Original Article

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The Influence of Varicocelectomy Age on Semen Parameters and Fertility Rates

Varikoselektomi Yaşının Semen Parametreleri ve Fertilite Üzerine Etkisi

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ABSTRACT

Objective: Varicocele is the most frequently observed correctable cause of infertility in men. In this study, we aimed to evaluate the influence of age at the time of varicocelectomy on semen parameters and fertility.

Methods: Infertile men who underwent microsurgical varicocelectomy between January 2012 and December 2019 were retrospectively evaluated. Patients were divided into 4 age groups as follows: group 1 including patients aged ≤25 years old, group 2 including patients aged ≥26 and ≤30 years old, group 3 including patients aged ≥31 and ≤35 years old, and group 4 including patients aged ≥36 years old.

Results: A total of 138 infertile men were divided into 4 groups. There were 18 men in group 1, 58 men in group 2, 44 men in group 3, and 18 men in group 4. There were significant improvements in the mean sperm concentration, progressive motility, and total motile sperm count values in all groups after surgery. Significant improvement in sperm morphology was detected only in groups 1 and 2 (p=0.007 and p=0.005, respectively). There was no significant difference between the groups in terms of preoperative and postoperative sperm parameters. Total fertility rate and the number of patients having children with natural conception or assisted reproductive techniques were lower in group 4 but these differences were not statistically significant (p=0.083 and p=0.454, respectively).

Conclusion: Varicocelectomy can be recommended for all infertile men regardless of age. There was no difference in postoperative semen parameters and fertility rates between the age groups.

Keywords: Age, infertility, varicocelectomy, semen parameters

ÖZ

Amaç: Varikosel erkeklerde en sık görülen düzeltilebilir infertilite nedenidir. Varikoselektomi sonrası postoperatif semen parametrelerinin düzeldiği ve gebelik oranlarının önemli ölçüde arttığı birçok çalışma ile gösterilmiştir. Literatürde yaşın postoperatif sonuçlara etkisini bildiren az sayıda çalışma vardır ve sonuçlar çelişkilidir. Bu çalışmada varikoselektomi sırasındaki yaşın semen parametreleri ve fertilite üzerine etkisini değerlendirmeyi amaçladık.

Yöntemler: Ocak 2012 ile Aralık 2019 tarihleri arasında mikrocerrahi ile varikoselektomi yapılan infertil erkekler retrospektif olarak değerlendirildi. Hastalar 4 yaş grubuna ayrıldı: Grup 1≤ 25 yaş hastaları, grup 2≥26 ve ≤30 yaş hastaları, grup 3 ≥31 ve ≤35 yaş hastaları ve grup 4 ≥36 yaş hastaları içermekteydi.

Bulgular: Toplam 138 infertil erkek 4 gruba ayrıldı. Grup 1'de 18 erkek, grup 2'de 58 erkek, grup 3'te 44 erkek ve grup 4'te 18 erkek vardı. Sadece grup 1 ve 2'de sperm morfolojisinde anlamlı iyileşme saptandı (sırasıyla, p=0,007 ve p=0,005). Ameliyat öncesi ve sonrası sperm parametreleri açısından gruplar arasında anlamlı fark yoktu. Toplam fertilite oranı ve doğal konsepsiyon veya yardımcı üreme teknikleriyle çocuğu olan hasta sayısı grup 4'te daha düşüktü ancak bu farklar istatistiksel olarak anlamlı değildi (sırasıyla, p=0,083 ve p=0,454).

Sonuç: Yaşına bakılmaksızın tüm infertil erkeklere varikoselektomi önerilebilir. Yaş grupları arasında postoperatif semen parametreleri ve doğurganlık oranları açısından fark yoktur.

Anahtar Sözcükler: Yaş, infertilite, varikoselektomi, semen parametreleri

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Introduction

Varicocele is the pathological dilatation of the venous plexus of testes and it is the most frequently observed correctable cause of male infertility (1). The incidence of varicocele is around 15% in the general population but this rate rises to 35-40% and 69-81% in primary and secondary infertile men, respectively (2,3). Although several hypotheses like reflux of adrenal metabolites, increased oxidative stress and scrotal temperature have been suggested, the exact mechanism of how varicocele impairs semen parameters has still not been fully elucidated (4-6). Sclerotherapy, embolization, open or laparoscopic surgery are the main treatment options for varicocele but microsurgical varicocelectomy is accepted as the most successful technique (7). It has been shown by several studies that semen parameters improve and pregnancy rates significantly increase postoperatively (8-11). The current European Association of Urology guideline recommends surgery in infertile patients with any abnormality in semen parameters, and clinical varicocele if the spouse has a good ovarian reserve to increase fertility rates (12). It has been shown that parameters like volume, motility, and morphology are affected by aging (13,14). In current guidelines, there are no lower or upper age limits recommended for varicocelectomy in infertile adults and there is no age group stated in which varicocelectomy is more successful.

In this study, we investigated the influence of age at the time of varicocelectomy on semen parameters and fertility. Patients were divided into 4 different age groups and changes in semen parameters after microscopic varicocelectomy and fertility rates were compared. There are a limited number of studies reporting the impact of age on postoperative results in the literature and reports are conflicting. In most of these studies, patients were divided into 2 or 3 groups depending on the ages of the patients. Also, in some studies the effect of the spouse's age on fertility was not investigated and fertility rates were not reported. The differences of this study from the previous ones were that we grouped patients into 4 different age groups, we evaluated the effect of the age of the spouse and reported the fertility rates after varicocelectomy.

Methods

Infertile men who had microsurgical varicocelectomy due to clinically palpable varicocele between January 2012 and December 2019 were evaluated retrospectively. Failure to conceive after one year of regular unprotected sexual intercourse was defined as infertility. Medical histories and findings of physical examinations were obtained from the patient files. Age, duration of infertility and follow-up, fertility status, sides of the varicocele, and ages of the spouses were noted. The diagnosis of varicocele was verified by Scrotal Doppler ultrasonography in all patients. Two semen analyses at least 4 weeks apart were obtained from each patient, after 3-5 days of abstinence. Analysis with better parameters was accepted as preoperative baseline semen analysis.

Semen analysis was carried out in accordance with the World Health Organization (WHO) laboratory manual for the examination and processing of human semen, 5th edition (WHO, 2010) to measure semen volume, sperm concentration, progressive motility, non-progressive motility, normal morphology, and vitality (15). The same staff member performed all semen analyzes. Total motile sperm count (TMSC) was calculated by using the formula: ejaculate volume (mL) x concentration per mL x motile fraction. Patients with subclinical varicoceles, with associated female factor infertility, patients with a follow-up duration of less than one year, and with hormonal pathology that might affect sexual function were excluded from the study. Microsurgical inguinal varicocelectomy was performed in all patients. Control semen analysis was carried out six months after the operation. Patients were evaluated in 4 groups based on their ages: group 1 (GR1) including men aged ≤25 years, group 2 (GR2) including men aged ≥26 and ≤ 30 years, group 3 (GR3) including men aged ≥31 and ≤35 years, and group 4 (GR4) including men aged ≥36 years. Median ages, duration of infertility, duration of follow-up, fertility rates, sides of the varicoceles, ages of the spouses, preoperative and postoperative sperm parameters were compared.

Statistical Analysis

The SPSS (Statistical Package for the Social Sciences) 24.0 program was used for statistical analysis. The Kruskal-Wallis test was performed for group comparisons of three or more parameters with no normal distribution. The difference between groups was evaluated by using the Mann-Whitney U test. Comparisons of preoperative and postoperative measurements were performed by using the Wilcoxon Signed-Rank test. The relationship between the measurements was determined by using the Spearman's rank-order correlation analysis. Binary regression analysis was used to evaluate the effect of varicocelectomy age on fertility rates. A p value <0.05 was considered to be statistically significant. All results were shown as median and interquartile ranges (IQR). This study was approved by the Institutional Ethics Committee (approval number: 2021/333). Owing to the study design patient consent was waived.

Results

A total of 138 infertile men who underwent varicocelectomy met the criteria and were divided into 4 groups based on their age at the time of surgery. There were 18 men in GR1 (≤25 years old), 58 men in GR2 (≥26 and ≤30 years old), 44 men in GR3 (≥31 and ≤35 years old), and 18 men in GR4 (≥36 years old). Patient characteristics are shown in Table 1. There was no significant difference in the median duration of follow-up between groups (p=0.081). The median spouse age in GR4 [33 years (IQR =31.75-36.5)] was significantly higher compared to GR1 [22 years (IQR =21-23.25)], GR2 [26 years (IQR =25-28)], and GR3 [28 years (IQR =28-29)] (p=0.001). Significant improvements in the median sperm concentration, progressive motility, and TMSC values were detected in all groups after surgery (p=0.007, p=0.026 and p=0.004, respectively for

Table 1. Detailed characteristics of the patients

	GR1 (n=18)	GR2 (n=58)	GR3 (n=44)	GR4 (n=18)	p
Age (years)	24 (23-25)	28.5 (27-29)	32 (31-33)	38 (36.75-40)	0.001
Duration of infertility (months)	13.5 (12-24)	18 (12-24)	22 (13-36)	24 (18-51)	0.002
Laterality (n, %)					0.221
Left	12 (66.7)	30 (51.7)	25 (56.8)	14 (78)	
Bilateral	6 (33.3)	28 (48.3)	19 (43.2)	4 (22)	
Duration of follow-up (months)	67.5 (61.5-84)	70 (62-81.5)	66 (57.5-82)	61 (56-68.5)	0.08
Age of the spouse (months)	22 (21-23.25)	26 (25-28)	28 (28-29)	33 (31.75-36.5)	0.001

All values are median (interquartile range)

GR1; p=0.001, p=0.04 and p=0.001, respectively for GR2; p=0.007, p=0.001 and p=0.001, respectively for GR3 and p=0.002, p=0.02 and p=0.035, respectively for GR4) (Table 2). Significant improvement in sperm morphology was detected only in GR1 and GR2 (p=0.007 and p=0.005, respectively). The changes in sperm morphology in GR3 and GR4 were not statistically significant (p=0.121 and p=0.143, respectively). There was no significant difference between the groups in terms of preoperative and postoperative sperm parameters (Table 3 and 4). Detailed fertility rates are shown in table 5. Thirteen patients (72.22%) in GR1, 41 (70.7%) patients in GR, 29 (65.9%) patients in GR3, and 7 (38.89%) patients in GR4 had children within the specified follow-up periods. Total fertility rate, number of patients having children with natural conception, and number of patients having children with ART were lower in GR4 but these differences were not statistically significant. When the whole cohort was evaluated, no significant correlation was found between age at varicocelectomy and postoperative semen volume, sperm concentration, progressive motility, TMSC, and sperm morphology (Spearman's rho =-0.103/p=0.228, Spearman's rho =0.157/p=0.066, Spearman's rho =-0.028/p=0.746, Spearman's rho= -0.027/p=0.754, and Spearman's rho =-0.030/p=0.725, respectively). Also, no significant relationship was found between the age of the spouse and fertility (p=0.984). We performed a binary regression analysis to evaluate the effect of varicocelectomy age on fertility rate and no relationship was found between the age of varicocelectomy and the fertility rate [Exp (B): -0.053, 95% confidence interval (0.86-1.03), p=0.948]

Discussion

Today, it is widely accepted that varicocele repair positively affects semen parameters and fertility rates. However, there is a paucity of data about the effects of patient age on these parameters. Some authors suggest that varicocele has progressive toxic effects on the testis and several studies reported a significant decrease in sperm concentration and motility in men with untreated varicoceles (2,16). The higher incidence of varicocele in patients with secondary infertility supports this suggestion. Therefore, varicocele repair can be expected to be more successful in younger patients and men with a shorter duration of infertility.

Hassanzadeh-Nokashty et al. (17) evaluated 67 men divided into 4 age groups as patients aged <25 years (n=17), patients aged between 25-29 years (n=18), patients aged between 30-34 years (n=17), and patients aged ≥35 years (n=15). They reported significant improvements in total sperm count, motility, and morphology in all age groups after varicocelectomy. The highest improvements were observed in men <25 years old, but they didn't evaluate the fertility rates and there was no information about the age of the spouse. Hsiao et al. (18) evaluated semen parameters after varicocelectomy in men divided into 3 age groups: Men aged <30 years, men aged between 30 and 39 years, and men aged ≥40 years. The mean spouse age was significantly higher in men aged ≥40 years (25.7±0.5, 32.2±0.3, and 37.7±0.5, respectively). Significant improvements were detected in sperm concentration and total sperm count in all groups but interestingly significant change in motility was detected only in men aged between 30 and 39 years old and no significant change was detected in sperm morphology in any group. They reported pregnancy rates of 33.3% in men aged <30 years, 39.2% in men aged between 30 and 39 years, and 24.1% in men aged ≥40 years. Bolat et al. (19) evaluated the impact of varicocelectomy in men who were ≤20 years old, men between 21-30 years old, and men ≥31 years old. They reported an increase in mean TMSC and percentage of sperms with normal morphology in all groups but no difference in natural fertility rates. Yazdani et al. (20) compared semen parameters and pregnancy rates of men younger than 30 years with men older than 30 years. Significant improvements were detected in the mean sperm concentration, motility, and morphology postoperatively in both groups. The increase in sperm concentration in the younger group was significantly higher compared to the older group. There were no statistically significant differences in other semen parameters and pregnancy rates (51.1% and 44.7% for group 1 and group 2, respectively) between the two groups. Kimura et al. (21) found that improvement in sperm concentration and motility was greater in men ≤37 years old and younger age was a predictor of early improvement in TMSC. However, Palmisano et al. (22) evaluated 228 men who underwent left microscopic varicocelectomy and reported a significant improvement in sperm concentration only in men ≥35 years old.

Table 2. Comparison of preoperative and postoperative sperm parameters in each group

	GR1 (n=18)			GR2 (n=58)			GR3 (n=44)			GR4 (n=18)		
	Pre.	Post.	p	Pre.	Post.	p	Pre.	Post.	p	Pre.	Post.	p
Sperm volume (mL)	3.61 (2.31-4.46)	3.45 (2.37-5.12)	0.845	3.58 (2.57-4.63)	3.97 (3.08-4.74)	0.201	3.38 (2.62-4.76)	3.9 (2.85-4.75)	0.07	3.75 (2.42-4.99)	3.34 (1.61-4.59)	0.078
Sperm conc. ($x10^6$/mL)	5.14 (2.8-9.25)	13 (3.2-24.5)	**0.007**	6.3 (2.75-10)	15.76 (3.9-25)	**0.001**	6.9 (2.03-16.5)	12.2 (6.05-19.55)	**0.007**	7.9 (3.5-30.5)	23 (5-36.75)	**0.002**
Progressive motility (%)	30 (23-38)	39.5 (25.25-48.25)	**0.026**	36 (20.75-42.5)	40 (27-47)	**0.04**	31.5 (13-42)	35.5 (24.25-50.5)	**0.001**	28.5 (13.5-37.5)	35 (29-41.5)	**0.020**
Non-progressive motility (%)	8.67 (6.75-10)	7.05 (5-9)	0.208	7 (6-9)	7 (5.75-9)	0.582	8 (6.25-10)	7 (6-10.75)	0.486	7.5 (6-9)	8.5 (6.75-10.2)	0.645
Non-motile sperm (%)	61.38 (55.5-69.25)	55 (46.5-65.75)	0.118	56.5 (49.5-68.25)	53 (46.75-63)	0.037	60 (49-78)	55.5 (44-66)	**0.001**	62 (53.5-75.5)	57 (51-62.25)	**0.014**
TMSC ($x10^6$)	6.87 (2.71-14.55)	19.32 (4.31-39.06)	**0.004**	7.73 (1.73-15.91)	16.12 (3.97-46.85)	**0.001**	8.29 (1.2-19.38)	17 (5.58-32.01)	**0.001**	5.25 (4.02-27.2)	15.64 (4.66-44.3)	**0.035**
Morphology (% of normal forms)	0 (0-1)	1 (0-2)	**0.007**	0.5 (0-1)	1 (0-2)	**0.005**	0 (0-1)	0.5 (0-2)	0.121	0 (0-1.25)	1 (0-1.5)	0.143

Pre.: Preoperative, Post.: Postoperative, Conc.: Concentration, TMSC: Total motile sperm count
All values are median (interquartile range)

Zini et al. (23) retrospectively analyzed 115 infertile men older than 40 years old and 466 infertile men younger than 40 years old. Sixty-three percent of the men younger than 40 years old underwent varicocelectomy and 52% of the men older than 40 years underwent varicocelectomy. The mean age of the spouse was 37.7±3.7 in men older than 40 years old and 33.2±4 in men younger than 40 years old and this difference was statistically significant. Spontaneous pregnancy rates in men older than 40 years old and in men younger than 40 years old were 49% and 39%, respectively. No significant difference was detected. We detected improvements in sperm concentration, motility, and TMSC in all age groups similar to the results in the literature. However, contrary to the data in the literature, change in the morphology was only significant in men ≤30 years old (GR1 and GR2); no significant change in morphology was detected in men >30 years old (GR3 and GR4). Also, there was no significant difference in postoperative semen parameters between groups in our study. We detected similar fertility rates in group 1 (72.22%), group 2 (70.6%) and group 3 (65.9%). However, the fertility rate of GR4 (38.89%) was lower compared to other groups, but this difference was not statistically significant (p=0.083). The median duration of infertility and the median age of the spouse values were also significantly higher in GR4. The number of patients in this group was small. This might prevent a healthy comparison and a significant difference could be found if there were more patients.

The fertility status of the spouse is also important when evaluating male infertility. Men with partners who have fertility problems are excluded from the studies investigating the pregnancy rates after varicocelectomy. However, the age of the spouse is a crucial factor affecting fertility rates. Fertility potential decreases to 50% at age 35 compared to the fertility potential of a 25-year-old woman (24). Fırat and Erdemir (25) investigated the outcome of varicocelectomy in 3 groups. In group 1 both men and their partners were ≥35 years old, in group 2 men were ≥35 and their partners were <35 years old, and in group 3 both men and their partners were <35 years old. The median age of the spouse was 36 (35-38) in group 1, 30 (21-34) in group 2, and 25 (21-33) in group 3. No significant difference was detected in pregnancy rates between the groups. In their prospective study with 120 men, Zhang et al. (26) stated that ages of the patient and spouse were not associated with spontaneous pregnancy rate after varicocelectomy. We determined the median age of spouses in each group as well. The median age of the spouse was lowest for GR1 (23.22±3.69) and highest for GR4 (33.66±4.79) as expected. The difference in the median age of spouses between the groups was statistically significant (p=0.001) but no significant relationship was found between the age of the spouse and fertility (p=0.984).

Study Limitations

This study had a few important limitations. Firstly, it was a retrospective study. The low number of patients in GR1 and GR4 was another limitation. It would be more valuable if patients over the age of 40 could be evaluated in a separate group. The highest median age of the spouse was in GR4, but this value was below 35. A study including the evaluation of fertility rates in a group of men with a median spouse age >35 years will be more useful.

Table 3. Comparison of preoperative semen parameters between groups

	GR1 (n=18)	GR2 (n=58)	GR3 (n=44)	GR4 (n=18)	p
Sperm volume (mL)	3.61 (2.31-4.46)	3.58 (2.57-4.63)	3.38 (2.62-4.76)	3.75 (2.42-4.99)	0.957
Sperm concentration (x10^6/mL)	5.14 (2.8-9.25)	6.3 (2.75-10)	6.9 (2.03-16.5)	7.9 (3.5-30.5)	0.493
Progressive motility (%)	30 (23-38)	36 (20.75-42.5)	31.5 (13-42)	28.5 (13.5-37.5)	0.368
Non-progressive motility (%)	8.67 (6.75-10)	7 (6-9)	8 (6.25-10)	7.5 (6-9)	0.609
Nonmotile sperm (%)	61.38 (55.5-69.25)	56.5 (49.5-68.25)	60 (49-78)	62(53.5-75.5)	0.415
TMSC (x10^6)	6.87 (2.71-14.55)	7.73 (1.73-15.91)	8.29 (1.2-19.38)	5.25 (4.02-27.2)	0.977
Morphology (% of normal forms)	0 (0-1)	0.5 (0-1)	0 (0-1)	0 (0-1.25)	0.579

TMSC: Total motile sperm count
All values are median (interquartile range)

Table 4. Comparison of postoperative semen parameters between groups

	GR1 (n=18)	GR2 (n=58)	GR3 (n=44)	GR 4 (n=18)	p
Sperm volume (mL)	3.45 (2.37-5.12)	3.97 (3.08-4.74)	3.9 (2.85-4.75)	3.34 (1.61-4.59)	0.293
Sperm concentration (x10^6/mL)	13 (3.2-24.5)	15.76 (3.9-25)	12.2 (6.05-19.55)	23 (5-36.75)	0.437
Progressive motility (%)	39.5 (25.25-48.25)	40 (27-47)	35.5 (24.25-50.5)	35 (29-41.5)	0.853
Non-progressive motility (%)	7.05 (5-9)	7 (5.75-9)	7 (6-10.75)	8.5 (6.75-10.2)	0.265
Non-motile sperm (%)	55 (46.5-65.75)	53 (46.75-63)	55.5 (44-66)	57 (51-62.25)	0.915
TMSC (x10^6)	19.32 (4.31-39.06)	16.12 (3.97-46.85)	17 (5.58-32.01)	15.64 (4.66-44.3)	0.916
Morphology (% of normal forms)	1 (0-2)	1 (0-2)	0.5 (0-2)	1 (0-1.5)	0.631

TMSC: Total motile sperm count
All values are median (interquartile range)

Table 5. Comparison of fertility rates between groups

	GR1 (n=18)	GR2 (n=58)	GR3 (n=44)	GR4 (n=18)	p
Overall fertility (%)	13 (72.22)	41 (70.7)	29 (65.9)	7 (38.89)	0.083
Way of fertility					0.454
Natural conc. (%)	8 (44.44)	18 (31.03)	14 (31.8)	5 (27.78)	
ART (%)	5 (27,78)	23 (56.09)	15 (34.09)	2 (11.11)	

Conc: Conception, ART: Assisted reproductive techniques

Conclusion

In literature, various age groups were used in different studies. There is no standardized age-group distinction. In some studies, patients were divided into only two groups and men with large age differences were evaluated in the same group. Although these factors make it difficult to reach a certain conclusion, it is generally accepted that in all age groups semen parameters significantly improve after varicocelectomy, and there is no difference in fertility rates between the age groups. This study also supports these results. Varicocelectomy can be recommended to all infertile men regardless of age. However, the age of the spouse should be considered as fertility potential decreases significantly after the age of 35 in women.

Ethics

Ethics Committee Approval: This study was approved by the Institutional Ethics Committee (approval number: 2021/333).

Informed Consent: Owing to the study design patient consent was waived.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: A.İ., C.E., B.D., S.K., İ.O., M.A., Concept: A.İ., Design: A.İ., C.E., B.D., S.K., İ.O., M.A., Data Collection or Processing: A.İ., C.E., B.D., S.K., İ.O., M.A., Analysis or Interpretation: A.İ., C.E., B.D., S.K., İ.O., M.A., Literature Search: A.İ., C.E., B.D., S.K., İ.O., M.A., Writing: A.İ., C.E., B.D.

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