ARAB JOURNAL OF UROLOGY
2025, VOL. 23, NO. 1, 53–61
https://doi.org/10.1080/20905998.2024.2400630

ORIGINAL ARTICLE

OPEN ACCESS Check for updates

Does age matter? Impact of age on testicular function and pregnancy outcomes following microsurgical varicocelectomy in patients with grade 3 varicocele

Haitham ElBardisi [a,b,c], Ahmad AlMalki [a,c], Kareim Khalafalla [a,c], Walid El Ansari [d,e,f], Mohamed Arafa [a,b,g], Mohammed Mahdi [a,h,i], Khalid AlKubaisi [a], Sami AlSaid [a,b], Onder Canguven [a,b] and Ahmad Majzoub [a,b]

[a]Department of Urology, Hamad Medical Corporation, Doha, Qatar; [b]Department of Urology, Weill Cornell Medical-Qatar, Doha, Qatar; [c]Department of Urology, College of Medicine, Qatar University, Doha, Qatar; [d]Department of Surgery, Hamad Medical Corporation, Doha, Qatar; [e]College of Medicine, Qatar University, Doha, Qatar; [f]Department of Clinical Population Health, Weill Cornell Medicine-Qatar, Doha, Qatar; [g]Department of Andrology, Cairo University, Cairo, Egypt; [h]Department of Urology, University of Texas Health Science Center, Houston, TX, USA; [i]Department of Urology, MD Anderson Cancer Center, Houston, TX, USA

ABSTRACT

Objective: To evaluate the effects of age on semen and hormonal parameters following microsurgical varicocelectomy among patients with grade 3 varicocele, and to compare fertility outcomes between younger (<40 years) and older (≥40 years) men.

Methods: Retrospective cohort study of infertile patients with clinical left grade 3 varicocele who underwent microsurgical subinguinal varicocelectomy (MV). Patients meeting the inclusion criteria ($N = 550$) were divided into two groups based on their age at the time of MV: <40 ($n = 441$) and ≥40 years ($n = 109$). Preoperative semen analysis and hormonal profiles were collected, and follow-up data including pregnancy outcomes were gathered at 3 and 6 months post-surgery.

Results: Post-surgery, the younger group showed significant improvements in sperm count and total motility ($p < 0.001$ for each) as well as progressive motility ($p = 0.005$), while older men exhibited a significant increase in progressive motility ($p = 0.002$). For each group, there were no significant changes in hormonal levels post-surgery. Comparative analysis across the two age groups showed no significant differences in the postoperative extent of semen improvements or pregnancy.

Conclusion: MV is a viable option for older infertile patients as it is for younger infertile men with grade 3 varicocele, and both groups can achieve similarly high rates of pregnancy outcomes.

ARTICLE HISTORY
Received 16 July 2024
Accepted 31 August 2024

KEYWORDS
Male infertility; semen analysis; microsurgical subinguinal varicocelectomy; spontaneous pregnancy; age impact

Introduction

Varicocele is one of the most common causes of male infertility. Its prevalence ranges from 15% to 20% among all men and is implicated in 40% to 80% of cases of primary and secondary infertility, respectively [1] Varicocele is commonly an asymptomatic condition, but it may necessitate treatment if associated with pain, abnormalities in semen parameters, or causing ipsilateral testicular atrophy [2]. Varicocele potentially impairs the function of the testes through several mechanisms, such as elevated scrotal temperature, restricted blood flow leading to ischemia, an increase in oxidative stress, and the backward flow of metabolites from the adrenal gland [1,3].

The Dubin and Amelar grading system, established in 1970, categorized varicoceles into three distinct grades based on clinical examination. A Grade 1 varicocele can only be felt during the Valsalva maneuver when the patient is standing. Grade 2 can be detected by palpation even when the patient is standing but not performing Valsalva. Grade 3 varicoceles are prominent enough to be seen through the scrotal skin [4]. This classification does not include subclinical varicoceles detected through ultrasonography [5]. As the grade of varicocele increases, it significantly impacts testicular function [6], manifesting in various detrimental effects. This includes alterations in spermatogenesis [6] at both the cellular [7] and ultrastructural levels [8,9], reduction in testicular size [10], changes in seminiferous tubule content [11], and decreased testosterone hormonal production [12,13].

Varicocelectomy is the standard method for treating a clinically significant varicocele. Various techniques, such as radiographic embolization, and laparoscopic,

CONTACT Kareim Khalafalla Dr.Kareim.moh2@gmail.com Clinical Associate Professor in Urology, College of Medicine, Qatar University - Urology department, Ambulatory Care Center, Hamad Medical Corporation, P.O 3050, Doha, Qatar

retroperitoneal, inguinal, and subinguinal procedures, are used to cease the negative effects of varicocele. Among these, microsurgical subinguinal varicocelectomy is considered the most effective treatment option [14,15].

The occurrence of varicocele is subject to variation by age with some studies suggesting an increase in incidence as men age [16]. The association between varicocele, age, and infertility remains an intriguing topic for investigation. Currently, guidelines from the American Urological Association, American Society of Reproductive Medicine [17], and the European Association of Urology [18] do not provide a definitive stance regarding an age limit for varicocelectomy, nor do they offer clear guidance on the implications of delaying surgical intervention for high-grade varicocele. Despite the presence of many meta-analyses and randomized clinical trials supporting the positive seminal, hormonal, and pregnancy outcomes occurring after varicocelectomy, according to the available literature [19–22], there are no studies that have mainly looked into the effects of delayed surgical intervention particularly in patients with grade 3 varicocele as well as its impact on future pregnancy rates. This lack of consensus highlights the need for further research and discussion to establish more detailed recommendations.

This study aims to fill the knowledge void by investigating the impact of age on men with grade 3 varicocele among patients from two age groups, one presenting at a younger age and the other presenting at an older age. This will be done through:

(1) Comparing the initial semen analysis and hormonal profile between patients from each group
(2) Comparing the improvement in semen analysis and hormonal profile after varicocelectomy between the two groups.
(3) Comparing spontaneous and assisted pregnancy outcomes between the two groups.

Methods

Study design and population

This retrospective study was conducted at a tertiary medical center, Hamad Medical Corporation, after receiving approval from the ethics committee with an informed consent waiver. The research focused on male patients with clinical grade 3 left varicocele who visited the male infertility unit between January 2015 and July 2020. We reviewed the files of 1500 patients presented with primary or secondary infertility, who were offered subinguinal microsurgical varicocelectomy (MV). Preoperative semen analysis and hormonal profile were collected, alongside follow-up data 6 months post-surgery. The couples were followed up for pregnancy outcome and the spontaneous pregnancy rate was recorded as well as that for couples who underwent assisted reproductive technique (ART).

Inclusion and exclusion criteria

Included were patients presenting with clinical left grade 3 varicocele associated with infertility who underwent microsurgical subinguinal varicocelectomy in the male infertility unit in our institute.

Exclusion criteria encompassed azoospermic or severe oligozoospermic individuals (<1 million/ml), those with genetic anomalies, or those receiving prior infertility treatments such as antioxidants, estrogen receptor modulators, or aromatase inhibitors during the peri-surgical period. Patients with a history of varicocelectomy, orchidopexy, or exposure to gonadotoxins were also excluded.

Group division

Patients were divided based on their age at the time of varicocelectomy into two groups under 40 years and 40 years or older. This age cut off was based on previously published literature indicating that older patients (≥40) with varicocele were associated with lower testicular size, softer testicular consistency, and lower testosterone levels, especially in older patients with bilateral and high-grade varicocele [23].

Study procedures

All the participants underwent a detailed history-taking and physical examination. The clinical varicocele diagnosis was made through a genital examination and graded using the Dubin and Amelar criteria [4]. To confirm the diagnosis, scrotal ultrasonography was performed to assess venous reflux during the Valsalva maneuver and measure the maximal venous diameter. Serum hormone levels, including testosterone (TT; reference values 10.4–35 nmol/L), luteinizing hormone (LH; reference values 1–9 IU/L), follicular stimulating hormone (FSH; reference values 1–19 IU/L), and estradiol (reference values 73–275 pmol/L), were collected from each participant between 7:00 and 9:00 am. The immunoassay chemiluminescence method (Architect i1000SR®, Abbott Systems, Illinois, USA) was used to analyze the collected samples in the endocrine laboratory of our facility.

Semen tests

Semen samples were collected from all participants after abstaining from intercourse for 2–7 days. Each semen sample was evaluated according to the WHO fifth edition guidelines [24]. Seminal oxidative stress was evaluated by measuring the static oxidation-reduction potential (sORP) of neat, liquefied semen samples using the MiOXSYS System (Caerus Biotech, Geneva), and the sORP level cut off was considered high if sORP > 1.41 mV/106/ml [25]. The Halosperm kit (Halotech DNA, S.L., Madrid) was used to measure sperm DNA fragmentation SDF based on the sperm chromatin dispersion test, and the SDF level cut-off was considered high if SDF was ≥ 30% [26].

Microsurgical varicocelectomy

Left microsurgical sub-inguinal varicocelectomy was carried out by the same team using a standardized approach [27]. Prior to the surgery, the patients were given 2 g of cefazolin intravenously, and the surgeries were performed under general anesthesia. The patients were placed in a supine position and draped properly. A 2 to 3-cm subinguinal incision was made, and the spermatic cord was held using ring forceps. The cord was inspected, and all dilated external spermatic veins were tied. The surgical microscope was used under 18× magnifications to carefully dissect the internal spermatic veins. These veins were then ligated using titanium clips and cut. All identified lymphatics were spared, and the vas deference was left intact in its sheath together with vasal vessels. Arterial flow was checked using Doppler at the beginning and end of the surgery. After achieving hemostasis, the incision was closed in two layers using Polyglactin absorbable sutures.

Sample size

Sample size calculation was performed using the Epi info 7 software from the Centers for Disease Control and Prevention (CDC). We set the expected frequency at 50% with a confidence interval of 95% and an acceptable margin of error. A minimum sample size of 384 patients was required to achieve adequate power for detecting significant differences in the study's outcomes. Given that our study included 550 patients, the sample size exceeds the calculated minimum, providing sufficient power to support the validity and reliability of our findings.

Statistical analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS, version 25). The normal distribution of variables was tested using histogram and Shapiro–Wilk test. Continuous values were presented as median and interquartile range, while categorical variables as numbers (percentages). The Kruskal–Wallis test was used to compare variables between the total study population, patients <40 years and ≥40 years of age. Spearman's correlations were determined between patients' age and all the included continuous variables. Pre- and post-operative results were compared in each study group using Wilcoxon signed-rank test. The changes in semen and hormone parameters between the two study groups were compared using Mann–Whitney test. Chi Squared test was used to assess the extent of improvement in semen and hormone parameters and the pregnancy rate for patients < or ≥40 years of age at 6 months after MV. Nonparametric tests were chosen as data was not normally distributed. A p value of < 0.05 was considered statistically significant.

Results

This study assessed the impact of microsurgical varicocelectomy on semen and hormonal parameters among 550 men with clinically confirmed grade 3 varicocele, stratified into two age groups: <40 years ($n = 441$) and ≥40 years ($n = 109$).

Preoperative (baseline) characteristics of the study population

Table 1 shows that demographically, the median age for the younger group was 30 years (IQR 25–34), and for the older group, 45 years (IQR 41–51), with corresponding significant differences in BMI and smoking status. Clinically, the older group had a significantly larger right spermatic vein diameter. Pertaining to laboratory investigations, the older group exhibited significantly poorer semen quality and sperm function in terms of lower progressive and total motility and sORP. Hormonal analysis revealed that the older group had significantly higher LH and lower TT levels.

Unilateral varicocelectomy was undertaken 80.2% of the sample (364 vs 77 patients in younger and older age groups respectively) while bilateral varicocelectomy was conducted in 19.8% (77 vs 32) patients in younger and older age groups, respectively (data not presented).

Preoperative correlations

Table 2 depicts the preoperative correlations between age and semen and hormone parameters. Patient age was significantly positively correlated with the wife's age, body mass index (BMI), and SDF, as well as right vein diameter; but significantly negatively correlated with total motility and progressive motility, and TT. The remaining variables were no correlated with age.

Postoperative outcomes

Table 3 and Figure 1 show the post-operative changes at 6 months in semen and hormone parameters pre/post varicocelectomy in patients < or ≥40 years of age. In the younger group, there were post-varicocelectomy

Table 1. Preoperative characteristics of the study population.

Variable	Total sample	Age		P value
	N = 550	<40 years n = 441	≥40 years n = 109	
Demography				
Age (years)	32 (26 – 38)	30 (25 – 34)	45 (41 – 51)	*<0.001*
Wife Age (years)	28 (24 – 32)	26 (23.25 – 30)	31.5 (28 – 35)	*<0.001*
BMI (Kg/m^2)	25.24 (22 – 29.01)	24.7 (21.4 – 28.4)	28.1 (25.4 – 30.7)	*<0.001*
Smoking n (%)				*0.015*
Yes	294 (53.5)	231 (52.4)	64 (58.3)	
No	138 (25.1)	104 (23.6)	34 (31.1)	
Ex-smoker	118 (21.4)	106 (24)	11 (10.7)	
Clinical				
Testis Size (cm^3)				
Right	15 (12 – 18.35)	15.3 (12 – 18.3)	14.9 (11.8 – 18.7)	0.771
Left	15 (9.6 – 15)	15 (9.6 – 15)	15 (9.6 – 15)	0.381
Spermatic Vein size (mm)				
Right	2.5 (2 – 3.1)	2.5 (2 – 3.1)	2.8 (2.2 – 3.4)	*0.020*
Left	4.3 (3.6 – 5)	4.3 (3.6 – 5)	4.4 (3.6 – 5)	0.469
Varicocele n (%)	550 (100%)	441 (100%)	109 (100%)	0.365
Left grade 3	191 (34.6%)	162 (36.9%)	29 (27.3%)	
Right varicocele				
Laboratory				
Semen				
Semen volume (ml)	3 (2 – 4.5)	3 (2 – 4.5)	2.5 (1.75 – 3.9)	0.083
Sperm count (x10^6/ml)	26 (9.4 – 45)	26 (9.4 – 46.2)	25 (9 – 40)	0.375
Total motility (%)	50 (24 – 58.75)	50 (27 – 60)	40 (14.25 – 55)	*0.006*
Progressive motility (%)	15 (1.25 – 30)	15 (5 – 32)	5 (0 – 20)	*<0.001*
Normal forms (%)	12 (5 – 41.75)	15 (5 – 42.25)	11 (4 – 41.25)	0.179
Sperm Function				
SDF (%)	24 (19 – 39)	23.5 (18 – 35)	30 (20 – 49.5)	0.741
sORP (mVolt/10^6 sperm)	2.51 (1.08 – 4.86)	2.5 (1.1 – 4.9)	2.6 (0.8 – 3.8)	*0.016*
Hormones				
Estradiol (pmol/ml)	93 (72 – 116)	92 (71.7 – 115.7)	93.3 (73 – 118)	0.573
FSH (IU/L)	5 (3 – 6.4)	4.8 (3 – 6)	5 (3 – 7.9)	0.601
LH (IU/L)	3.2 (2 – 6)	3 (2 – 5.1)	5 (3 – 8)	*<0.001*
TT (nmol/L)	16.81 (13.3 – 21.6)	17.3 (14.1 – 22)	13.9 (10.7 – 18.6)	*<0.001*

Cell values represent median (range), except where stated; SDF: Sperm DNA Fragmentation; ORP: Oxidation Reduction Potential; FSH: Follicular Stimulation Hormone; LH; Luteinizing Hormone: TT: Testosterone; italicized cells indicate statistical significance.

Table 2. Preoperative correlations between age and semen and hormone parameters.

Parameter	Age	
	r[a]	*p* value[b]
Age (years)	1	
Wife Age (years)	0.548	*<0.001*
BMI (Kg/m^2)	0.466	*<0.001*
Right testis Size (cm^3)	0.086	0.232
Left testis Size (cm^3)	0.026	0.551
Rt vein size (mm)	0.185	*<0.001*
Lt vein size (mm)	−0.075	0.116
Semen volume (ml)	0.060	0.201
Sperm count (x106/ml)	−0.030	0.529
Total motility (%)	−0.118	*0.013*
Progressive motility (%)	−0.110	*0.021*
Normal forms (%)	0.003	0.957
sORP (mVolt/10^6 sperm)	−0.066	0.655
SDF (%)	0.192	*0.009*
Estradiol (pmol/ml)	0.100	0.057
FSH (IU/L)	0.260	*<0.001*
LH (IU/L)	0.029	0.565
TT (nmol/L)	−0.270	*<0.001*

[a]Spearman Correlation: [b] 2-tailed; SDF: Sperm DNA Fragmentation; ORP: Oxidation Reduction Potential; FSH: Follicular Stimulation Hormone; LH; Luteinizing Hormone: TT: Testosterone; italicized cells indicate statistical significance.

significant improvements in sperm count and total and progressive motility. In the older group, there was significant improvements in progressive motility only. No other improvements were observed in the remaining variables in both groups.

Table 4 depicts the extent of improvements after MV. There were no significant differences observed in the extent of improvement between the younger and older groups across any of the variables examined, with both groups showing similar improvements across the evaluated parameters.

Fertility outcomes

Table 5 shows the pregnancy outcome by age. Natural and assisted conception rates post-intervention did not differ significantly between the groups.

Discussion

Varicocele negatively impacts fertility [1], and surgical varicocelectomy is considered the most effective treatment option to correct the negative effects of varicocele on testicular function [28]. However, previous research that appraised the effect of age on the outcome of varicocelectomy examined patients with a mixture of grades of varicoceles (grades 1–3) and most did not follow up with the patients to assess the impact as to whether pregnancy was achieved after varicocelectomy or otherwise [23,29,30,31,32,33]. Based on these methodological

Table 3. Post-operative changes at 6 months in semen and hormone parameters pre/post varicocelectomy in patients < or ≥40 years of age.

Parameter	Age					
	<40 years (*n* = 441)			≥40 years (*n* = 109)		
	Pre-op	Post-op	P value	Pre-op	Post-op	P value
Semen						
Semen volume (ml)	3 (2 – 4.5)	3 (2 – 4.5)	0.631	2.5 (1.75 – 3.9)	2.5 (2 – 4)	0.359
Sperm count (x10^6/ml)	26 (9.4 – 46.2)	34 (13.5 – 58)	*<0.001*	25 (9 – 40)	26 (10.1 – 45)	0.406
Total motility (%)	50 (27 – 60)	51 (35 – 62)	*<0.001*	40 (14.25 – 55)	44 (20 – 55)	0.176
Progressive motility (%)	15 (5 – 32)	16 (5–33)	*0.005*	5 (0 – 20)	15 (1 – 27)	*0.002*
Normal forms (%)	15 (5 – 42.25)	16.5 (5-42)	0.280	11 (4 – 41.25)	10 (5 – 29)	0.788
Sperm Function						
sORP (mVolt/10^6 sperm)	23.5 (18 – 35)	25 (14 – 35)	0.456	30 (20 – 49.5)	30 (22 – 41.5)	0.500
SDF (%)	2.5 (1.1 – 4.9)	2.1 (1.2 – 4.1)	0.077	2.6 (0.8 – 3.8)	2.5 (1.9 – 4.1)	0.268
Hormones						
Estradiol (pmol/ml)	92 (71.7 – 115.7)	96 (70 – 121)	0.792	93.3 (73 – 118)	85.5 (62.9 – 118)	0.171
FSH (IU/L)	4.8 (3 – 6)	4 (3 – 5.4)	0.128	5 (3 – 7.9)	4.7 (3.1 6.9)	0.529
LH (IU/L)	3 (2 – 5.1)	3 (2 – 6.325)	0.079	5 (3 – 8)	5 (3 – 9.3)	0.893
TT (nmol/L)	17.3 (14.1 – 22)	16.6 (12.4 – 21.4)	0.636	13.9 (10.7 – 18.6)	13.4 (8.9 – 21.7)	0.390

Cell values represent median (range) SDF: Sperm DNA Fragmentation; ORP: Oxidation Reduction Potential; FSH: Follicular Stimulation Hormone; LH; Luteinizing Hormone: TT: Testosterone; italicized cells indicate statistical significance.

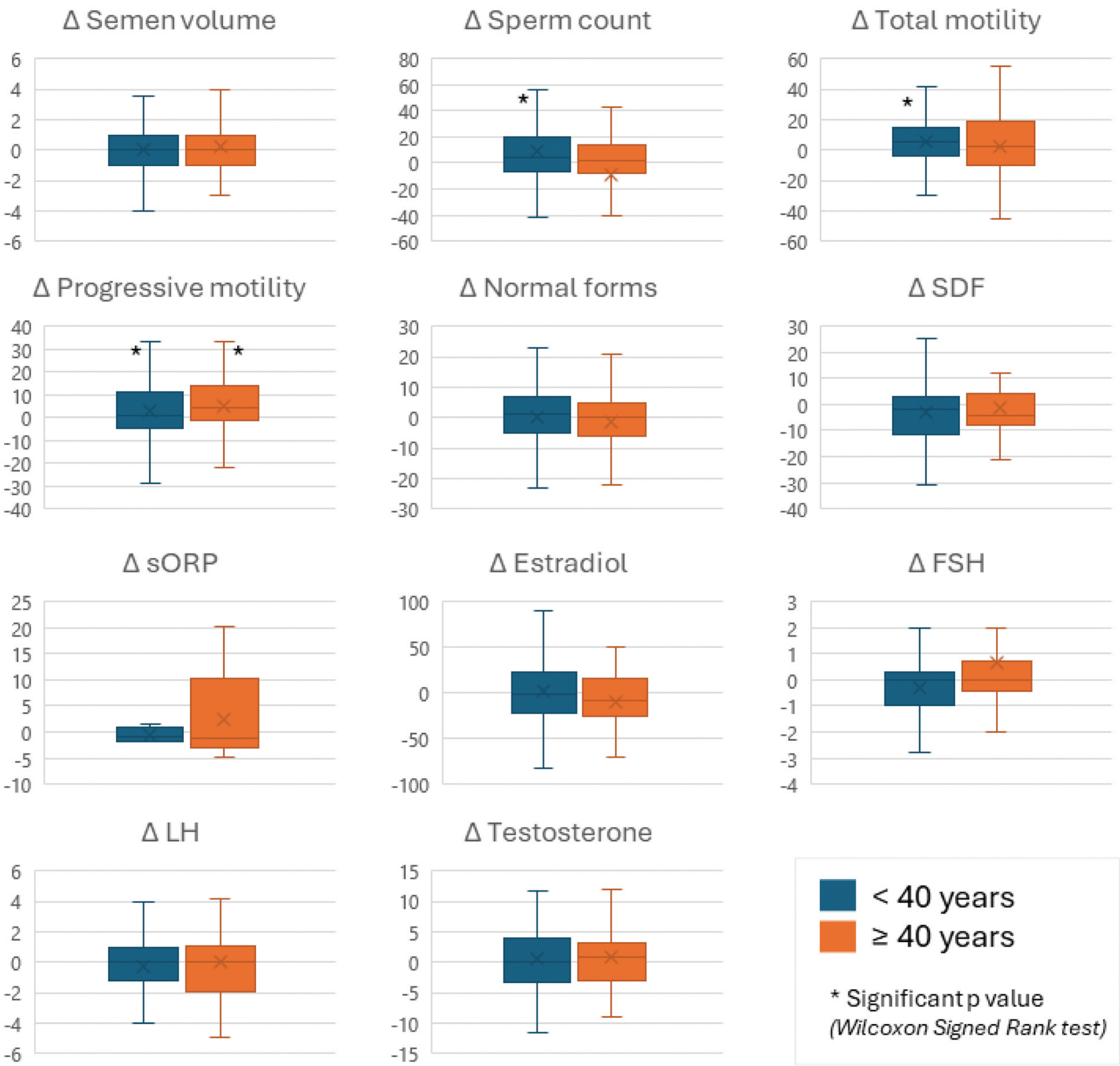

Figure 1. Changes in semen and hormone parameters pre- and post-varicocelectomy in patients < or ≥40 years of age.

Table 4. Extent of improvement in semen and hormone parameters for patients < or ≥40 years of age at 6 months after MV.

Parameter	Age		P value
	<40 years	≥40 years	
Semen			
Semen volume	42.9	48.7	0.224
Sperm concentration	60.5	56.4	0.306
Total motility	61.1	58.7	0.405
Progressive motility	51.2	54.7	0.350
Morphology	52.9	48.0	0.278
Sperm Function			
SDF	55.6	65.0	0.323
sORP	75.0	80.0	0.722
Hormones			
Estradiol	53.4	66.7	0.140
FSH	38.3	30.6	0.264
LH	46.3	40.5	0.340
TT	54.5	59.5	0.372

All cells represent % (except p-value), SDF: Sperm DNA Fragmentation; ORP: Oxidation Reduction Potential; FSH: Follicular Stimulation Hormone; LH; Luteinizing Hormone: TT: Testosterone.

Table 5. Pregnancy outcome between patients < or ≥40 years of age.

Pregnancy	Overall	Age		P value
		<40 years	≥40 years	
Yes				0.381
Natural	(32.4)	(35.7)	[25]	
Assisted	(26.1)	(23.5)	(31.8)	

Cell values represent frequency (%); Pregnancy outcome for 142 patients.

and sample limitations of previous studies, there remains a lack of consensus about the association of a patient's age with the fertility benefits after varicocelectomy, particularly in cases with high-grade varicoceles, with some researchers preferring ART rather than varicocelectomy for older patients. Such an 'age cut-off' proposition for a beneficial fertility outcome following varicocelectomy has not been examined in depth among patients with exclusive grade three varicocele, as well as the impact of the procedure on subsequent pregnancy. The current study undertook this task.

We appraised the association between MV for grade 3 varicocele and semen and hormonal parameters among a large cohort of 550 infertile men (441 men <40 years old and 109 men ≥40 years); and compared the post-operative changes and their extents within and across both groups of patients; and followed up these patients to gauge whether the post-operative semen changes led to the ultimate outcome of pregnancy and their rates across both groups. To our knowledge, this is the first study to undertake such an in-depth appraisal of these parameters.

Our main findings are that, after MV, when each age group is compared to its pre-operative levels (i.e. intra-group comparisons), younger men exhibited significant improvements in sperm concentration, total and progressive motility; whilst older men (≥40 years) significantly improved only in progressive motility. However, inter-group comparisons showed that despite the preoperative significant age-related differences in some semen and hormonal parameters, the extent of post-operative improvements was not significantly different between the age groups. Similarly, pregnancy rates were comparable, with 56.80% of the older group and 59.20% of the younger group achieving pregnancy ($p = 0.381$). Below, we discuss these findings in detail.

Preoperatively, when comparing the two age groups, the <40 years group demonstrated significantly better seminal parameters, including total and progressive motility, as well as sORP. In contrast, the >40 years group exhibited significantly lower testosterone levels and correspondingly higher LH levels, indicating better gonadal function in the younger age group. In addition to that, the current study observed that older age was significantly negatively correlated with total and progressive motility and TT and positively correlated significantly with BMI and SDF. These findings support the literature, as progressive testicular deterioration was evident with age, particularly with high-grade varicocele [10]. For instance, a study found that among adults aged ≥40 years, varicocele was associated with lower testicular size, softer testicular consistency, and lower TT levels, especially in older patients with bilateral and high-grade varicocele [23]. In agreement, another study emphasized that among men with a mean age of 60.7 years, those with varicoceles had significantly smaller and softer testicles; and higher varicocele grades were more strongly associated with soft testicles than lower-grade varicoceles [34]. Others similarly noted that patients with grade 3 varicocele had lower sperm count and fertility index compared to those with grade 1 and 2 varicocele [6].

Following microsurgical varicocelectomy (MV), we noted that patients under 40 years of age showed improvements in sperm concentration, total motility, and progressive motility. On the other hand, patients above 40 years demonstrated enhancements solely in progressive motility. Similar studies utilizing the same MV technique [30,31] divided their cohorts into three ascending age groups and observed increases in sperm concentration and motility across all categories post-MV. However, compared to our strict grade 3 varicocele sample, these two studies had about half their patients with lower grades 1 and 2 [30,31], which are less deleterious compared to grade 3 [6,23,34,35]. This may explain the variance in sperm concentration outcomes when compared to our findings, casting doubt on the comparability of these results.

As for the extent of improvements after MV, the current study found the differences in the extent of improvement between the younger and older groups did not reach statistical significance for any of the parameters examined. Such lack of significance for the extent of improvement across age groups is congruent with others who similarly noted no significant differences in the mean improvement of some semen parameters (concentration, motility, morphology) across their two patient groups aged ≥40 years and <40 years with grade 2 or 3 varicocele after MV [33]. Collectively, such findings strongly suggest that MV can still benefit older patients with high-grade varicocele as it does for younger patients. This is particularly important for older males with high grade varicocele exploring fertility options, as varicocelectomy remains a viable option, especially if they have abnormal semen parameters, or hypogonadism, with a younger spouse, saving them the extra time and effort of exploring other modalities e.g. ART.

In terms of pregnancy, 56.8% and 59.2% of our patients achieved pregnancy in the younger and older groups respectively. We are unable to directly compare these pregnancy rates with others as no studies to date assessed the triad of age, repair of grade 3 varicocele, and subsequent pregnancy. The current sample's pregnancy rates raise three important points. First, in terms of spontaneous pregnancy, our post-varicocelectomy spontaneous pregnancy rate of 32.4% was close to the mean 36.5% spontaneous pregnancy rate reported by a recent comprehensive meta-analysis of 9 studies (3 prospective, 6 retrospective) [36] comprising a mixture of grades 1, 2 and 3 varicoceles. Second, for those who did not achieve spontaneous post-MV pregnancy and require in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI), improvements after MV contribute to better ART outcomes should it be required. A body of evidence has demonstrated that varicocelectomy performed prior to IVF/ICSI improves pregnancy outcomes [37,38,39]. However, one study comparing grade 3 varicocele men who underwent MV vs those who did not, found no difference in IVF/ICSI pregnancy rates. However, there was a significantly longer time to assisted pregnancy in the varicocelectomy group (6.0 ± 0.5 vs 2.7 ± 0.4 years) [40], suggesting the possibility of other contributing factors affecting the difficulty in achieving pregnancy. Unfortunately, the authors did not undertake regression analysis to appraise whether other factors might have confounded the pregnancy outcomes.

In addition, pertaining to the overall (spontaneous and assisted) pregnancy, our findings echo a study by Zini et al. (2008) of grades 2 and 3 infertile men aged <40 years ($n = 466$) and ≥40 years ($n = 115$) who achieved post-MV overall pregnancy rates of 53% and 59% for younger and older groups respectively, very close to our observed rates. Of particular note are the extremely close rates for the ≥40 years group for the current and Zini's studies (59.20% vs 59% respectively) [33], presenting compelling evidence that pregnancy rates are still comparable with other studies after MV for older age groups even when they are exclusive grade 3 patients.

The findings from this study carry several practical implications that are highly relevant to existing literature. Firstly, age should not be viewed as a barrier to microsurgical varicocelectomy in men with grade 3 varicocele, as both younger and older patients showed comparable improvements in semen parameters and pregnancy rates. This challenges the preference for assisted reproductive techniques (ART) over surgery in older men, reinforcing varicocelectomy as a viable option. Secondly, clinicians can use these results to more effectively counsel older patients, highlighting that treatment decisions should be based on individual factors such as varicocele grade and baseline semen parameters, rather than age alone. Finally, this study supports the broader use of varicocelectomy in the management of male infertility.

The current study has limitations. Retrospective study designs have their inherent limitations, our findings are from a single center, and the availability of a control group would have been beneficial to validate the results. Hence, future research would benefit from prospective, multicenter, controlled studies, particularly on exclusive grade 3 varicoceles to validate the results. In addition, studies reporting outcomes of MV would benefit from reporting their outcomes by varicocele grade rather than presenting aggregate results in order to facilitate precise head-to-head comparisons with other studies. Nevertheless, the study has many strengths, to our knowledge, this is the first study to undertake an in-depth appraisal of the topic, comparing the intra-group and inter-group improvements in semen analysis and hormonal profile and their extents among the largest cohort to date of younger and older patients with grade 3 varicocele after MV, with the novel appraisal of the pregnancy outcomes between the two groups. Furthermore, all surgical procedures were undertaken by the same group of experienced surgeons, thus limiting possible bias due to surgeon experience and learning curves.

Conclusion

MV is a viable option for older infertile patients as it is for younger infertile men with grade 3 varicocele, and both groups can achieve high rates of pregnancy outcomes similarly. After microsurgical varicocelectomy, younger men tend to show significant improvements among more parameters (sperm concentration, and total and progressive motility) than older men (progressive motility only). However, there are no statistically significance differences in the extent of improvement and successful pregnancy between the younger and older groups across all the parameters examined. These findings have important clinical implications in terms of counseling patients, particularly those above 40 years with high-grade varicocele when selecting treatment modalities for their infertility.

Acknowledgments

The authors thank the Laboratory technicians and Coordinators at the Male infertility Unit at the Ambulatory care center, Hamad Medical Corporation.

Disclosure statement

No potential conflict of interest was reported by the author (s).

ORCID

Haitham ElBardisi http://orcid.org/0000-0003-3902-7924
Ahmad AlMalki http://orcid.org/0000-0002-4155-6676
Kareim Khalafalla http://orcid.org/0000-0001-9476-4869
Walid El Ansari http://orcid.org/0000-0003-0961-1302
Mohamed Arafa http://orcid.org/0000-0003-0107-8857
Mohammed Mahdi http://orcid.org/0000-0003-0607-2489
Khalid AlKubaisi http://orcid.org/0009-0001-2834-1371
Sami AlSaid http://orcid.org/0000-0002-1209-1283
Onder Canguven http://orcid.org/0000-0002-1010-0609
Ahmad Majzoub http://orcid.org/0000-0001-7423-6241

Author contributions

Conceptualization: Haitham ElBardisi, Mohamed Arafa, Ahmad Majzoub
Methodology: Haitham ElBardisi and Mohamed Arafa
Formal analysis: Ahmad Majzoub
Data Curation: Kareim Khalafalla, Mohammed Mahdi and Walid El Ansari
Writing – Original Draft: Haitham ElBardisi, Mohamed Arafa, Ahmad Majzoub, Ahmad AlMalki and Kareim Khalafalla
Writing – Review & Editing: Khalid AlKubaisi, Sami AlSaid, Onder Canguven Haitham ElBardisi, Mohamed Arafa, Ahmad Majzoub, Ahmad AlMalki and Kareim Khalafalla
Supervision: Mohamed Arafa and Ahmad Majzoub

References

[1] Jensen CFS, Østergren P, Dupree JM, et al. Varicocele and male infertility. Nat Rev Urol. 2017;14(9):523–533. doi: 10.1038/nrurol.2017.98
[2] Peterson AC, Lance RS, Ruiz HE. Outcomes of varicocele ligation done for pain. J Urol. 1998;159 (5):1565–1567. doi: 10.1097/00005392-199805000-00043
[3] Clavijo RI, Carrasquillo R, Ramasamy R. Varicoceles: prevalence and pathogenesis in adult men. Fertil Steril. 2017;108(3):364–369. doi: 10.1016/j.fertnstert.2017.06.036
[4] Dubin L, Amelar RD. Varicocele size and results of varicocelectomy in selected subfertile men with varicocele. Fertil Steril. 1970;21(8):606–609. doi: 10.1016/S0015-0282(16)37684-1
[5] Zampieri N, Dall'agnola A. Subclinical varicocele and sports: a longitudinal study. Urology. 2011;77 (5):1199–1202. doi: 10.1016/j.urology.2010.09.057
[6] Steckel J, Dicker AP, Goldstein M. Relationship between varicocele size and response to varicocelectomy. J Urol. 1993;149(4):769–771. doi: 10.1016/S0022-5347(17)36203-1
[7] MacLeod J. Seminal cytology in the presence of varicocele. Fertil Steril. 1965;16(6):735–757. doi: 10.1016/S0015-0282(16)35765-X
[8] Zini A, Defreitas G, Freeman M, et al. Varicocele is associated with abnormal retention of cytoplasmic droplets by human spermatozoa. Fertil Steril. 2000;74 (3):461–464. doi: 10.1016/S0015-0282(00)00703-2
[9] Terquem A, Dadoune JP. Morphological findings in varicocele: an ultrastructural study of 30 bilateral testicular biopsies. Int J Androl. 1981;4(5):515–531. doi: 10.1111/j.1365-2605.1981.tb00735.x
[10] Lipshultz LI, Corriere JN Jr. Progressive testicular atrophy in the varicocele patient. J Urol. 1977;117 (2):175–176. doi: 10.1016/S0022-5347(17)58387-1
[11] Johnsen SG, Agger P. Quantitative evaluation of testicular biopsies before and after operation for varicocele. Fertil Steril. 1978;29(1):58–63. doi: 10.1016/S0015-0282(16)43038-4
[12] Hudson RW. The endocrinology of varicoceles. Fertil Steril. 1988;49(2):199–208. doi: 10.1016/S0015-0282(16)59700-3
[13] Cayan S, Kadioglu A, Orhan I, et al. The effect of microsurgical varicocelectomy on serum follicle stimulating hormone, testosterone and free testosterone levels in infertile men with varicocele. BJU Int. 1999;84(9):1046–1049. doi: 10.1046/j.1464-410x.1999.00353.x
[14] Lv JX, Wang LL, Wei XD, et al. Comparison of treatment outcomes of different spermatic vein ligation procedures in varicocele treatment. Am J Ther. 2016;23(6): e1329–e34. doi: 10.1097/MJT.0000000000000232
[15] Liu Q, Zhang X, Zhou F, et al. Comparing endovascular and surgical treatments for varicocele: a systematic review and meta-analysis. J Vasc Interv Radiol. 2022;33(7):834–40.e2. doi: 10.1016/j.jvir.2022.03.013
[16] Levinger U, Gornish M, Gat Y, et al. Is varicocele prevalence increasing with age? Andrologia. 2007;39 (3):77–80. doi: 10.1111/j.1439-0272.2007.00766.x
[17] Schlegel PN, Sigman M, Collura B, et al. Diagnosis and treatment of infertility in men: AUA/ASRM guideline PART II. J Urol. 2021;205(1):44–51. doi: 10.1097/JU.0000000000001520
[18] Minhas S, Bettocchi C, Boeri L, et al. European association of urology guidelines on male sexual and reproductive health: 2021 update on male infertility. Eur Urol. 2021;80(5):603–620. doi: 10.1016/j.eururo.2021.08.014
[19] Yuan R, Zhuo H, Cao D, et al. Efficacy and safety of varicocelectomies: a meta-analysis. Syst Biol Reprod Med. 2017;63(2):120–129. doi: 10.1080/19396368.2016.1265161
[20] Mahdi M, Majzoub A, Khalafalla K, et al. Effect of redo varicocelectomy on semen parameters and pregnancy outcome: an original report and meta-analysis. Andrologia. 2022;54(10):e14525. doi: 10.1111/and.14525
[21] Russo GI, Asmundo MG, Perelli S, et al. Relationship between varicocele and male hypogonadism: a review with meta-analysis. Endocrines. 2022;3(1):100–106. doi: 10.3390/endocrines3010009
[22] Lira Neto FT, Roque M, Esteves SC. Effect of varicocelectomy on sperm deoxyribonucleic acid fragmentation rates in infertile men with clinical varicocele:

a systematic review and meta-analysis. Fertil Steril. 2021;116(3):696–712. doi: 10.1016/j.fertnstert.2021.04.003
[23] Besiroglu H, Otunctemur A, Dursun M, et al. The prevalence and severity of varicocele in adult population over the age of forty years old: a cross-sectional study. Aging Male. 2019;22(3):207–213. doi: 10.1080/13685538.2018.1465913
[24] World Health Organization. WHO laboratory manual for the examination and processing of human semen. 5th ed. Geneva: World Health Organization; 2010.
[25] Arafa M, Agarwal A, Al Said S, et al. Semen quality and infertility status can be identified through measures of oxidation-reduction potential. Andrologia. 2018;50(2): e12881. doi: 10.1111/and.12881
[26] Fernández JL, Muriel L, Goyanes V, et al. Simple determination of human sperm DNA fragmentation with an improved sperm chromatin dispersion test. Fertil Steril. 2005;84(4):833–842. doi: 10.1016/j.fertnstert.2004.11.089
[27] Zini A. Varicocelectomy: microsurgical subinguinal technique is the treatment of choice. Can Urol Assoc J. 2007;1(3):273–276. doi: 10.5489/cuaj.84
[28] Cannarella R, Shah R, Hamoda TAA, et al. Does varicocele repair improve conventional semen parameters? A meta-analytic study of before-after data. World J Mens Health. 2024;42(1):92–132. doi: 10.5534/wjmh.230034
[29] Kimura M, Nagao K, Tai T, et al. Age is a significant predictor of early and late improvement in semen parameters after microsurgical varicocele repair. Andrologia. 2017;49(3):e12620. doi: 10.1111/and.12620
[30] Reşorlu B, Kara C, Sahin E, et al. The significance of age on success of surgery for patients with varicocele. Int Urol Nephrol. 2010;42(2):351–356. doi: 10.1007/s11255-009-9589-y
[31] Hsiao W, Rosoff JS, Pale JR, et al. Older age is associated with similar improvements in semen parameters and testosterone after subinguinal microsurgical varicocelectomy. J Urol. 2011;185(2):620–625. doi: 10.1016/j.juro.2010.09.114
[32] El-Shazly M, Eissa B. Laparoscopic varicocelectomy in infertile men: does age matter? Urol Int. 2013;91(2):192–196. doi: 10.1159/000350860
[33] Zini A, Boman J, Jarvi K, et al. Varicocelectomy for infertile couples with advanced paternal age. Urology. 2008;72(1):109–113. doi: 10.1016/j.urology.2008.02.029
[34] Canales BK, Zapzalka DM, Ercole CJ, et al. Prevalence and effect of varicoceles in an elderly population. Urology. 2005;66(3):627–631. doi: 10.1016/j.urology.2005.03.062
[35] Takahara M, Ichikawa T, Shiseki Y, et al. Relationship between grade of varicocele and the response to varicocelectomy. Int J Urol. 1996;3(4):282–285. doi: 10.1111/j.1442-2042.1996.tb00535.x
[36] Wang Q, Yu Y, Liu Y, et al. Outcome of varicocelectomy on different degrees of total motile sperm count: a systematic review and meta-analysis. Syst Biol Reprod Med. 2019;65(6):430–436. doi: 10.1080/19396368.2019.1655813
[37] Ashkenazi J, Dicker D, Feldberg D, et al. The impact of spermatic vein ligation on the male factor in in vitro fertilization-embryo transfer and its relation to testosterone levels before and after operation. Fertil Steril. 1989;51(3):471–474. doi: 10.1016/S0015-0282(16)60556-3
[38] Esteves SC, Oliveira FV, Bertolla RP. Clinical outcome of intracytoplasmic sperm injection in infertile men with treated and untreated clinical varicocele. J Urol. 2010;184(4):1442–1446. doi: 10.1016/j.juro.2010.06.004
[39] Gokce A, Demirtas A, Ozturk A, et al. Association of left varicocoele with height, body mass index and sperm counts in infertile men. Andrology. 2013;1(1):116–119. doi: 10.1111/j.2047-2927.2012.00014.x
[40] Pasqualotto FF, Braga DP, Figueira RC, et al. Varicocelectomy does not impact pregnancy outcomes following intracytoplasmic sperm injection procedures. J Androl. 2012;33(2):239–243. doi: 10.2164/jandrol.110.011932