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Relationship between inflammatory markers, hormonal profiles, and sperm parameters

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ABSTRACT

OBJECTIVE: The aim of this study is to evaluate the relationship between semen parameters, complete blood count, and hormone levels on the day of spermiogram.

METHODS: Semen parameters of 230 patients who were examined for full blood count test and hormone levels on the day of spermiogram were included in the study. Patients were grouped according to the total motile sperm count (TMSC), semen parameters, hemogram, and hormone levels were compared between groups.

RESULTS: No statistically significant difference was found between groups in neutrophil ratios, neutrophil, lymphocyte, platelet counts, neutrophile-to-lymphocyte ratio (N/L), and platelet-to-lymphocyte ratio (P/L). However, white blood cell (WBC) and lymphocyte counts were weakly positively correlated with sperm concentration (p=0.021, p=0.026), and a weakly significant positive correlation was found with WBC and neutrophil count for motility (p=0.038, p=0.004). FSH level was found to be lower in cases with TMSC >20 m than those with TMSC <5 m and 5-10 m (p=0.004, p=0.022). LH was found to be lower in cases with TMSC >20 m than those with TMSC <5 m (p=0.048). A negative correlation was found for both FSH and LH levels with sperm concentration, motility, and TMSC (p<0.001, p=0.014).

CONCLUSION: In this study, a significant negative correlation was demonstrated between FSH, LH levels and sperm concentration, motility, TMSC. N/L and P/L cannot be used as predictive markers of sperm quality. The results of a significant positive correlation between WBC, neutrophil counts, and sperm parameters encourage researchers to conduct prospective randomized controlled trials with larger sample sizes and different inflammatory and hormonal markers.

Keywords: FSH; LH; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio; semen parameters.

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Male infertility has been associated with various factors such as genetic disorders, venous insufficiency, and infections, but the mechanism of reproductive response to systemic changes has not been clearly elucidated [1]. Since a link between the genitourinary and immune systems has been established, inflammatory processes in male infertility have become the focus of researchers [2].

In the diagnosis and response to treatment of many inflammatory diseases, the levels of inflammatory markers in the blood and their ratio to each other are widely used (e.g. neutrophil/ lymphocyte (N/L), platelet/ lymphocyte (P/L)) [3]. However, there is limited information on the use of these markers in infertility.

It is clear that hormonal changes affect the hypothalamic-pituitary-testicular axis and lead to impaired

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sperm production. Early data on the relationship between hormone levels and semen parameters have been studied only in infertile patients or patients with systemic problems [4–6], subsequent studies in fertile men have attempted to establish hormonal thresholds for predicting sperm quality [7], the link between inflammatory indicators, hormone profiles, and semen measures has not been investigated in any published research.

Our study's objective is to assess the association between semen parameters, complete blood count, and hormone levels on the day of spermiogram.

MATERIALS AND METHODS

Among the patients whose spemiogram tests were examined at Zeynep Kamil Women and Children's Training and Research Hospital between January 2019 and December 2020, 230 patients with full blood and hormone values were included in the study. After 2–5 days of abstinence, semen samples were collected from the patients by ejaculation, and a spermiogram was performed in the andrology laboratory of Zeynep Kamil Women and Children's Training and Research Hospital and evaluated in accordance with the 2010 World Health Organization guidelines.

Patients who were eligible for participation (no systemic diseases, no chronic medication use) were included in the study. Patients were evaluated for total motile sperm count (TMSC), age, semen parameters (volume, number, concentration, motility), hemogram values (white blood cell (WBC), neutrophil (Neu), lymphocyte (Ly), platelet (Plt), neutrophil percentage (Neu%), hemoglobin (Hgb), hematocrit (Hct%)), hormone levels (thyroid stimulating hormone (TSH), follicle-stimulating hormone (FSH), prolactin (PRL), luteinizing hormone (LH)) were compared between groups. Correlation analysis between hemograms, hormone levels, and sperm parameters was used.

The study design was approved by the Zeynep Kamil Women and Children's Training and Research Hospital Clinical Research Ethics Committee (Approval number: 186, date: 09.12.2020). Database management complies with legislation on privacy and this research is in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

All statistical analyses were performed using NCSS (Number Cruncher Statistical System) 2007 for statistical analysis (Kaysville, Utah, USA) program. Descriptive statistics were used to analyze the study data (mean, standard deviation, median, first quartile, third quartile, frequency, percentage, minimum, maximum). The conformity of the quantitative data to the normal distribution was tested using the Shapiro-Wilk test and graphical tests. Kruskal-Wallis test and Dunn-Bonferroni test were used for quantitative variables that did not have a normal distribution when comparisons were made between more than two groups. Pearson correlation analysis to determine the level of correlation between the quantitative data used. Statistical significance was accepted as $p<0.05$. Correlation interpretations have been put forward (Table 1) [8].

Highlight key points

- Sperm concentration was found to be positively correlated with the WBC and lymphocyte counts.
- A negative correlation was found between FSH, LH levels and sperm concentration.
- Neutrophil/ lymphocyte (N/L), platelet/ lymphocyte (P/L) cannot be used as predictive markers of sperm quality.

Table 1. Interpretations of correlations [8]

r	Correlation degree
0.00–0.19	Very weak
0.20–0.39	Weak
0.40–0.59	Moderate
0.60–0.79	Strong
0.80–1.00	Very strong

SD: Standard deviation

RESULTS

When patients were grouped according to sperm parameters, age and semen volume did not differ statistically significantly between groups ($p>0.05$). As expected, there was a substantial difference in sperm concentration and motility (A+B) in patients with TMSC >20 million and the others ($p<0.001$) (Table 2).

When laboratory parameters were evaluated, neutrophil ratios, neutrophil, lymphocyte, platelet counts, N/L, P/L, hemoglobin, hematocrit, TSH, and PRL levels were not statistically different between groups. WBC

Table 2. The group features according to TMSC

	TMSC (million)				
	<5 n=38	5–10 n=14	10–20 n=34	>20 n=144	p
Age	36 (31, 40)	38 (33, 41)	36 (32, 41)	35 (31, 39)	**0.294**
Volume (mL)	2.5 (1.5, 3.75)	2.25 (1.5, 3)	2.25 (1.5, 3.5)	3 (2, 4)	**0.173**
Concentration (m/mL)	3.05 (1.4, 5.2)	10.15 (7.82, 27.5)	18.5 (11.3, 30)	54 (36, 81)	<**0.001***
A+B (%)	23.5 (8.5, 32.5)	31 (25, 43)	40 (27, 52)	57 (47, 68)	<**0.001***
TMSC (m)	0.98 (0.54, 2.85)	7.6 (6.05, 8.32)	15.16 (12.6, 16.5)	73.53 (45.6, 133.2)	<**0.001***

TMSC: Total motile sperm count, A+B (%): Sperm concentration and motility; Kruskal-Wallis test, reported as median (first quartile, third quartile); *: P<0.01.

Table 3. Evaluation of laboratory findings of the groups

	TMSC (million)				
	<5 n=38	5–10 n=14	10–20 n=34	>20 n=144	p
WBC count	7.61 (6.74, 8.63)	8.25 (7.93, 10.2)	7.2 (6.27, 8.46)	7.83 (6.75, 9.8)	**0.049***
Neutrophil ratio (%)	56.7 (54.55, 61.4)	58.05 (54.5, 63.1)	56.1 (51, 62.4)	57.4 (52.7, 61.75)	**0.701**
Neutrophil count	4.33 (3.46, 5.3)	5.02 (4.49, 5.35)	4.37 (3.33, 4.97)	4.46 (3.77, 5.43)	**0.068**
Lymphocyte count	2.46 (2.25, 2.78)	2.63 (2.2, 3.12)	2.27 (1.82, 2.68)	2.52 (2.06, 3.06)	**0.142**
PLT count	253.5 (217.5, 288)	258.5 (224, 284)	220 (188, 285)	257 (215, 291)	**0.275**
N/L	1.65 (1.43, 1.96)	1.8 (1.67, 2.23)	1.79 (1.32, 2.18)	1.79 (1.44, 2.16)	**0.601**
P/L	100.13 (85.6, 123.9)	93.43 (72.73, 121.7)	98.47 (86.9, 119.7)	100.89 (84.98, 120.58)	**0.951**
HGB	15.25 (14.5, 15.95)	15.85 (15.5, 16.1)	15.5 (15, 16.1)	15.75 (15.1, 16.4)	**0.070**
HCT	44.75 (42.5, 46.6)	46.85 (45.4, 47.8)	44.8 (43.7, 47.5)	45.65 (43.9, 47.7)	**0.085**
FSH (mIU/mL)	4.68 (2.89, 6.23)	4.98 (3.49, 8.4)	4.08 (2.87, 5.7)	3.03 (2.13, 4.45)	<**0.001****
LH (mIU/mL)	3.65 (2.9, 5.16)	2.97 (2.3, 4.34)	3.65 (2.94, 4.89)	2.96 (2.11, 4.24)	**0.017***
TSH	1.17 (0.94, 1.99)	1.37 (0.95, 1.66)	1.36 (1.01, 1.84)	1.33 (1.03, 1.92)	**0.862**
PRL	7.98 (6.47, 11.35)	9.51 (8.28, 12.49)	9.37 (6.64, 15.03)	9.74 (7.43, 13.55)	**0.409**

WBC: White blood cell; PLT: Platelet; N/L: Neutrophil to lymphocyte ratio; P/L: Platelet to lymphocyte ratio; HGB: Hemoglobin; HCT: Hemotocrit; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; TSH: Thyroid stimulating hormone; PRL: Prolactin; Kruskal-Wallis test, reported as median (first quartile, third quartile); *: P<0.05; **: P<0.01.

counts showed a significant difference between the TMSC groups. Post-hoc evaluations revealed that WBC counts in cases with TMSC between 5–10 were higher than those with TMSC between 10–20 (p=0.049) (Fig. 1). FSH levels of cases with TMSC >20 were lower than those with TMSC <5 and TMSC between 5–10 (p=0.004, p=0.022) (Fig. 2). In addition, the levels of LH were found to be lower in cases with TMSC >20 than those with TMSC <5 (p=0.048) (Fig. 3, Table 3).

Pearson correlation was performed to determine the link between laboratory values and sperm parameters. No statistically significant relationship was found between semen volume and WBC, neutrophil, lymphocyte and platelet count, N/L, P/L, TSH, FSH, and LH levels. Although it was very weak, a significant positive correlation was found between volume and PRL levels (r=0.168, p=0.026).

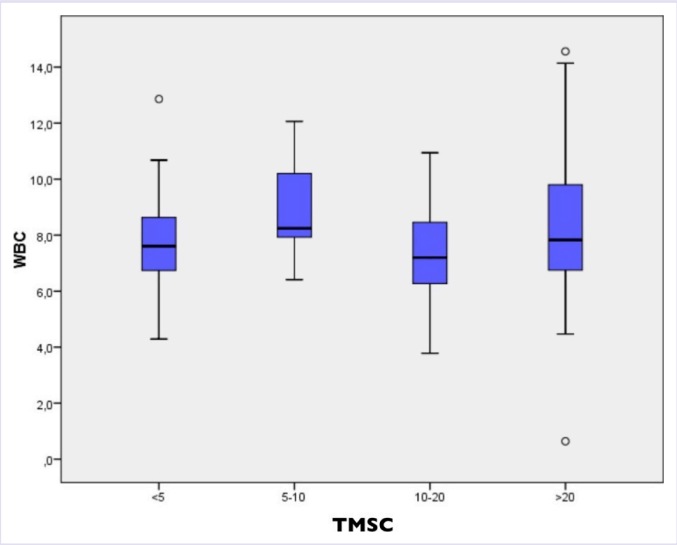

Figure 1. WBC distribution by TMSC groups.

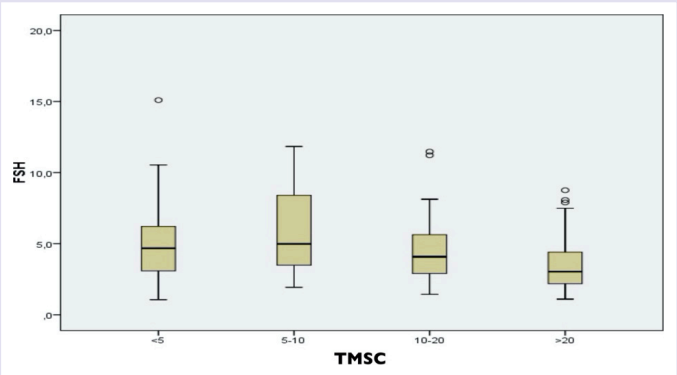

Figure 2. FSH distribution by TMSC groups.

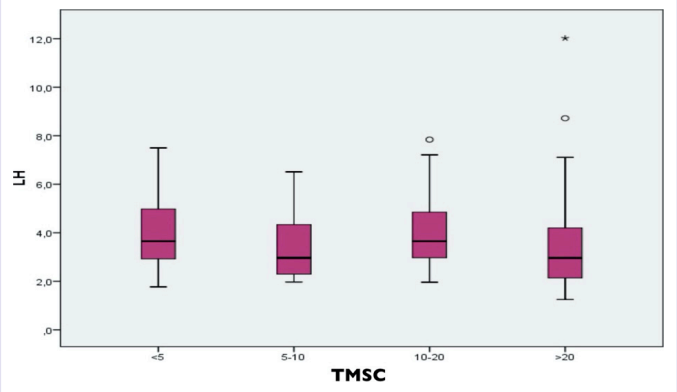

Figure 3. LH distribution by TMSC groups.

Sperm concentration was weakly positively correlated with WBC and lymphocyte counts (p=0.021, p=0.026, respectively). A weak negative correlation was found for FSH and LH levels with sperm concentration and a moderate negative correlation was found with PRL (p>0.005) (Table 4).

Table 4. Relationship between laboratory values and sperm parameters

	Volume (mL)	Concentration (m/mL)	A+B (%)	TMSC (m)
WBC count				
r	-0.055	0.153	0.137	0.160
p	**0.409**	**0.021***	**0.038***	**0.015***
Neutrophil count				
r	0.035	0.088	0.188	0.195
p	**0.597**	**0.187**	**0.004****	**0.003****
Lymphocyte count				
r	-0.007	0.198	0.048	0.119
p	**0.911**	**0.003****	**0.472**	**0.073**
PLT count				
r	0.056	0.047	0.056	0.102
p	**0.395**	**0.475**	**0.395**	**0.123**
N/L				
r	0.057	-0.059	0.146	0.089
p	**0.393**	**0.375**	**0.027***	**0.178**
P/L				
r	0.066	-0.133	-0.006	-0.025
p	**0.320**	**0.045***	**0.933**	**0.703**
TSH				
r	-0.047	0.070	0.009	0.045
p	**0.539**	**0.356**	**0.910**	**0.549**
FSH				
r	-0.111	-0.339	-0.208	-0.350
p	**0.141**	**<0.001****	**0.006****	**<0.001****
LH				
r	0.055	-0.200	-0.165	-0.185
p	**0.467**	**0.007****	**0.029***	**0.014***
PRL				
r	0.168	-0.052	-0.009	0.018
p	**0.026***	**0.489**	**0.910**	**0.815**

WBC: White blood cell; PLT: Platelet; N/L: Neutrophil to lymphocyte ratio; P/L: Platelet to lymphocyte ratio; TSH: Thyroid stimulating hormone; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; PRL: Prolactin; A+B (%): Sperm concentration and motility; Pearson correlation analysis *: P<0.05; **: P<0.01.

No statistically significant correlation was found for motility (A+B) with lymphocyte count, platelet count, P/L, TSH, and PRL levels. A weakly significant positive correlation was found for motility with WBC and neutrophil counts (p=0.038, p=0.004, respectively). A very

weak negative correlation was found between the neutrophil to platelet ratio (r=0.146, p=0.027). A significant negative correlation was found weakly for FSH level and very weakly for LH level between motility (r=-0.208, p=0.006 and r=-0.165, p=0.029, respectively) (Table 4).

No statistically significant correlation was found for TMSC with lymphocyte and platelet counts, N/L, P/L, TSH, and PRL levels. TMSC correlated positively with WBC and neutrophil count (p=0.015, p=0.003), but negatively correlated with FSH and LH levels, very weakly (p<0.001, p=0.014) (Table 4).

DISCUSSION

The relationship between acute or chronic inflammation and male infertility has recently gained importance. Inflammatory diseases are responsible for approximately 15% of cases of male infertility [9]. Major molecules regulating the inflammatory response are leukocytes and neutrophils. Neutrophils, which are found in seminal fluid, cause many different types of oxygen radicals and irreversibly damage spermatozoa in this way [10, 11].

Many markers have been studied for predicting sperm quality, including neutrophil/ lymphocyte (N/L) and platelet/ lymphocyte (P/L), which have been presented in common clinical practice as a simple and affordable method for determining inflammation [1, 3]. In a study comparing N/L and P/L values of 106 infertile men with normal and aberrant semen analysis results, no statistically significant difference was obtained between study and control groups for N/L and P/L ((93.57±28.09 vs. 95.32±35.47) and (1.80±0.75 vs. 1.84±0.78), respectively) [1].

The association between inflammatory indicators and sperm parameters was examined by Oztekin et al. [3]. A total of 160 volunteers were divided into two groups with normal and aberrant spermiograms, and no significant difference was found in neutrophils, lymphocytes, platelets, or red blood cell distribution width (RDW). The N/L, P/L, and RDW/platelet ratio (RPR) between the study and control groups were not statistically significantly different from each other (p=0.77, p=0.62, and p=0.45, respectively).

Yucel et al. [12] studied the effects of inflammatory biomarkers on semen parameters in 352 patients who had undergone testicular sperm extraction (TESE) for nonobstructive azoospermia (NOA). It was reported that N/L and P/L were significantly higher in the category of unsuccessful TESE results. They showed that N/L is an independent factor for the presence of sperm in TESE. In a recent study aimed at investigating the predictive power of the proinflammatory markers N/L, P/L, monocyte-to-eosinophil ratio (MER), and eosinophil-to-lymphocyte ratio (ELR) for sperm retrieval during micro-TESE procedures in patients with NOA, it was found that N/L, MER and P/L were significantly higher in cases with successful TESE results (p<0.001, p=0.001 and p<0.001, respectively). No significant difference between the groups in terms of ELR [13].

In our study, no statistically significant difference was found in neutrophil ratios, neutrophil, lymphocyte, plt counts, N/L, and P/L between groups selected according to TMSC. However, WBC and lymphocyte counts were found to be positively correlated with sperm concentration (p=0.021, p=0.026) and a significant positive correlation was found for motility with leukocyte and neutrophil counts (p=0.038, p=0.004). Although correlation analyses revealed a positive correlation between N/L and motility (p=0.146), sperm concentration was positively correlated with lymphocyte count and inversely correlated with P/L, it was not possible to present both N/L and P/L as predictive markers of sperm quality.

Gonadotropins have been shown to play a major role in spermatogenesis and sperm maturation [14, 15]. Circulating levels of sex hormones have been reported to be strongly associated with sperm parameters [4, 7]. Some studies found a negative correlation between serum FSH and LH and spermiogram parameters such as sperm count, motility, and morphology [16]. Some others declared a significant positive correlation with testosterone level and motility [17].

In a recent study with a large sample, it was reported that LH, FSH, and testosterone were all inversely related to total sperm motility. However, after adjusting for FSH and testosterone, only LH showed an independent negative correlation with progressive sperm motility [18]. They discussed that an increase in the concentrations of LH and FSH might indicate that the testicles do not have sufficient capacity for normal spermatogenesis. Thus, Devranoglu et al. [13] presented FSH level as an independent variable for successful TESE results in azoospermic patients. Our study supports this conclusion by demonstrating a significant decrease in FSH and LH in the TMSC >20 group and finding a negative correlation of FSH and LH with sperm concentration, motility, and TMSC, respectively.

This study has several limitations, such as the fact that it was a single center and retrospective design, so it was not possible to assess participants' lifestyle habits such as smoking, alcohol use, or body mass index (BMI). However, the study has several strengths, including the close section of study groups according to TMSC and the determination of clinical, laboratory, and hormonal parameters on the same day of the spermiogram. In addition, as far as we know, this study is the first to compare both inflammatory markers and hormone levels with semen parameters and to establish correlations between them.

Conclusion

In this study, a significant negative correlation was proved for FSH and LH levels with sperm concentration, motility, and TMSC. For prolactin, a positive correlation was found with semen volume. It is concluded that N/L and P/L cannot be used as predictive markers of sperm quality. The results of positive correlation between WBC count, neutrophil count, and sperm parameters encourage researchers to conduct prospective randomized controlled studies with higher sample sizes and different inflammatory and hormonal markers.

Ethics Committee Approval: The Zeynep Kamil Women and Children's Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 09.12.2020, number: 186).

Authorship Contributions: Concept – MBY, RGI, ZC; Design – MBY, RGI, ZC; Supervision – MBY, RGI, ZC; Fundings – ZC; Materials – ZC; Data collection and/or processing – RGI, ZC; Analysis and/or interpretation – MBY; Literature review – MBY, RGI; Writing – MBY, RGI, ZC; Critical review – MBY, RGI, ZC.

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