Research Article / Araştırma Makalesi

The Effect of Hemogram Parameters in Predicting IVF-ICSI Cycle Success with Antagonist Protocol

Hemogram Parametrelerinin Antagonist Protokollü IVF-ICSI Siklus Başarısını Öngörmede Etkisi

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Abstract

Background: In IVF-ICSI cycles with GnRH antagonist protocol, the aim is to investigate the effects of hCG day hemogram values on OPU and IVF-ICSI success, implantation and clinical pregnancy rates.
Materials and Methods: Patients who underwent IVF-embryo transfer (ET) cycle after controlled ovarian stimulation (COS) ICSI treatment in a secondary care center between 2019 and 2020 were retrospectively examined. The effects of the differences in Hgb, HCT, Plt, WBC, P-LCR, PDW, RDW-CV, RDW-SD, and MPV values, which are among the hCG day CBC parameters of the cases, on the total oocyte (immature (M1)+mature (M2)+ germinal vesicle (GV)) and M2 oocyte counts obtained after OPU, the number of fertilized oocytes (two pronuclei (2PN)) obtained after IVF-ICSI, implantation and clinical pregnancy rates were evaluated.
Results: During the study, 171 patients were evaluated. No significant correlations were found between the Hgb, HCT, WBC, P-LCR, PDW and MPV values of the cases and the number of aspirated follicles, total oocytes and M2 oocytes after OPU (p>0.05). No significant correlations were found between the number of 2PN and frozen embryos obtained after IVF-ICSI, implantation and clinical pregnancy rates (p>0.05). A negative, low or insignificantly strong statistically significant correlation (r=-0.160 and p=0.037) was found between the platelet count and the number of follicles aspirated after OPU. It was observed that there were negative, low or insignificantly strong statistically significant correlations between the RDW-CV values of the cases and the number of 2PN and frozen embryos obtained after IVF-ICSI (r=-0.164, p=0.032 and r=-0.224, p=0.004, respectively). In addition, negative, low or insignificantly strong statistically significant correlations were found between the RDW-SD value and the number of follicles aspirated after OPU, total oocytes, and M2 oocytes (r=-0.247, p=0.001; r=-0.24, p=0.003; r=-0.220, p=0.004 respectively). Negative, low or insignificantly strong statistically significant correlations were found between the RDW-SD value and the number of 2PN, and frozen embryos obtained after IVF-ICSI (r=-0.219, p=0.004; r=-0.229, p=0.003 respectively).
Conclusions: In conclusion, no significant correlation could be found between women's hCG day Hgb, Hct, WBC, P-LCR, PDW and MPV values and OPU results or IVF-ICSI success, and these values were not predictive during the treatment process. It was determined that none of the hemogram parameters affected the implantation or clinical pregnancy rates in the treatment cycles. Although we found that OPU results worsened with increasing Plt or RDW-SD values, and fertilization success decreased with increasing RDW-SD and RDW-CV values, the strength of these correlations was weak.

Key Words: In-vitro fertilization, Hemogram parameters, Intracytoplasmic sperm injection, Pregnancy outcomes, Implantation

Öz.

Amaç: GnRH antagonist protokollü IVF-ICSI sikluslarında, olguların hCG günü hemogram değerlerinin OPU ve IVF-ICSI başarısına, implantasyon ve klinik gebelik oranlarına etkisini araştırmak amaçlandı.
Materyal ve Metod: İkinci basamak bir merkezde, 2019-2020 yılları arasında kontrollü ovaryan stimülasyon (KOS) sonrası ICSI tedavisi uygulanan IVF-embriyo transferi (ET) siklusu yapılan hastalar retrospektif olarak tarandı. Olguların hCG günü CBC parametrelerinden Hgb, HCT, Plt, WBC, P-LCR, PDW, RDW-CV, RDW-SD ve MPV değerlerindeki farklılıkların; OPU sonrası elde edilen toplam oosit (immatür (M1)+matür (M2)+ germinal vezikül (GV)) ve M2 oosit sayıları, IVF-ICSI sonrası fertilize oosit (iki pronükleus (2PN)) sayıları, implantasyon ve klinik gebelik oranlarına etkisi korelasyon analizleri ile değerlendirildi.
Bulgular: Çalışma süresince 171 hasta değerlendirildi. Olguların Hgb, HCT, WBC, P-LCR, PDW ve MPV değerleri ile OPU sonrası aspire edilen follikül sayısı, toplam oosit ve M2 oosit sayısı arasında; IVF-ICSI sonrası elde edilen 2PN ve freeze embriyo sayısı, implantasyon ve klinik gebelik oranları arasında anlamlı korelasyonlar bulunamadı (p>0.05). Platelet sayısı ile OPU sonrası aspire edilen follikül sayısı arasında negatif yönde, düşük veya önemsiz derecede kuvvetli istatistiksel olarak anlamlı bir korelasyon (r=-0.160 ve p=0.037) tespit edildi. Olguların RDW-CV değeri ile IVF-ICSI sonrası elde edilen 2PN ve freeze embriyo sayısı arasında negatif yönde, düşük veya önemsiz derecede kuvvetli istatistiksel olarak anlamlı korelasyonlar olduğu görüldü (sırasıyla r=-0.164, p=0.032 ve r=-0.224, p=0.004). Ayrıca, RDW-SD değeriyle OPU sonrası aspire edilen follikül sayısı, toplam oosit, M2 oosit sayısı; IVF-ICSI sonrası elde edilen 2PN ve freeze embriyo sayısı arasında negatif yönde, düşük veya önemsiz derecede kuvvetli istatistiksel olarak anlamlı korelasyonlar saptandı (sırasıyla r=-0.247 ve p=0.001; r=-0.24 ve p=0.003; r=-0.220 ve p=0.004; r=-0.219 ve p=0.004; r=-0.229 ve p=0.003).
Sonuç: Sonuç olarak, kadınların hCG günü Hgb, Hct, WBC, P-LCR, PDW ve MPV değerleri ile OPU sonuçları veya IVF-ICSI başarısı arasında anlamlı bir ilişki saptanamayıp, bu değerlerin tedavi sürecinde öngördürücü olmadığı görüldü. Hemogram parametrelerinden hiçbirinin tedavi sikluslarındaki implantasyon veya klinik gebelik oranlarını etkilemediği tespit edildi. Artan Plt veya RDW-SD değeriyle OPU sonuçlarının kötüleştiğini; artan RDW-SD ve RDW-CV değerleri ile fertilizasyon başarısının düştüğünü tespit etsek de bu korelasyonların gücü zayıftı.

Anahtar kelimeler: In-vitro fertilizasyon, Hemogram parametreleri, Intrasitoplazmik sperm enjeksiyonu, gebelik sonuçları, Implantasyon

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Introduction

It is estimated that 8-12% of couples worldwide are affected by infertility (1). In-vitro fertilization (IVF) is a type of assisted reproductive therapy (ART) and a complex procedure designed to combat the current issue of infertility and produce healthy live births. These extracorporeal fertilization of gametes procedures include conventional IVF and intracytoplasmic sperm injection (ICSI) (2). In these procedures, controlled ovarian stimulation (COS) protocols help to (3) achieve adequate oocyte count and ideal endometrial maturation. After a successful oocyte pick-up (OPU) procedure, it is inevitable to get a higher chance of pregnancy thanks to the free of error ICSI procedure and quality embryo selection. OPU findings and IVF-ICSI success are affected (4, 5) by various factors such as the age and health of the couples, the woman's body mass index (BMI), hormonal values, egg quality, ovarian reserve, and the presence of endometrial structure in pregnancy-appropriate receptivity.

The diagnosis of a wide range of pathologies, including anemia, infectious diseases, bleeding disorders, and immunological and hematological issues, can be achieved (6) by evaluating the quantitative and structural changes in cells during a hemogram test (complete blood count (CBC). Iron deficiency in women results in low hemoglobin and hematocrit (HCT) values are associated with infertility, abortion, low birth weight and preterm birth. It has been discovered that anemic women with inadequate iron levels are more susceptible to ovulation issues (7).

White blood cell (WBC) count and mean platelet volume (MPV) are systemic indices of inflammation, and studies demonstrate that chronic inflammatory processes can have detrimental impacts on gonadal activities in both men and women (8-11). Mean platelet volume is also an indicator of platelet activation since platelet size and platelet activation has a linear relationship between them. Due to the fact that the platelet distribution width (PDW) depicts the heterogeneity of platelet function, the activation or malfunction of platelets, endothelial cells, and monocytes has been reported in infertile women (8, 12, 13).

Numerous research on the function of CBC parameters, which are inflammatory markers exist. However, in predicting IVF success, there is a need to investigate the association between other CBC parameters and IVF-ICSI treatment success. In addition to inflammatory CBC parameters such as the WBC and MPV values on the day of human chorionic gonadotropin (hCG) injection, in this study, in IVF-ICSI cycles with a gonadotropin-releasing hormone (GnRH) antagonist protocol, we investigated how anemia or platelet functions affect the treatment process, implantation, and clinical pregnancy rates of the cases.

Materials and Methods

In the clinic of our Assisted Reproduction Treatment Center, 171 IVF-embryo transfer (ET) cycles that received ICSI treatment following COS were retrospectively reviewed between 2019 and 2020. In order to carry out the study, ethics committee approval was obtained from Private Memorial Şişli Hospital ethical committee for this study (Issue and Date: 003-09 May 2022) For all phenomena, the GnRH antagonist protocol was applied to achieve COS. The treatment has been initiated on the second or third day of the cycle. The subjects received a subcutaneous injection of 250 mcg of recombinant human chorionic gonadotropin (r-hCG) following the discovery of follicles measuring 17 mm or larger during follicular follow-up with transvaginal ultrasonography (TV-USG).

34-36 hours after recombinant human chorionic gonadotropin administration, oocyte retrieval (OPU) was performed under general anesthesia and TV-USG guidance. The oocyte-containing intrafollicular fluid was aspirated using an OPU needle (Cook 1735, 17 G) and transferred to 14 ml tubes (Falcon, BD France). Under a stereomicroscope(Nicon, Japan), oocytes from follicular fluid placed into a Petri dish (Corning 90 ml) were picked. The hyaluronidase enzyme was given to the selected oocytes, and the cumulus cells around the oocytes were separated with the aid of a 135-175 mm pipette. Oocytes isolated from cumulus cells were transferred to a specialized culture medium, housed in an incubator, and preserved until ICSI treatment. Germinal vesicle (GV), metaphase I (M1), metaphase II (M2), and pronucleus (PN) were defined as formations based on the maturation status of the oocytes collected during the oocyte collection process. The M2 oocytes were treated with intracytoplasmic sperm injection.

Following 3-5 days of sexual abstinence, a semen sample was sought from the male partner. Within 30 minutes of sampling, semen fluid was expected to become liquid. After examining the volume, viscosity, and pH of the semen, its morphology was assessed. Sperm count and its morphology were analyzed in accordance with World Health Organization (WHO) requirements by examining sperm under a 20X magnification light microscope (14). Then the sperm was made ready for the ICSI treatment.

Transfer of a fresh embryo was realized between days 3 and 6 following OPU. In addition to frozen transfer cycles following embryo cryopreservation, fresh transfer cycles and the number of transplanted embryos were also recorded. Blood levels of beta-hCG were used to determine the pregnancy status of the cases 12 days after the transfer. 7-10 days later, the endometrial cavity of women with a positive pregnancy test (beta-hCG>30IU/L) was evaluated by TV-USG to evaluate the gestational sac (GS). Seven weeks after ET, clinical pregnancies were confirmed by GS and fetal heartbeat on TV-USG or by identification of trophoblastic tissue in the abourtus material. After establishing a differential diagnosis for ectopic pregnancy, it was determined that biochemical pregnancy formed in cases in which no GS was visible on TV-USG. The implantation rate is defined as the ratio of the number of pregnancies with a formed gestational sac to the number of embryos transplanted. In the light of these definitions, the CBC parameters of Hgb, Hct, Plt (Platelet), WBC, P-LCR (Platelet large cell

ratio), PDW, RDW-CV (Red blood cell distribution width variation coefficient), RDW-SD (Red blood cell distribution width standard deviation) on the hCG cases and differences in MPV values; The effects on total oocytes (immature (M1) + mature (M2) + germinal vesicle (GV)) and M2 oocytes obtained after OPU, fertilized oocytes (two pronuclei (2PN)) numbers after IVF-ICSI, implantation and clinical pregnancy rates were investigated.

Age, duration and cause of infertility, history of assisted reproductive technology (ART) (unsuccessful intrauterine insemination (IUI) and IVF attempt), and demographic features of the couples; The female partner's BMI, gravity, total antral follicle (AF) count in both ovaries prior to treatment, follicle stimulating hormone (FSH) and luteinizing hormone (LH) values on the third (D3) day of the cycle, and r-hCG levels were evaluated.

Statistical Analysis

Continuous variables were represented by mean ± standard deviation, (minimum-maximum), while numbers and percentages represented categorical data. The Kolmogorov-Smirnov Goodness of Fit Test was used to analyze intergroup normality of continuous variables. As the data did not follow a normal distribution, the Kruskal Wallis Analysis (aPost hoc: Mann Whitney U Test with Bonferroni correction) was used to compare the three groups, while the Mann Whitney U Test was used to compare the two groups. Chi-Square Test and Fisher's Exact Test were used to compare categorical data. The IBM SPSS Package Program version 26.0 was used for the analyses (IBM Corporation, Armonk, NY, USA). The statistical significance level was taken as $p<0.05$ The significance level established by the Mann Whitney U test with Bonferroni correction was determined as $p<0.0016$.

In correlation analysis, the correlation coefficient "r" was used to measure the correlation coefficient. This coefficient's value ranges from -1 to 1, and it was determined that the closer "r's" absolute value is to 1, the greater the association (linear relationship between the variables).

Results

While the median age of 171 women who underwent assisted reproductive technology was 31 (range: 21-47), the median age of their partners was 34 (range: 23-60), and the average length of marriage was 5.68 years. Patients had a median BMI of 24.8 (17.8-35.6) kg/m2. While 25.1% of cases had a history of one failed IVF attempt, 15.9% had a history of two or more failed attempts. While 16.4% of the cases had a history of one failed IUI attempt, 18.1% of the cases had a history of two or more unsuccessful IUI attempts. Considering the causes of infertility requiring in-vitro fertilization, it was determined that female infertility (40.3%) was the most common cause cumulatively, while male infertility (other abnormal spermiogram parameters other than azoospermia, varicocele, endocrine reasons, congenital problems, etc.) was the cause for which IVF-ICSI was planned most frequently when the reasons were evaluated alone (Table 1).

Table 1. Certain sociodemographic characteristic of the cases

	Med (min-max)
Age (year) ***	31 (21-47)
Age of the Partner (year)	34 (23-60)
Date of Marriage	5,68 (0,58-22)
Gravida	0 (0)a
BMI (kg/m^2)	24.8 (17.8-35.6)
Failed IVF attempt	
0	101 (59,1%)
1	43 (25,1%)
2	14 (8,2%)
≥3	13 (7,7%)
Failed IUI attempt	
0	107 (62,6%)
1	28 (16,4%)
2	26 (15,2%)
≥3	10 (5,9%)
Infertility etiology	
Unexplained infertility	21 (12,3%)
Male infertility	63 (36,9%)
• **Azoospermia**	9 (5,3%)
• **Other causes**	54 (31,6%)
Female infertility	69 (40,3%)
• **Tubal causes**	21 (12,3%)
• **PCOS**	18 (10,5%)
• **POI**	6 (3,5%)
• **Endometriomas**	4 (2,3%)
• **Other causes**	20 (11,3%)
Female and male infertility	15 (8,8%)
PGD	3 (1,8%)
Total	171 (100,0)

BMI: *Body mass index,* ***IVF:*** *In-vitro Fertilisation ,* ***IUI:****Intrauterine insemination,* ***PCOS:*** *Polycystic ovary syndrome,* ***POI:****Primary ovarian insufficiency,* ***PGD:***

Preimplantation genetic diagnosis.

Table 2 provides the median, lowest, and maximum values for the CBC parameters of the cases. No significant association was detected between the values of hemoglobin, Hct, WBC, P-LCR, PDW, and MPV and the number of follicles aspirated following OPU, the total number of oocytes, and M2 oocytes (p>0.05). In addition, there was no association between these CBC values and the number of 2PN and frozen embryos retrieved after IVF-ICSI, implantation, and clinical pregnancy rates (p>0.05) (Table 3).

A negative, low or insignificantly strong statistically significant correlation was detecterd between the platelet count and the number of follicles aspirated following OPU (r=-0.160 and p=0.037) (Table 3).

Statistically significant negative, weak or insignificantly strong associations between the RDW-CV values of the cases and the number of 2PN and frozen embryos acquired during IVF-ICSI (r=-0.164, p=0.032 and r=-0.224, p=0.004, respectively) were found. In addition, with RDW-SD value, number of follicles aspirated after OPU, total oocytes, and number of M2 oocytes;Negative, low, or insignificantly strong statistically significant correlations were found between the number of 2PN and frozen embryos obtained after IVF-ICSI (r=-0.247 and p=0.001, respectively; r=-0.24 and p=0.003; r=-0.220 and p=0.004, r=-0.219 and p=0.004, r=-0.229 and p=0.003) (Table 3).

Tablo 2. Analysis of hemogram parameters of the cases

	Median value (min-max).
Hgb (g/dL)	13.0 (9.0-15.5)
Hct (%)	40.0 (31.0-94.0)
PLT (10^3/µL)	291.0 (160.0-531.0)
WBC (10^3/µL)	8.0 (4.0-16.0)
P-LCR (%)	24.0 (12.2-43.0)
PDW (fL)	12 (8.8-22.0)
RDW-CV (%)	13 (10.9-19.0)
RDW (fL)	40.7(34.4-55.0)
MPV (fL)	9.5 (6.0-14.0)

***Hgb**: Hemoglobin, **Hct**: Hematocrit, **Plt**: Platelet, **WBC**: Leukocytes, **P-LCR**: Platelet large cell ratio, **PDW**: Platelet Distribution Width, **RDW-CV**: Red blood cell distribution width variation coefficient, **RDW-SD**: Red blood cell distribution width standard deviation and **MPV**: Mean platelet volume.*

Table 3. Correlation analysis of hemogram parameters of the cases and the results of OPU and IVF-ICSI treatment

			Hgb	**Hct**	**Plt**	**WBC**	**P-LCR**	**PDW**	**RDW-CV**	**RDW-SD**	**MPV**
OPU	**Aspirated follicule**	**r**	.006	.009	**-.160**	.031	-.037	-.125	-.132	**-.247****	-.018
		p	.934	.907	**.037**	.691	.636	104	.085	**.001**	.816
		N	171	171	**171**	171	169	171	171	**171**	171
	Total oocyte	**r**	-.016	-.019	-.120	.039	-.058	-.171*	-.113	**-.224****	-.073
		p	.835	.803	118	.608	.451	.025	140	**.003**	.343
		N	171	171	171	171	169	171	171	**171**	171
	M2 oocyte	**r**	.054	.033	-.118	.017	-.036	-.111	-.149	**-.220****	-.033
		p	.480	.667	.123	.828	.639	147	.052	**.004**	.671
		N	171	171	171	171	169	171	171	**171**	171
IVF-ICSI	**2 PN**	**r**	.022	.040	-.149	.014	-.106	-.138	**-.164***	**-.219****	-.115
		p	.778	.606	.052	.858	169	.072	**.032**	**.004**	134
		N	171	171	171	171	169	171	**171**	**171**	171
	Obtained frozen embryos	**r**	-.010	.027	-.055	-.088	-.018	-.105	**-.224****	**-.229****	-.048
		p	.902	.729	.487	.263	.819	.184	**.004**	**.003**	.544
		N	163	163	163	163	161	163	**163**	**163**	163
Implantation rate		**r**	-.092	-.193	-.079	.094	.022	-.131	-.090	-.044	-.067
		p	.457	115	.524	.446	.858	.285	.468	.720	.589
		N	68	68	68	68	68	68	68	68	68
Clinical pregnancy rate		**r**	-.030	-.109	.022	.076	-.067	-.205	.017	-.013	-.041
		p	.809	.375	856	539	.585	.093	.891	.913	.738
		N	68	68	68	68	68	68	68	68	68

*Spearman's rank correlation coefficient

***OPU:** Oocyte retrieval procedure**, IVF-ICSI**: In-vitro fertilization-intracytoplasmic sperm injection, **M2 oocyte:** Mature oocyte, **2PN:** Two pronuclei (fertilized oocyte), **Hgb**: Hemoglobin, **Hct**: Hematocrit, **Plt**: Platelet, **WBC**: Leukocytes, **P-LCR**: Platelet large cell ratio, **PDW**: Platelet Distribution Width, **RDW-CV**: Red blood cell distribution width variation coefficient, **RDW-SD**: Red blood cell distribution width standard deviation and **MPV:** Mean platelet volume.*

Discussion

In this study, no significant association was found between the HCG day CBC parameters of women, Hgb, Hct, WBC, P-LCR, PDW, and MPV values, and OPU results or IVF-ICSI success; therefore, these values were not predictor for treatment outcomes. It was determined that none of the hemogram parameters impacted implantation or clinical pregnancy rates during the treatment cycles.

It was determined that the higher the Plt value on the hCG day of the cases, the fewer the number of aspirated follicles during OPU. Red cell distribution width standard deviation was found to be inversely proportional to the number of follicles aspirated and collected oocytes following OPU, or the success of fertilization following IVF-ICSI. Similarly, it was found that as RDW-CV value increased, fertilization success

in cycles reduced. Within this context, the weakness of the intensity of negative correlations in all analyses should not be neglected.

Tola (8), demonstrated that increasing the Plt value in cases of unexplained infertility boosted the number of embryos retrieved following IVF treatment and the fertilization rate. Furthermore, Tola discovered that the MPV value and the number of embryos created were inversely proportional in her study. One possible explanation for the discrepancy in our study's result is that the researcher only collected data on women who were not obese and had unexplained infertility. However, as evidenced by our findings, it was concluded that none of the inflammatory marker CBC values were indicative of clinical pregnancy rates.

Red cell distribution width (RDW), is a measure of the variability of red blood cell volume that is used as part of the standard CBC (15). RDW typically increases when iron deficiency anemia, folate deficiency anemia, and vitamin B12 deficiency anemia occur (16). The iron level is vital in supporting ovarian functions (7), while the folate level is important in embryo development (17). Indeed, the increase in RDW-SD value and decrease in the number of follicles aspirated and collected oocytes following OPU, as well as the decrease in fertilization success with increasing RDW-SD and RDW-CV values, can be explained in light of this piece of information.

An et al., (9) discovered that the PDW value had a negative impact on embryo quality in IVF-ICSI cycles. Although a linear relationship between the rate of quality embryos and the rate of pregnancy was expected, they were unable to establish any statistically significant relationship between PDW value and clinical pregnancy rates. Similarly, we concluded that the cases' PDW value had no effect on the implantation or clinical pregnancy rates in the cycles.

The current study's main limitations can be listed as; it was designed retrospectively, had a small population of infertile women, and used patient data from a single ART center. Nonetheless, the findings merit consideration, and it is believed that prospective studies with a larger number of cases, as well as sub-parameters such as the quality of the embryo acquired after ICSI on the third and fifth days, are required to obtain much more significant results from the studies.

Conclusion

In conclusion, we found that in IVF-ICSI cycles, none of the CBC values influenced implantation or clinical pregnancy rates. Another result suggests that the hemogram parameters Hgb, Hct, WBC, P-LCR, PDW, and MPV had no effect on OPU or IVF-ICSI success. We detected that the OPU outcomes deteriorated as Plt, or RDW-SD values increased; and that fertilization success decreased as RDW-SD and RDW-CV values increased. Even though the correlation impact remains weak, we believe that these results contribute to the literature.

Ethical Approval: *Ethical approval was obtained from Private Memorial Şişli Hospital for this study (Date: 09.05.2022, No:003)*

Author Contributions:
Concept: U.D., N.P., G.O., Y.Ç.
Literature Review: U.D., N.P., G.O., Y.Ç.
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Analysis and interpretation: U.D., N.P., G.O., Y.Ç.
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