2.3 (0.1 - 77.7)	0.515
TSH*	2.2 (0 - 77.7)	2.3 (0.1 - 77.7)	0.515
Estradiol**	1400 (215 - 5600)	1397.5 (290 - 3420)	0.917
Estradiol*	42.8 (0 - 3364)	41.7 (25.1 - 832.6)	0.747
FSH*	6.9 (1.4 - 49.8)	6.6 (3.9 - 13.3)	0.325
Progesterone**	0.6 (0.1 - 5.8)	0.6 (0.2 - 1.6)	0.967
LH**	1.9 (0.5 - 6.2)	1.2 (0.1 - 6.4)	<0.001
LH*	5.9 (1.5 - 34.1)	5.9 (3.1 - 21.3)	0.851
Follicle*	11 (1 - 32)	9.5 (1 - 38)	0.366

*Serum samples were taken on the 2nd or 3rd day of menstruation
**Serum samples were taken on the day of HCG

Table 3. Correlation analysis result of hemogram parameters

		oocyte	Age	Embryo count
Eosinophil*	r	-0.002	0.003	0.003
	p	0.986	0.971	0.971
Estradiol*	r	-0.128	-0.076	-0.008
	p	0.124	0.364	0.928
FSH*	r	-0.090	0.124	-0.157
	p	0.287	0.142	0.061
Hematocrit*	r	-0.171*	0.040	-0.181*
	p	0.044	0.643	0.032
Hemoglobin*	r	-0.125	0.052	-0.131
	p	0.141	0.545	0.123
LH*	r	0.085	-0.008	0.116
	p	0.309	0.926	0.165
MPV*	r	0.061	-0.105	0.091
	p	0.476	0.217	0.284
Neutrophil*	r	-0.031	0.091	-0.011
	p	0.713	0.285	0.898
PLT*	r	0.039	0.132	-0.022
	p	0.644	0.121	0.795
RBC count*	r	-0.103	-0.027	-0.126
	p	0.227	0.754	0.140
ST3*	r	0.126	-0.252**	0.145
	p	0.136	0.003	0.086
ST4*	r	-0.023	0.027	0.065
	p	0.789	0.750	0.447
TSH*	r	-0.086	-0.080	-0.003
	p	0.310	0.343	0.971
	p	0.794	0.606	0.720
FSH*	r	-0.090	0.124	-0.157
	p	0.287	0.142	0.061
TSH*	r	-0.086	-0.080	-0.003
	p	0.310	0.343	0.971
Estradiol*	r	0.605**	-0.268**	0.559**
	p	0.000	0.001	0.000
Progesterone*	r	0.080	-0.084	0.032
	p	0.326	0.300	0.694
Antral follicle count*	r	0.805**	-0.427**	0.718**
	p	0.000	0.000	0.000
WBC count*	r	0.022	0.044	0.031

*Serum samples were taken on the 2nd or 3rd day of menstruation
+/- signs show the direction of correlation

Table 4. Comparisons according to embryo grades

	G1	G2	G3	p
Eosinophil	0.1 (0 - 1.6)	0.1 (0 - 3.8)	0.1 (0.1 - 0.5)	0.638
Estradiol	42.8 (12.4 - 3364)	45.7 (0 - 429.6)	41.6 (7 - 94.1)	0.539
FSH	6.9 (1.8 - 49.8)	6.6 (3.3 - 16.4)	6.9 (1.4 - 15.4)	0.973
Hematocrit	40.1 (31.3 - 47.6)	39.5 (32.7 - 46.2)	40.4 (33.7 - 48.9)	0.763
Hemoglobin	13.3 (10.4 - 15.3)	13.1 (9.6 - 15.2)	13 (10.8 - 16)	0.531
LH	5.9 (1.8 - 34.1)	5.2 (1.7 - 30.1)	5.3 (1.5 - 11.9)	0.38
MPV	7.9 (6 - 11.7)	7.8 (5.8 - 11.7)	7.7 (6.5 - 12.6)	0.243
Neutrophil	4 (1.9 - 11.5)	3.9 (2 - 6.5)	4.2 (1.4 - 5.5)	0.481
PLT	274.5 (173 - 439)	277.5 (176 - 401)	268 (158 - 387)	0.931
RBC count	4.6 (3.7 - 5.3)	4.6 (3.8 - 5.5)	4.6 (4.2 - 5.3)	0.653
ST3	3.3 (1.7 - 10.9)	3.4 (2.8 - 19.1)	3.2 (2.8 - 3.8)	0.138
ST4	1.2 (0.5 - 3.3)	1.3 (0.9 - 4.1)	1.3 (1.1 - 1.5)	0.677
TSH	2.3 (0 - 77.7)	2.1 (0 - 7.3)	2 (1.1 - 7.2)	0.481
WBC count	6.7 (4.3 - 14.7)	6.7 (4.2 - 13)	6.8 (5 - 8.7)	0.641
LH	5.9 (1.8 - 34.1)	5.2 (1.7 - 30.1)	5.3 (1.5 - 11.9)	0.38
TSH	2.3 (0 - 77.7)	2.1 (0 - 7.3)	2 (1.1 - 7.2)	0.481
Estradiol	1490 (381 - 5600)	1300 (288 - 3018)	970 (215 - 2018)	0.03
Progesterone	0.6 (0.1 - 5.8)	0.6 (0.1 - 3.5)	0.5 (0.1 - 1.1)	0.109
LH	1.5 (0.1 - 6)	1.6 (0.3 - 6.4)	2.1 (1.1 - 4.4)	0.067
NLR	1.7 (0.8 - 5.2)	1.9 (0.5 - 6)	2 (0.9 - 3)	0.747
PLR	124.5 (51.8 - 313.2)	130.4 (58.1 - 390)	134.1 (72.1 - 214)	0.578

LH median values measured on HCG day were significantly lower in pregnant group (p<0.001). Also there was a significant difference in embryo grade according to Estradiol median values on day of HCG (p=0.03). The median values Estradiol obtained in G1, G2 and G3 were 1490 pg/ml, 1300 pg/ml and 970 pg/ml respectively. The mean number of platelets was detected 385.4 109 /lt (173 - 434109 /lt) in not pregnant group and 255.5109 /lt (158 - 439109 /lt) in pregnant group (p<0.001). PLR was found 110.9 (63.6 - 313.2) in pregnant group and 110.5 (51.8 - 390) in those who were not pregnant and the difference was statistically significant (p=0.002). Corralation results as follows; strong positive correlation between Estradiol levels and oocyte- numbers (r=0.605, p<0.000), weak negative correlation between Estradiol levels and age (r=0.268, p<0.001) and strong positive correlation between Estradiol levels and embryos number (r=0.559, p<0.000) were detected. A negative correlation was found between the number of oocyte- collected and the number of embryos occured with hematocrit values measured on HCG day. As the hematocrit values decreased, the number of oocyte- collected (0.171 p <0.040) and the number of embryos (r = -0.1181 p <0.032) increased. A significant relationship was found between the platelet levels measured on HCG day and pregnancy rates (p<0.05) (Table 3). Results according to embryo grades are shown in Table 4. There was no significant relationship between embryo grade and the evaluated values (p>0.05).

DISCUSSION

IVF is thought to be an effective treatment option in infertile women who cannot become pregnant with other treatment procedures (19). Numerous factors have been shown in scientific studies affecting the success of IVF. There are many studies on the effect of inflammation on IVF success (20). Inflammation is a key feature of endothelial disfunction (21-23). In this study, we aimed to investigate whether hemogram and hormone parameters have an effect on IVF success. Verit et al. found that mild inflammation affects slightly the success of IVF (24). Tola looked at hemogram parameters (WBC, platelet, neutrophil, and lymphocyte, NLR, PLR and MPV) in his study on non-obese patients with unexplained infertility. She found a significant positive correlation between

platelet and lymphocyte count and fertilization rate. In that study, two groups (explained and unexplained infertile) were compaired (7). In our study, the differences between the pregnant and not pregnant patients with UI were compaired. We found as the hematocrit values decreased, the number of oocyte- collected and the number of embryos increased. It is thought that increased hematocrit may impair implantation due to increased risk of thrombosis. We found a significant relationship between platelet, PLR and hematocrit levels and fertilization rate. Increased platelet count and decreased PLR are indicative of inflammation, which explains this significant effect on IVF results. In another study, there was no difference between unexplained infertile women and fertile women in WBC and lymphocyte levels between 20-24th days of menstrual cycle (25).

In IVF patients with unexplained infertility; glycodelin, vascular endothelial growth factor and interleukin-1 beta were seen in serum and follicle fluid, and these proinflammatory factors had no effect on the implantation success (26). Some studies have shown that patients with UI have elevated IFN g, IL2, and decreased TGF b levels compared with fertile women (TGF b is known as an endogenous anti-inflammatory cytokine (21). Furthermore, serum IL-2, IL-4, IL-6, IL-21, TNF-a and IFN-g levels were found to be elevated (11). But this parameters is not cost effective and is not screened as a routinely. The positive aspect of our study is that these parameters are both cost effective and routinely used parameters and do not provide additional costs. In our study, only hemogram parameters were used instead of expensive vascular endothelial growth factor and interleukin-1 beta. We found that these parameters as effective as others and cost saving. In another study, they found no correlation with hemogram parameters and a negative correlation was determined with LH levels and negative correlation with LH levels, positive correlation with lymphocyte count, positive correlation with PLR and PCOS was found (27). For UI, lymphocytes were identified only as a positive predictive marker and PLR was identified only a negative predictive marker (7,11). Increased PLR in endothelial disfunction results in hemostatic functions and thrombosis in arterioles (28,29). Çakıroğlu et all revealed that, there was a positive correlation between PLR and missed abortus in PCOS patients. Additionally, they were reported a negative correlation between MPV values and clinical pregnancy and implantation rates (27). Disruption of endometrial receptivness is considered among the causes of implantation failure and abortus in patients with UI and studies emphasize that immune factors play a very important role in implantation failure s (30). Increased platelet and decreased PLR are indicative of thrombosis and inflammation (27,31) . Again, the increase in platelet count indicates the on-going proinformatosis status (27). In our study, we observed a decrease in pregnancy rates with increased platelet and decreased PLR in accordance with these studies. At the same time, the increase in hematocrit levels and the decrease in pregnancy rates may show us the effects of increased thrombosis. In our study, the mean LH level on HCG day was 1.2 mU/mL. in pregnant and 1.9 mU/mL. in non-pregnant patients and this may give us some preliminary information about the negative impact of early luteinization on pregnancy. Grade 2 and grade 3 embrio are seen more frequently as the levels of estradiol decrease, and grade 1 embrio counts are seen more as the levels of estradiol increase. This situation shows us the effect of esradiol level on embryo quality. The limitation of our study was the other infalamatory parameters have not been studied simultaneously, and they reflected the data of a single IVF clinic.

CONCLUSION

We found that increased hematocrit levels, increased platelet counts and decreased PLR have negative effects on IVF success. As a result, increased inflammation and thrombosis may adversely affect pregnancy rates. When starting IVF treatment, hemogram parameters can be used as a guideline for us as a simple and routine examination to predict pregnancy success. And this is cost-effective method to measure the inflammation status rather than the other markers. However, there is a need for prospective studies in larger series and in which other inflammatory markers are examined at the same time.

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Pervin Karli ORCID: 0000-0003-4907-5890
Ayse Zehra Ozdemir ORCID:0000-0003-4232-4794
Cagri Gulumser ORCID: 0000-0002-6624-285X

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