Klinik Araştırma

Clinical Features of Patients with Primary and Secondary Infertility

Pirimer ve Sekonder İnfertil Hastaların Klinik Özellikleri

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ABSTRACT

Purpose: *To investigate, in detail, the spermiogram results of cases with primary and secondary infertility and to evaluate the obtained results in light of the data from the literature.*

Materials and Methods: *A total of 942 cases that had spermiograms performed for primary and secondary infertility at our hospital's andrology laboratory between November 2008 and December 2010 were included in the study. After the semen was liquefied, macroscopic and microscopic evaluations were performed. Microscopic evaluations involved the assessment of sperm concentration and motility and the evaluation of morphology according to the Kruger strict criteria, all of which were performed in accordance with the criteria of the World Health Organization (WHO). The motility of each sperm was scored according to four categories, which were: rapid forward motility (a), slow forward motility (b), non-progressive motility (c), and immotile (d). Comparison of the spermiogram results of cases with primary and secondary infertility was performed retrospectively according to age (years), volume (ml), sperm concentration (ml/106), total motility (A+B+C) (%), motility A (%), motility B (%), motility C (%), motility D (%), the Total Progressive Motile Sperm Count (TPMSC) and normal morphology (% normal) values. The characteristics of primary and secondary infertility in cases diagnosed with varicocele were also compared. All results were compared statistically.*

Results: *During the comparisons performed on patients with varicocele according to the type of infertility, no statistical differences were identified with regards to the evaluated parameters. Based on the comparisons performed according to the type of infertility, cases with secondary infertility had higher age, sperm concentration (ml/106), total motility (A+B+C) (%), motility A (%), motility B (%), TPMSC, and normal morphology (% normal) values compared to cases with primary infertility, while motility C (%) and motility D (%) values were higher in cases with primary infertility.*

Conclusion: *As expected, varicocele did not alter sperm parameters when infertility was present. Spermiogram results demonstrated various differences depending on the presence of varicocele, infertility type and many other factors.*

Key words: *Varicocele, infertility, sperm concentration, morphology.*

ÖZET

Amaç: *Primer ve sekonder infertil olguların spermiyogram sonuçlarının ayrıntılı bir şekilde incelenmesi ve çıkan sonuçların literatür verileri eşliğinde değerlendirilmesi amaçlanmıştır.*

Gereç ve Yöntem: *Çalışmaya Kasım 2008 ile Aralık 2010 tarihleri arasında hastanemiz androloji laboratuvarında primer ve sekonder infertilite sebebi ile spermiyogram yapılan 942 olgu dahil edildi. Semen likefiye olduktan sonra makroskobik değerlendirme yapıldı ve Dünya Sağlık Örgütü (WHO) kriterlerine göre volüm, sayı, motilite ve Kruger Strict kriterlerine göre morfoloji değerlendirilmesi yapıldı. Her bir spermin motilitesi; hızlı ileri hareketli (a), yavaş ileri hareketli (b), yerinde hareketli (c) ve hareketsiz (d=immotil) olmak üzere 4 kategoride skorlandı.*

Bulgular: *Varikosel tanısı olan ve olmayan hastaların karşılaştırılmasında yaş, morfoloji (% normal), sperm konsantrasyonu, motilite total (A+B+C) (%), motilite A (%), motilite B (%), Total Progresif Motil Sperm Sayısı (TPMSS), baş (%) ve boyun (%) değerleri varikosel tanısı olmayan olgularda daha yüksek olarak bulunurken sadece motilite D değeri varikoselli olgularda daha yüksek olarak saptandı. Varikoselli hastalarda infertilite tipine göre yapılan karşılaştırma sonucunda yukarıda verilen parametreler açısından istatiksel farklılık saptanmadı. İnfertilite tipine göre yaptığımız karşılaştırma sonucunda sekonder infertilite özelliklerine sahip olguların yaş, morfoloji (% normal), sperm konsantrasyonu (ml/106), TPMSS, motilite total (A+B+C) (%), motilite A (%), motilite B (%) değerleri primer infertilli olgulara göre daha yüksek olarak saptanırken motilite C ve motilite D değerleri ise primer infertiliteli olgularda daha yüksek değerlerde saptanmıştır.*

Sonuç: *Varikoselli olup olmamanın infertilite olması durumunda sperm parametrelerini etkilemediği gözlenmektedir. Spermogram sonuçları infertilite tipine, varikoselli olma durumuna göre ve diğer birçok etkene bağlı olarak değişiklikler göstermektedir.*

Anahtar Kelimeler: *Varikosel, infertilite, sperm konsantrasyonu, motilite, morfoloji*

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INTRODUCTION

Infertility is defined as the inability of couples to conceive despite regular sexual intercourse (two days a week) without protection for a period of one year1. Infertility is observed in 10-15% of couples of reproductive age. The frequency and causes of infertility varies from one society to another. Among couples, men are responsible for infertility in 30-40% of the cases, while women are responsible for the infertility in 40-50% of the case1,2. Therefore, there is a male factor involved in nearly half of all couples with infertility3. In cases where the infertility is associated with a male problem, the problem often stems from an impairment of sperm parameters. Although the underlying cause of male infertility is known in nearly 40-60% of cases, there are still many cases in which the causative factors cannot be identified. The aim of the current study was to retrospectively analyze the data of patients who had spermiograms performed for primary and secondary infertility, and to evaluate these results in light of the data from the literatur.

MATERIALS AND METHODS

Following the approval of the ethics committee, this study was conducted by retrospectively analyzing the data of patients who had spermiograms performed for primary and secondary infertility at our hospital's andrology laboratory between November 2008 and December 2010. At total of 942 male patients whose spermiograms were requested for the assessment of male fertility were included in the study. These assessments were requested within the context of evaluations performed on infertile couples admitted to the obstetrics and gynecology polyclinic. Sperm evaluation was performed with the Olympus CX41 brand phase contrast microscope, while sperm motility and concentration were evaluated with a Makler count camera. A total of 500 sperm were counted in each semen sample. The motility of each sperm was scored according to four categories, which were: rapid forward motility (a), slow forward motility (b), non-progressive motility (c), and immotile (d). Sperm that moved outside of the microscope area by linear motility were considered as displaying forward motility. The total percentage of sperm with linear motility, with non-linear motility and with non-progressive motility was considered as the total motility. Sperm samples with 50% or more forward motility (both rapid forward motility and slow forward motility) or with more than 25% rapid forward motility were considered as being normal in terms of sperm motility.

STATISTICAL ANALYSIS

The SPSS 18.0 package program was used for the statistical analysis of the data. Categorical measurements were summarized as number and percentages, while quantitative measurements were summarized as mean and standard deviations. In case the assumptions were satisfied during the comparison of quantitative measurements between groups, the independent group t-test was used; in case the assumptions were not satisfied, the Mann-Whitney test was used instead. In all tests, the level of statistical significance was accepted as 0.05.

RESULTS

All of the patients were married. The mean age of the patients was determined as 30.3 ± 6.7 (years). The number of primary infertility cases included in the study was 604 (64%), while the number of secondary infertility cases included into the study was 339 (36%). The average period of sexual abstinence for the patients included into the study was 4 ± 1.5 days, while their mean sperm value was 3.3 ± 1.78 ml, mean sperm concentration was 48,3 ± 33.4 ml/106, and TPMSC was 85.5 ± 74.7 X 106. An evaluation of the patients' morphological anomalies revealed that 60% ± 14% had head anomalies, 23% ± 11% had neck anomalies, and 14% ± 8.5% had tail anomalies. Evaluation of primary and secondary infertility in cases diagnosed with varicocele revealed that primary infertility was present in 112 (65.5%) of these cases, while secondary infertility was present in 59 (35.5%) of these cases. Based on the comparison of infertility among patients included in the study, a further comparison between cases of primary and secondary infertility is provided in **Table 1**.

	Primary Infertility (n:603)	Secondary infertily (n:339)	P
Age (years)	29,0 ± 6,2	32,8 ± 6,8	0,001
Volume (ml)	3,33 ± 1,9	3,3 ± 1,4	0,818
Sperm concentration (ml/10^6)	46,2 ± 3 3,1	52,0 ± 33,7	0,011
Motility-Total (A+B+C) (%)	58,6 ± 14,2	61,2 ± 12,2	0,003
Motility-A (%)	6,8 ± 5,9	7,8 ± 5,9	0,011
Motility-B (%)	44,1 ± 13,4	46,4 ± 11,4	0,005
Motility-C (%)	7,9 ± 4,9	7,1 ± 4,1	0,005
Motility-D (%)	41,4 ± 14,3	38,6 ± 12,4	0,003
Total Progressive Motile Sperm Count (10^6)	80,9 ± 74,1	92,9 ± 74,5	0,018
Morphology (% normal)	3,3 ±2,3	3,8 ±2,4	0,001
Head Anomaly (%)	59,2 ± 14,2	60,6 ± 13,7	0,112
Neck Anomaly (%)	23,1 ± 11,1	22,1 ± 10,9	0,148
Tail Anomaly (%)	14,3 ± 8,9	13,5 ± 7,9	0,168

Table 1. Comparison according to infertility type.

Based on the comparison that was performed according to the type of infertility, statistically significant differences were identified with regards to age (years), sperm concentration (ml/106), total motility (A+B+C)(%), motility A (%), motility B (%), motility C (%), motility D (%), the TPMSC (106), and morphology (% normal) values.

	Primary infertility (n:112)	Secondary infertility (n:59)	P
Age (years)	29,1 ± 6,0	29,8 ± 6,1	0,450
Morphology (%normal)	3,2 ± 2,2	2,9 ± 1,9	0,346
Volume (cc)	3,3 ± 1,5	3,5 ± 1,5	0,467
Sperm concentration ($ml/10^6$)	38,0 ± 31,5	38,4 ± 29,9	0,930
Motility-Total (A+B+C) (%)	56,1 ± 13,7	53,5 ± 18,8	0,302
Motility-A (%)	6,3 ± 6,0	5,2 ± 5,0	0,180
Motility-B (%)	41,4 ± 12,9	40,7 ± 17,2	0,779
Motility-C (%)	8,1 ± 5,4	8,3 ± 5,1	0,788
Motility-D (%)	40,0 ± 16,9	39,3 ± 18,6	0,795
Total Prgressive Motile Sperm Count (10^6)	68,2±71,5	62,3±62,5	0,590
Head Anomaly (%)	56,5 ± 13,3	57,2 ± 15,1	0,753
Neck Anomaly (%)	26,4 ± 11,7	23,6 ± 11,6	0,139
Tail Anomaly (%)	14,0 ± 6,6	16,0 ± 9,2	0,104

Table 2. Comparison of varicocele status according to infertility.

The characteristics of varicocele patients with primary and secondary infertility are shown in Table 2. Based on the comparisons that were performed, no statistically significant differences were identified with regards to the parameters on this table (P>0.005).

Table 3 provides a general evaluation of patients diagnosed with varicocele. Based on the comparison performed between patients with and without varicocele, statistically significant differences were identified with regards to age (years), sperm concentration (ml/106), total motility (A+B+C)(%), motility A (%), motility B (%), motility D (%), the TPMSC (106), and the morphology (% normal) head (%) and (%) neck values (P<0.05).

	Patients with varicocele (n:171)	Patients without varicocele (n:771)	P
Age (Years)	29,3 ± 6,0	30,6 ± 6,8	0,017
Morphology (%normal)	3,1 ± 2,1	3,5 ± 2,4	0,018
Volume (cc)	3,4 ± 1,5	3,3 ± 1,8	0,520
Sperm concentration ($ml/10^6$)	38,1±30,5	50,5±33,6	<0,001
Motility-Total (A+B+C+) (%)	55,2 ± 15,7	60,5 ± 12,8	<0,001
Motility-A (%)	5,9 ± 5,7	7,4 ± 5,9	0,003
Motility-B (%)	41,2 ± 14,5	45,7 ± 12,2	<0,001
Motility-C (%)	8,1 ± 4,9	7,6 ± 4,6	0,169
Motility-D (%)	44,6 ± 15,8	39,4 ± 13,0	<0,001
Total progressive motile sperm count (10^6)	66,2 ± 68,4	89,4 ± 75,1	<0,001
Head anomaly (%)	56,7 ± 13,9	60,3 ± 13,9	0,002
Neck anomaly (%)	25,4 ± 11,8	22,2 ± 10,8	0,001
Tail anomaly (%)	14,7 ± 7,6	13,9 ± 8,7	0,205

Table 3. Comparison of patients with or without varicocele.

DISCUSSION

Infertility is defined as the inability of couples to conceive despite regular sexual intercourse (two days a week) without protection for a period of one year. Infertility is observed in 10-15% of couples of reproductive age. The frequency and causes of infertility varies from one society to another. Among couples, men are responsible for infertility in 30-40% of the cases, while women are responsible for the infertility in 40-50% of the cases. Presently, 10-15% of couples have forms of infertility that cannot be identified or elucidated by current standard diagnostic tests.[1,2] There is a male factor involved in nearly half of all couples with infertility.[3] IIn cases where the infertility is associated with a male problem, the problem often stems from an impairment of sperm parameters. For this reason, it is very important to perform thorough and detailed evaluations in men in cases of infertility. In their study evaluating the effect of age on sperm parameters, Eskenazi et al. demonstrated that age had a negative effect on these parameters, but was unable to obtain clear and unambiguous data regarding the effect on sperm concentration.[4] Hellstrom et al. conducted a similar study on 1174 men who were 45 years of age of older, where they also identified similar results, while at the same time observing a slight decrease in sperm count.[5] In a study where they objectively evaluated the semen samples of elderly men by using a computerized technique; Rolf et al. reported a decrease in sperm motility with age, and described that the effects on the semen and testis parameters of pathophysiological events caused by age could be directly associ-

ated with the specific effects of age, just as they might also be associated with other conditions that develop with age such as vascular disorders, obesity, infections, and the accumulation of toxic substances.[6] Significant variability was observed in the sperm motility (a+b motility) of patients with varicocele. In their studies, Schiff et al. identified a mean motility of 42.6%, Blumer et al. identified a mean motility of 46.5%, Yurdakul et al. identified a mean motility of 38%, and Özbek et al. identified a mean motility of 28%.[7,8,9,10] Although the relationship between varicocele and sperm production is currently debated, studies have identified a decrease in the sperm concentration and motility of varicocele patients that was greater than the decrease in patients without varicocele. The most significant advantage of evaluating sperm according to the Kruger strict criteria is the correlation observed between the ratio of sperm considered to be morphologically normal and the success achieved in In Vitro Fertilization (IVF). According to the Kruger strict test, the fertilization rate per oocyte is 7.6% in cases where normal morphology is less than 4%, while the fertilization rate reaches 63.9% in cases where normal morphology is above 4.[11] Morphological evaluation of sperm is a sensitive indicator of spermatogenesis quality and fertility.[11,12] For 85 couples with unexplained infertility, sperm morphology was reported as being significantly worse in comparison to fertile couples in the control group.[13] In a prospective study conducted by Wichmann et al. on 907 patients by using the 1980 WHO criteria, sperm morphology was shown to be an independent factor with regards to fertilization outcome.[14] Impaired sperm morphology generally decreases the probability of achieving pregnancy, and delays/prolongs the time until the first pregnancy.[15] A review of the literature showed that evaluations based on the Kruger strict criteria are generally prominent, and that the limit value within the context of these studies is generally accepted as 4%. Taking a sperm morphology limit value of 4% is very important for effectively predicting both spontaneous pregnancy and the probability of achieving pregnancy by assisted reproductive techniques.[16]

In a study conducted on 365 infertile patients to assess semen quality in patients with and without varicocele, evaluation of medical history along with physical examinations, semen analysis, semen culture, and assessment IgG, IgA, serum FSH and T values were performed in all patients. A total of 7 (26.6%) cases diagnosed with varicocele and 268 (73.4%) cases without varicocele were evaluated. While a significant decreases were observed in the motile sperm percentage (24.58+/-21.68 vs. 21.01 +/-12.62) and to a lesser extent in the sperm concentration (15.50+/-23.30 vs. 16.50+/-15.22), a comparison of cases with and without varicocele failed to demonstrate a clear and direct relationship between varicocele and infertility.[17]

In another study conducted on 89 men with primary and secondary infertility and comparing their hormonal profile and semen parameters with their demographic data, no significant differences were identified between the sperm parameters of men with primary and secondary infertility. In a meta-analysis performed on 29,914 patients from 57 centers across 26 countries, increased age was identified as a risk factor for low semen volume.[18] In a study conducted with 716 patients, the mean age of the patients was identified as 29.6 years, and increased severity of varicocele was associated with a decrease in sperm concentrations.[19] In a study comparing the clinical characteristics of men with primary and secondary infertility, 225 of the cases were described as having primary infertility, while 90 were described as having secondary infertility. The mean age for men with secondary infertility was determined as 39.6 years, while the mean age for men with primary infertility was determined as 35.4 years. Sperm concentration was determined as 51.3 million/ml for cases with secondary infertility, and 36.0 million/ml for cases with primary infertility. Normal sperm morphology was identified as 30.6% for cases with secondary infertility and 24.1% for cases with primary infertility, while total motile sperm count was 31.1% for cases with secondary infertility and 46.5% for cases with primary infertility. No significant relationship was identified between the groups with regards to the duration of infertility, smoking and alcohol use, and the severity of varicocele, while the prediction of the total motile sperm count for men with secondary infertility was identified as an independent factor. In conclusion, while men with secondary infertility were generally older than men with primary infertility, they also had significantly better sperm concentrations.[20]

Based on comparisons performed according to the type of infertility, cases with secondary infertility had higher age, sperm concentration (ml/10^6), total motility (A+B+C) (%), motility A (%), motility B (%), TPMSC and morphology (% normal) values compared to cases with primary infertility, while motility C (%) and motility D (%) values were higher in cases with primary infertility. Based on comparisons performed in varicocele patients according to the type of infertility, no significant differences were identified with regards to age, volume, sperm concentration, motility, morphology, head anomaly, neck anomaly, and tail anomaly. Based on comparisons performed between patients with and without varicocele, total motility (A+B+C)(%), motility A (%), motility B (%), the TPMSC (10^6) the morphology (% normal) value, and the head (%) and neck (%) values were identified as being higher in cases without varicocele, while only the value for motility D (%) was identified as being higher in cases with varicocele. These values were in agreement with the literature.

CONCLUSION

Infertility is becoming an increasingly common public health problem. For this reason, it is necessary to place greater emphasis on the detailed evaluation of men. There are factors associated with infertility in men that can be corrected by treatment to ensure pregnancy through physiological means; and in other circumstances, the use of assisted reproduction techniques can largely solve the problems related to infertility. Therefore, studies on this subject are of considerable importance for gaining a proper understanding of underlying causes, and for developing effective solutions, especially for Turkey, where epidemiological studies are lacking. We believe that our study is significant with regards to the large number of cases it included in our country, and that there is a need to conduct further similar studies on this subject.

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