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ARTICLE

Evaluation of the effects of antioxidant treatment on sperm parameters and pregnancy rates in infertile patients after varicocelectomy: a randomized controlled trial

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Abstract

In this study, we aimed to evaluate the effect of oral antioxidant treatment on semen parameters and pregnancy rates in infertile men who underwent varicocelectomy. The study was conducted between January 2016 and January 2018. Subinguinal microscopic varicocelectomy was performed in 90 patients who were referred for infertility and diagnosed with clinical varicocele. The patients were divided into two groups. The first group received antioxidant treatment for 6 months after the operation ($n = 62$); the second group did not receive treatment after the operation ($n = 28$). The semen analysis was performed at the time of diagnosis and at 6 months postoperatively. The postoperative treatment semen parameters and pregnancy rates between the two groups were compared. The improvement in total sperm count ($+45.9\%$ vs $+26.8\%$), total motile sperm count ($+50.6\%$ vs $+29.7\%$), sperm concentration ($+71.4\%$ vs $+54.5\%$), sperm count in normal morphology ($+75.7\%$ vs $+39.9\%$), and total ($+28.6\%$ vs $+18.3\%$) and progressive motile sperm count ($+60.4\%$ vs $+38.9\%$) were significantly higher in the treated group than in the untreated group ($p = 0.011$, $p < 0.001$, $p = 0.008$, $p < 0.001$, $p = 0.024$ and $p < 0.001$, respectively). The clinical pregnancy rate in the first group was significantly higher than that in the second group (29% vs 17.9%) ($p = 0.029$). We concluded that the antioxidant treatment provides an important contribution to varicocelectomy outcomes and improves pregnancy rates.

Introduction

Infertility is defined as the inability of couples to have children despite 1 year of unprotected sexual intercourse [1]. The worldwide incidence of infertility is ~15%, and male infertility is responsible for 50% of incidences [2]. Male infertility is an important medical and social problem affecting the well-being of couples. Varicocele is a disease characterized by abnormal dilation of veins in the pampiniform plexus and has a prevalence of 15% in the normal population and 40% in the infertile population [3]. Varicocele is the most common known cause of male infertility by leading to different pathophysiological mechanisms [4]. Oxidative stress, hormonal disorders, increased scrotal temperature, reflux of renal and adrenal metabolites, and testicular hypoperfusion associated with varicocele are the possible mechanisms [5]. In a large meta-analysis, it was demonstrated that semen parameters improved significantly following varicocelectomy [6]. An increase in pregnancy outcomes is also expected with varicocelectomy [7]. It has also been shown that sperm DNA damage, which is largely responsible for the deterioration in semen parameters, is also significantly improved by varicocelectomy [8]. Surgery is the gold standard treatment of varicocele [6]. Although there is such strong evidence about the relationship between varicocele and infertility, not every man with varicocele is infertile, and varicocele correction does not always lead to improvement in fertility [9]. However, patients who have undergone varicocelectomy do not always experience the expected improvement in semen parameters or may experience a gradual decrease in these values over time. Because the absolute predictive factors for success are not well defined, non-invasive therapies assisting varicocelectomy have emerged.

The efficacy of these treatments has usually been assessed by comparison of placebo with one or two drugs, the drugs with surgery and adjuvant drug therapy, and surgery

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with drug therapy alone [10]. Antioxidant therapy is one of the treatments used for this purpose. The primary reason for the prominence of antioxidant treatments is that the oxidative stress in varicocele is the main mediator causing testicular damage [5]. Antioxidant therapy can contribute to the reduction of oxidative stress by inhibiting the formation of the oxidative products and the improvement of infertility caused by varicocele.

Increased reactive oxygen species (ROS) exposure of spermatozoa leads to anatomical and functional impairments in the cells and eventually to cascades resulting in cell death [11]. In addition, increased levels of ROS disrupt mitochondrial DNA integrity and thus consume the energy resources of the spermatozoa [12]. Increasing levels of ROS cause the oxidant–antioxidant balance to degrade in favor of the oxidants and induce oxidative stress [9]. Supportive therapies that contribute to the reduction of oxidative stress can reduce the exposure of the sperm to radical damage, increase energy metabolism, and contribute to the healthy development of spermatogenesis steps by reversing this balance.

Zinc, selenium, vitamin C, and Coenzyme Q are antioxidant treatment agents that improve the spermatogenesis process by reducing oxidative stress and are significant contributors to male infertility [13–16]. It has been shown that multi-antioxidant treatments contribute to male fertility by causing significant improvement in semen parameters. Although these treatments have positive effects, no clear consensus exists on their utilization (in which patients (with varicocele, without varicocele), how long, and how (alone, in combination with surgery)).

In the present study, we compared the semen parameters and pregnancy rates of infertile patients who were treated with varicocelectomy and received antioxidant treatment after surgery with those who were treated with varicocelectomy but did not receive antioxidant treatment after surgery.

Materials and methods

Patient selection and formation of groups

Between January 2016 and January 2018, 157 infertile patients with low sperm counts (oligo- and/or astheno- and/or teratozoospermia) were included in this single-center, randomized trial. All patients were subjected to a standard infertility evaluation. All patients had grade I–III varicocele confirmed with Doppler ultrasound. The varicocele classification was made according to the classification recommended by World Health Organization (WHO) guidelines. Those palpable in Valsalva maneuver were classified as grade I; those palpable at rest but not visible were classified as grade II, and those palpable and visible at rest were classified as grade III varicocele [1]. The study is powered to detect an effect size of $d \geq 0.70$ as statistically significant in a two-tailed test with $\alpha = 0.05$ and power of 0.80 with $N = 24$ per condition. We included at least 29 patients in the groups, anticipating that some patients would not complete the study. Thirty-two patients were excluded from the study, 18 patients failed to meet the study criteria and 14 patients refused medication, and the remaining 93 patients were divided into two groups. The first group received antioxidant treatment for the next 6 months after the varicocelectomy ($n = 64$), and the second group did not receive antioxidant treatment after the varicocelectomy ($n = 29$). During the study period, 2 patients left the study and 1 patient was lost in the follow-up; the data of the remaining 90 patients, 62 in the first group and 28 in the second group, were analyzed. After the varicocelectomy, we used the simple random allocation method to allocate patients to antioxidant and non-antioxidant groups using Excel 2010 software (Microsoft Corporation, Washington, USA). The flowchart of the study is shown in Fig. 1. Treatment was not interrupted during the study period in the treatment group. Male patients older than 18 years and with infertility history ≥ 12 months were included in the study. The participants' spouses were younger than 35 years old, their hormone profiles and menstrual cycles were regular, and they had no known diseases that might cause infertility. Patients who had previously undergone a genitourinary system and/or varicocele surgery; had idiopathic infertility; had a disease affecting fertility and received a medical treatment affecting fertility for the previous 3 months; had a history of undescended testis, testicular cancer, testicular trauma, post-pubertal mumps and endocrine disorder, or an obstructive urogenital disease; who followed a fertility-specific diet; who ingested excessive alcohol, cigarettes, drugs, opioids, or hallucinogens; whose HIV serology was positive; or who had an acute infection and another identified cause of infertility were not included in the study. All phases of the study were carried out in accordance with the Declaration of Helsinki or its subsequent amendments. The institutional review board approved the study and all patients participating in the study gave written approval for the surgical procedure and the procedures to be performed.

Antioxidant treatment

One sachet of antioxidant used for supportive treatment contained 1 g of L-carnitine fumarate, 0.5 g of Acetyl-L-carnitine HCl, 1 g of fructose, 50 mg of citric acid, 90 mg of vitamin C, 10 mg of zinc, 200 mcg of folic acid, 50 mcg of selenium, 20 mg of coenzyme Q-10, and 1.5 mcg of vitamin B12. The recommended dosage was two sachets daily.

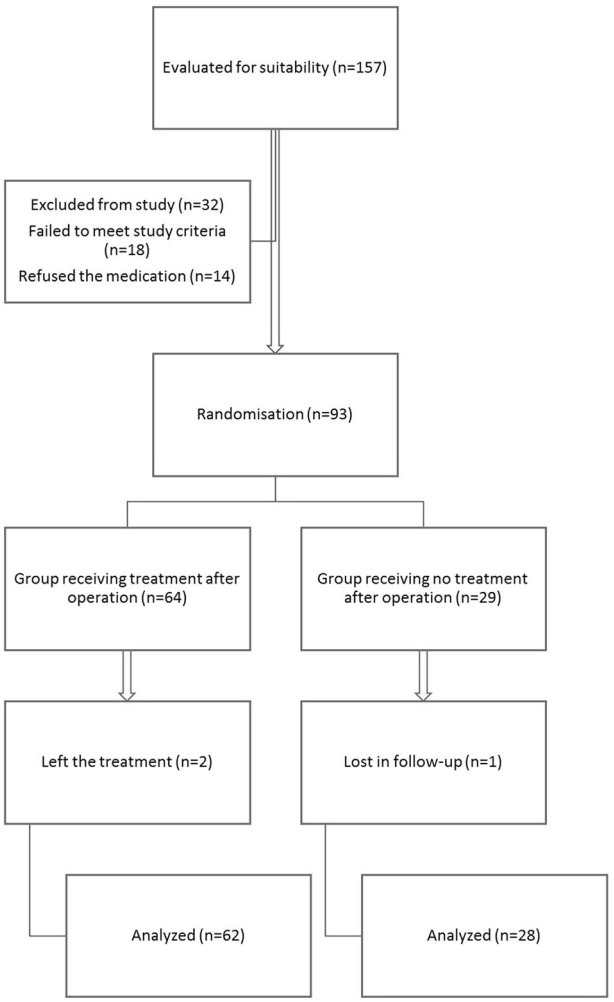

Fig. 1 Study flowchart

These antioxidants were produced by a nutraceutical manufacture. The patients paid for those treatments.

Semen analysis

Semen analysis was performed following the diagnosis of varicocele and 6 months after surgery in both groups. Semen analysis was performed within 1 h of sperm collection by computer-assisted semen analysis (CASA). MedeaLab CASA Version 4.1 (Germany) was used for this purpose. Semen samples were collected after 3–5 days of sexual abstinence. Ejaculate volume (ml), total sperm count ($x10^6$ / ejaculate), total motile sperm count (TMSC) ($\times 10^6$/ ejaculate), sperm concentration ($\times 10^6$/mL), sperm morphology, total and progressive motile sperm count, and leukocyte count (10^6/mL) were assessed according to the 5th edition of the World Health Organization (WHO) Laboratory Manual for the Examination and Processing of Human Semen [17]. Semen analysis was conducted by two experienced technicians in the andrology laboratory.

Outcome measures of the study

The primary outcome measure of the study was the comparison of semen volume, sperm concentration, total sperm count, TMSC, total and progressive motile sperm count, and sperm count in normal morphology between the groups. The secondary outcome measure was the comparison of pregnancy rates.

Operation technique

The microsurgical subinguinal technique was utilized for varicocelectomy. A subinguinal 3- to 4-cm oblique incision was performed under anesthesia with a laryngeal mask or spinal anesthesia. The incision was deepened to Camper's and Scarpa's fascia and the spermatic cord was clamped with a Babcock clamp and suspended with the help of a Farabeuf retractor. Cord structures were examined under a microscope at × 10 magnification. Internal spermatic artery (or arteries) and lymphatics were identified. The enlarged spermatic veins were dissected separately and ligated with 3/0 silk and then cut. The subcutaneous tissue was closed with 2/0 VICRYL rapide, the skin was closed subcuticular with 4/0 VICRYL rapide, and the procedure was terminated.

Statistical analysis

Descriptive statistics were expressed as the mean±standard deviation (SD) or frequency and percent (%). The Kolmogorov–Smirnov Z test was used to check the normality of the distribution. Independent t tests or Mann–Whitney U tests and χ^2-tests or Fisher's exact tests were used to compare quantitative data between groups according to their suitability. Paired samples t test was used to compare findings before and after treatment in each group. In the present study, the average increase values from baseline were compared between the two groups after 6 months of follow-up. P values < 0.05 were accepted for statistical significance. All statistical analysis was performed with the SPSS statistical software program (version 22.0).

Results

A total of 90 patients completed the study. The data of 62 patients in the first group and 28 patients in the second group were analyzed. Table 1 summarizes the demographic data and semen parameters of the patients before the surgical treatment, and no significant difference was found between the two groups.

The improvements in total sperm count, sperm concentration, sperm count in normal morphology, and total

Table 1 Demographic data and semen parameters of patients before surgery

Variables	Group I ($n = 62$)	Group II ($n = 28$)	P value
Age	32.86 ± 3.14	32.18 ± 2.44	0.329[a]
Body mass index (kg/m^2)	25.14 ± 2.28	26.81 ± 3.26	0.861[a]
Time elapsed from diagnosis to surgical treatment (day)	28.74 ± 5.88	33.29 ± 5.39	0.616[b]
Testis volume (ml)			0.765[a]
Right	19.12 ± 1.12	19.53 ± 1.02	
Left	18.42 ± 0.99	19.02 ± 0.86	
Varicocele grade			0.421[c]
Grade I	5 (8.1)	2 (7.1)	
Grade II	18 (29)	9 (32.1)	
Grade III	39 (62.9)	17 (60.8)	
FSH (mU/mL)	3.96 ± 0.96	4.82 ± 1.46	0.519[a]
Semen parameters			
Semen volume (ml)	3.62 ± 0.62	4.19 ± 0.52	0.291[a]
Total sperm number (10^6/ejaculate)	22.09 ± 3.89	21.64 ± 4.14	0.082[a]
Total motile sperm count (10^6/ejaculate)	17.28 ± 2.44	19.41 ± 1.69	0.225[a]
Sperm concentration (10^6/mL)	8.24 ± 1.88	7.82 ± 1.74	0.116[a]
Sperm morphology (normal forms, %)	1.89 ± 0.45	2.13 ± 0.66	0.626[a]
Total motility (%)	30.19 ± 5.16	26.38 ± 4.89	0.734[a]
Progressive motility (%)	16.25 ± 3.2	17.41 ± 3.1	0.068[a]
Peroxidase-positive leukocytes (10^6/mL)	0.16 ± 0.01	0.14 ± 0.03	0.812[a]

Values are given as mean ± standard deviation or number (%)

Group I: patients who received medical treatment after surgery; Group II: patients who did not receive medical treatment after surgery

[a]Independent t test

[b]Mann–Whitney U test

[c]χ^2 test

and progressive motile sperm count were significantly higher in the first group than in the second group. In the first and second groups, total sperm count increased by 45.9% and 26.8%, respectively, after 6 months ($p = 0.011$). The increase in sperm concentration was 71.4% and 54.5% in the two groups, respectively ($p = 0.008$). The increase in sperm count in normal morphology in the groups was 75.7% and 39.9%, respectively ($p < 0.001$). Increase in total motile sperm was 28.6% and 18.3%, respectively ($p = 0.024$), whereas the increase in progressive motile sperm count was 60.4% and 38.9%, respectively ($p < 0.001$). There was also a significant difference between the two groups in the improvement in TMSC ($p < 0.001$). Baseline and postoperative parameters were compared in two groups. All parameters, except semen volume in both groups and total motility percentage in the second group, increased significantly. Baseline semen parameters and comparison of the parameters and the percentage change rate in both groups 6 months after surgery are summarized in Table 2. Postoperative semen parameters of patients with grade 2 and 3 varicocele were compared in two groups. As there were only seven patients with grade 1 varicocele in both groups, they were not evaluated. Patients with grade 3 varicocele in the treated group had significant improvement in all semen parameters compared with patients with grade 2 varicocele. In the untreated group, the improvement in semen parameters of patients with grade 3 varicocele was significantly higher than the patients with grade 2 varicocele except in TMSC and sperm morphology values. Comparison of postoperative semen parameters in two groups according to varicocele grade is summarized in Table 3.

The contribution of antioxidant treatment to the increase in semen parameters was also reflected in the pregnancy rates. The clinical pregnancy rate in the first group was significantly higher than in the second group (18/62 (29%) vs. 5/28 (17.9%), $p = 0.029$). Nineteen of the pregnancies were spontaneous and four of them were obtained with assisted reproductive techniques.

Nausea complaint related to medication occurred in five patients in the first group. These symptoms were controlled by palliative treatment and did not require treatment termination. In the first group, complaint of gastroesophageal reflux occurred in four patients and it was controlled by palliative methods.

Table 2 Comparison of the semen parameters and the percentage change rate in both groups 6 months after surgery

Semen parameters	Group I ($n = 62$)		P value[1]	Percentage change rate (%)	Group II ($n = 28$)		P value[1]	Percentage change rate (%)	P value[2]
	Baseline parameters	After surgery parameters			Baseline parameters	After surgery parameters			
Semen volume (ml)	3.62 ± 0.62	3.65 ± 0.6	0.249	+0.83	4.19 ± 0.52	4.18 ± 0.42	0.318	−0.24	0.715
Total sperm count (10^6/ejaculate)	22.09 ± 3.89	32.22 ± 6.11	***<0.001***	+45.9	21.64 ± 4.14	27.44 ± 5.24	***0.0034***	+26.8	***0.011***
Total motile sperm count (10^6/ejaculate)	17.28 ± 2.44	26.03 ± 2.45	***0.024***	+50.6	19.41 ± 1.69	25.19 ± 1.88	***0.011***	+29.7	***<0.001***
Sperm concentration (10^6/mL)	8.24 ± 1.88	14.12 ± 2.11	***0.037***	+71.4	7.82 ± 1.74	12.08 ± 2.05	***0.029***	+54.5	***0.008***
Sperm morphology (normal forms %)	1.89 ± 0.45	3.32 ± 0.3	***0.041***	+75.7	2.13 ± 0.66	2.98 ± 0.21	***0.038***	+39.9	***<0.001***
Total motility (%)	30.19 ± 5.16	38.83 ± 10.4	***0.018***	+28.6	26.38 ± 4.89	31.22 ± 8.34	0.062	+18.3	***0.024***
Progressive motility (%)	16.25 ± 3.2	26.08 ± 7.62	***<0.001***	+60.4	17.41 ± 3.1	24.19 ± 5.44	***<0.001***	+38.9	***<0.001***
Peroxidase-positive leukocytes (10^6/mL)	0.16 ± 0.01	0.06 ± 0.002	***0.014***	−62.5	0.14 ± 0.03	0.04 ± 0.001	***0.027***	−71.4	0.462

Values are given as mean ± standard deviation

Group I: patients who received medical treatment after surgery; Group II: patients who did not receive medical treatment after surgery

Statistically significant P values are given in bold and italics

[1]Paired samples t test

[2]P value for comparison of percentage change rates, Independent t test

Table 3 Comparison of postoperative semen parameters according to varicocele grade in treated and non-treated groups

Semen parameters	Group I		P value[1]	Group II		P value[1]
	Varicocele grade 2 ($n = 18$)	Varicocele grade 3 ($n = 39$)		Varicocele grade 2 ($n = 9$)	Varicocele grade 3 ($n = 17$)	
Semen volume (ml)	3.32 ± 0.4	3.78 ± 0.9	***0.038***	3.88 ± 0.31	4.37 ± 0.62	***0.003***
Total sperm number (10^6/ejaculate)	31.82 ± 7.4	35.16 ± 8.6	***0.022***	25.48 ± 5.18	29.22 ± 6.13	***0.024***
Total motile sperm count (10^6/ejaculate)	23.13 ± 3.15	27.04 ± 3.8	***0.004***	24.79 ± 2.91	26.88 ± 3.21	0.058
Sperm concentration (10^6/mL)	13.12 ± 1.89	16.19 ± 3.3	***0.019***	11.19 ± 1.95	15.22 ± 3.11	***0.017***
Sperm morphology (normal forms, %)	3.22 ± 0.4	3.76 ± 0.9	***0.013***	2.96 ± 0.16	3.10 ± 0.33	0.145
Total motility (%)	36.83 ± 9.6	41.20 ± 11.2	***<0.001***	30.18 ± 6.88	34.42 ± 7.51	***0.007***
Progressive motility (%)	24.17 ± 7.31	29.02 ± 8.2	***0.034***	23.08 ± 4.81	26.11 ± 6.11	***0.033***
Peroxidase-positive leukocytes (10^6/mL)	0.07 ± 0.008	0.02 ± 0.004	***0.041***	0.08 ± 0.008	0.03 ± 0.009	***<0.001***

Values are given as mean ± standard deviation

Group I: patients who received medical treatment after surgery; Group II: patients who did not receive medical treatment after surgery

Statistically significant P values are given in bold and italics

[1]Paired samples t test

Discussion

We found that antioxidant treatment positively contributed to sperm parameters and pregnancy rates after varicocelectomy. As varicocelectomy, the gold standard of varicocele treatment, caused significant improvement in semen parameters and sperm DNA damage we performed surgery on all patients [6, 8]. However, it is not possible to achieve the positive effects of this procedure on every patient who undergoes varicocelectomy. For example, in the study conducted by Baazeem et al. in 2011, there was no positive effect on spontaneous pregnancy rates after varicocelectomy. On the other hand, the authors also found that the process caused a decrease in sperm DNA damage and seminal oxidative stress and improved sperm count and motility [18]. Despite the improvement in objective parameters, the fact that clinical outcomes are not always as expected has brought to the agenda the consideration of additional or alternative therapies to varicocelectomy.

In our study, we found that supportive antioxidant treatment contributed significantly to the semen parameters in patients who underwent varicocelectomy. In addition, antioxidant treatment has also improved clinical pregnancy rates. It has been demonstrated that the conception rate has significantly increased at > 20 million TMSC [19]. In our study, TMSC, which was < 20 million before treatment in both groups, exceeded this value after 6 months and this improvement was more prominent in the group receiving treatment. We think that the duration of the spermatogenesis process, which lasts 74 days, is the minimum treatment period necessary for these patients to get adequate benefit from medical treatment. There is a rapid decrease in seminal ROS level after varicocelectomy in the first month, and the improvement of sperm DNA damage proceeds for 6 months [20]. In 1999, Zini et al. [21] suggested that varicocelectomy in infertile men would accelerate the removal of residual sperm cytoplasm by the testis and epididymis and that the percentage of spermatozoa with residual cytoplasm, motile spermatozoa, and normal forms would increase for 6 months after the operation . The expected improvement period after varicocelectomy may be variable and requires 6 months after surgery to achieve optimal results [5]. For this reason, we conducted a control spermiogram at 6 months postoperatively to ensure the favorable outcomes of varicocelectomy and optimal benefit from medical therapy.

One hundred and fourteen patients who underwent varicocelectomy were divided into three groups in a prospective, randomized trial in which the effect of adjuvant antioxidant therapy on varicocele-induced infertility was assessed: those receiving a combination of adjuvant acetyl-L-carnitine, L-carnitine fumarate, and alpha-lipoic acid; those receiving a vitamin complex in addition to antioxidant; and those without any adjuvant treatment. Semen parameters and sperm DNA fragmentation levels were evaluated at the third month, and adjuvant antioxidant therapy was shown to improve sperm parameters and reduce sperm DNA fragmentation [22]. Unlike our study, only sperm concentration and motility were evaluated, and pregnancy rates were not taken into consideration in this trial.

One hundred and four patients with oligo-, astheno-, and/or teratozoospermia received antioxidant support therapy for 6 months and there was a significant increase in pregnancy rates with semen parameters in the treated group [23]. In this study, some patients had varicocele, whereas others did not. The improvement in semen parameters was more pronounced in the varicocele group. Presumably, oxidative stress and ROS caused by varicocele are responsible for this result. Alleviating varicocele-related ROS has been the common thread of the design of these studies, and accompanying antioxidant therapies have been proposed to increase the success of surgical treatment. In a study similar to ours, Badr et al. assessed the efficacy of saffron after varicocelectomy in infertile men in 2017. Saffron is a plant extract that is believed to improve semen parameters owing to its antioxidant properties. Sperm motility was significantly increased in the group using saffron capsules for 6 months after surgery compared with the group using placebo [24]. In another placebo-controlled trial with a similar methodology, the effect of melatonin was assessed and was shown to have positive effects on semen parameters, hormonal profile, and total antioxidant capacity [25]. In 2016, Barekat et al. have shown that *N*-acetylcysteine administration after varicocelectomy improves chromatin integrity and pregnancy rates [26]. In a recent meta-analysis that analyzed 10 randomized controlled studies, it was shown that adjuvant drug treatment, especially with antioxidants after varicocelectomy, could improve fertility outcomes by improving primarily sperm concentration, motility, DNA integrity, and serum follicle-stimulating hormone levels [27].

In a study that evaluated head-to-head the effect of varicocelectomy and oral L-carnitine on sperm parameters in infertile men, 31 patients underwent surgery and 31 patients received oral L-carnitine. The authors concluded that L-carnitine improved the semen parameters as much as surgery. However, they underlined that this effect was only observed in patients with grade III varicocele [28]. Patients continued treatment for 6 months. However, at the end of 6 months, the effect of treatment termination on semen parameters is uncertain. Unless the anatomic defect caused by varicocele is corrected, it is unwarranted to expect a lasting improvement in semen parameters with the currently available data. However, the medical treatment option alone may be an appropriate alternative in patients who refuse or

are unsuitable for surgical treatment. Although there are reports that antioxidant treatment has a positive effect on semen parameters, it should be kept in mind that there are studies presenting no effect on sperm motility, count, and morphology [29, 30]. In our study, the improvement in semen parameters of patients with grade 3 varicocele in both groups was higher than that of patients with grade 2 varicocele similar to the aforementioned study.

In 2014, Festa et al. evaluated the efficacy of 3 months of exogenous administration of coenzyme Q-10 in 38 infertile patients with grade I–II varicocele. After 3 months, they found significant improvement in sperm density, progressive motility, and total antioxidant capacity [31]. In another randomized, double-blind, placebo-controlled study, oral coenzyme Q-10 supplementation in idiopathic oligo-, astheno-, and/or teratozoospermic men increased seminal total antioxidant capacity and reduced oxidative stress but did not affect semen parameters [32]. ROS may cause sperm dysfunction, sperm death, and infertility by altering sperm parameters and inducing lipid peroxidation, protein modification, and DNA damage [33]. Antioxidants can reverse all these negative effects without changing sperm count and concentration. Selenium deficiency may cause anomalies in the spermatogenesis steps; moderate selenium deficiency may alter sperm morphology by disrupting sperm motility, and severe selenium deficiency may completely damage spermatogenesis [34].

Although antioxidants seem quite innocent, they may have potential side effects. Uncontrolled antioxidant therapy may lead to impairment of sperm parameters with a paradoxical effect [35]. The cause of this effect, called "antioxidant paradox," is the need for certain levels of antioxidant and ROS agents for normal cell function because some cells function at a reduced level [36]. Numerous studies in the literature report contradictory results regarding antioxidant treatments at different doses, with different agents and methods of administration. It is difficult to make a comparison between the applied agents because of the methodological and clinical heterogeneity of these studies or to make a definitive judgment about the optimal dose and duration for a specific oral treatment. However, oral antioxidant supplementation seems to be a viable option to try before the implementation of more difficult and more expensive treatment methods.

Our study is not without limitations. First, seminal oxidative stress and total antioxidant capacity were not evaluated. The low sample number might be a factor affecting the results. We assessed pregnancy rates, but information on live birth rates is lacking.

In our study, we found that antioxidant treatment significantly contributed to the outcomes of varicocelectomy and improved pregnancy rates. We concluded that antioxidants are important adjuncts to the surgical treatment in the treatment of infertility and can be recommended in appropriate patients in light of these findings. The role of antioxidants in the treatment of infertility can be more clearly demonstrated by studies that would analyze oxidative stress at the molecular level.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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