

Clinical Outcomes and Management of Post-varicocelelectomy on Male Fertility: A Comprehensive Review

Journal of Pharmacology and
Pharmacotherapeutics
17(1) 5–16, 2026
© The Author(s) 2025
Article reuse guidelines:
in.sagepub.com/journals-permissions-india
DOI: 10.1177/0976500X251321295
journals.sagepub.com/home/pha
 Sage

Mohammad Akbar Hossain¹

Abstract

Background: Varicocelelectomy is one of the main complications that, if left untreated, results in male infertility. Various approaches have been adopted to manage it, but there is a variation in the consensus.

Objectives: This systematic review aims to summarize the evidence on the various clinical trials and post-varicocelelectomy recovery for patients consuming different supplements or regimens.

Methodology: An organized and systematic literature search was conducted in five electronic databases from their inception till 2021. Upon applying the PICOT format and student inclusion criteria, only $n = 13$ articles fulfilled the eligibility criteria and were selected for this systematic review.

Results: A total of 13 studies were included in this systematic review, and different outcomes were measured in all the studies. Generalizing the outcomes measured, they are classified in semen parameters, including sperm count, sperm motility percentage, sperm with standard morphology percentage, semen volume, sperm density, hormonal profile including testosterone (nanograms/liter), follicle-stimulating hormone (international units/liter), luteinizing hormone (international unit/liter), seminal oxidative stress including total antioxidant capacity (mm Trolox equivalent per liter), and pregnancy outcome.

Conclusion: This systematic review suggests improved sperm count and pregnancy outcomes with pharmacotherapeutic interventions. Oral antioxidants, vitamin C, and vitamin E showed marked improvements in sperm density and reduction in sperm DNA damage. Oral supplements, that is, saffron, were also effective but needed larger, well-conducted randomized clinical trials to validate the findings and estimate the overall impact of these interventions in the post-varicocelelectomy period.

Keywords

Male infertility, pharmacotherapeutic interventions, sperm count, sperm density, sperm motility, varicocele, varicocelelectomy

Received 25 October 2024; accepted 22 January 2025

Introduction

Infertility in the current healthcare setting is one of the leading challenges to the global population. A couple is declared infertile if they fail to conceive after 1 year. In most cases of infertility, fertile females and infertile men account for 40–50%.¹ Several factors account for male infertility, ranging from physiological, hormonal, and anatomical abnormalities, that lead to erectile dysfunction, premature ejaculation, oligospermia, asthenospermia, azoospermia, teratozoospermia, non-obstructive azoospermia, and sperm DNA damage.² The sperm count fewer than 20 million, which indicates oligospermia. Under normal circumstances, a healthy male should have sperm counts from 40 to 50 million. Oligospermia is one of the factors responsible for more than 25% of total

infertility.³ The World Health Organization (WHO) recently reclassified levels lower than 15 million as oligospermia.⁴ Asthenospermia is another condition which is resulting in 50% non-motile sperm, possibly leading to infertility.⁵ However, non-obstructive azoospermia is a complete absence of spermatozoa in the ejaculate due to intrinsic and gonadal causes.⁶ Teratospermia is the less-than-abnormal morphology of more than 70% spermatozoa.⁷

¹Department of Pharmacology and Toxicology, Faculty of Medicine in Al-Qunfudah, Umm Al-Qura University, Makkah, Saudi Arabia

Corresponding author:

Mohammad Akbar Hossain, Department of Pharmacology and Toxicology, Faculty of Medicine in Al-Qunfudah, Umm Al-Qura University, Makkah 24382, Saudi Arabia.

E-mail: mahossain@uqu.edu.sa



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<http://www.creativecommons.org/licenses/by-nc/4.0/>) which permits non-Commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

In addition to these sperm deformities and abnormalities, varicocele is a common pathophysiological condition that influences all the above-defined causes of male infertility. Varicocele is defined as the dilated veins (varicose veins) of the testicles predominant on the left side.⁸ Varicocele is a common condition responsible for male infertility, and its repair profoundly improves male fertility.⁹ Clinically, varicocele is divided into three clinical grades—grade 1: palpable varicose vein upon Valsalva maneuver; grade 2: varicocele is a varicose vein without the Valsalva maneuver; and grade 3: a visible varicose vein through the scrotal skin and upon standing without the Valsalva maneuver.¹⁰ This study back then established the influence of varicocele on male fertility as a massive 25.4% of infertile males had varicocele.¹¹ Multiple factors lead to varicocele-induced infertility, including increased temperature of the testicles, hormonal imbalance, increased venous pressure, and reactive oxygen species (ROS). Pooling of blood may elevate the temperature of the testicles and affect spermatogenesis.¹²

Varicoceles affect different age groups regardless of race and region.^{13,14} Delays in diagnosis and treatment result in complications that may be incurable later on.¹⁵ Various non-invasive methods are used to diagnose varicocele in male patients, the simplest being physical examination and the most complex being color Doppler sonography, contact thermography, and radionuclide angiography.¹⁶ Both pharmacotherapeutic and surgical treatment options are available for varicocele-related infertility. Herbal supplements, vitamins, hormone replacement therapy, and surgical interventions are the standard procedures implemented to treat varicoceles.^{17–21} The Valsalva maneuver is a specialized procedure of forced breathing where excessive pressure is exerted on various body parts, with effects like increased blood pressure and heart rate.²² To date, various interventions have been implemented to improve the condition of patients suffering from varicoceles, ranging from invasive procedures to supplements. However, to date, there is limited consensus on the effectiveness and quality of the clinical studies aiming to treat and improve the outcome of patients suffering from varicoceles. Varicocelectomy is the only treatment available up till now to resolve infertility problems induced by varicocele. Furthermore, other pharmacotherapeutic adjuncts can be used as a treatment choice concomitantly with surgical intervention. There is a need of an hour for sufficient evidence generation for varicocele-induced male infertility and a comparison of various pharmacotherapeutic options available after varicocelectomy. This systematic review aims to summarize the evidence on the various clinical trials and post-varicocelectomy recovery for patients consuming different supplements or regimens.

Methodology

A systematic search of the literature in health sciences databases, mainly Medline and PubMed, was conducted to

identify the main research articles that are relevant to the aims of this research. The search was done using the Medical Subject Headings (MeSH) terms of Varicocele and/or Varicocele and male fertility, Varicocelectomy; Varicocele and/or teratozoospermia, oligospermia, and Pharmacotherapy of varicocele. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used as the main principle to conduct this review.

Selection Criteria

All clinical trials published in the English language were considered for this evidence-generation exercise. Only those studies which involved a properly defined intervention (medical or pharmacotherapy-based intervention) were considered for inclusion. Only studies with a confirmed diagnosis of varicocele were considered for inclusion. All observational studies and any study published in a language other than English were excluded from consideration.

Data Extraction

The data extraction from the selected studies was conducted using a standardized Excel sheet. The prime focus of the data extraction was on the characteristics of studies, nature of intervention and control, patients' details, disease classification, and other biomarkers relevant to the improvement of varicocele.

Outcomes and population that are explored in this systematic review:

Population of interest (P) = Male patients with varicoceles;
Intervention (I) = Any intervention in modern medicine/supplements or complementary and alternative medicines;
Comparator (C) = Placebo or any comparator whose effect was compared with the intervention;
Outcome (O) = Improvement in the level of hormones, physiology, and morphology of sperms or conception or gestation.

Quality Assessment of Studies and Data Analysis

To estimate the quality of the included trials, the Cochrane Risk of Bias tool was used.²³ This criterion assesses the quality of the clinical trials using this tool and addresses six domains of studies to determine the risk of bias: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other issues. Each of these items in the tool was labeled as “high risk,” “low risk,” or “unclear risk.”

Results

Upon performing the initial search at PubMed and Medline, $N = 1,102$ papers were identified using the MeSH terms

outlined in the “Methodology” section. Of these studies, upon applying the inclusion and exclusion criteria, $n = 13$ papers were found eligible for inclusion in this study. Details are described in Figure 1.

A variety of interventions were used among the included studies during the post-varicocelelectomy. These mainly include zinc sulfate/folic acid versus folic acid versus zinc sulfate, ketotifen only versus ketotifen after varicocelelectomy, ketotifen 1 mg, l-carnitine 250 mg, vitamin E (VIT E), vitamin C (VIT C) 250 mg, Korean red ginseng 1.5 g, Xuanju three grains (0.42 g/grain), 60 mg saffron capsules, 400 mg melatonin, antioxidant sachet, human chorionic gonadotropin (HCG) versus human menopausal gonadotropin (HMG) versus recombinant human follicle-stimulating hormone

(rhFSH), zinc sulfate versus folic acid versus zinc sulfate/folic acid. In most of the cases, grades 1, 2, and 3 patients were included among these 13 studies. Details are shown in Table 1.

Impact of Interventions on Sperm Count

Sperm count was addressed as a primary outcome among eight studies. Most of these studies have compared the effect of the intervention in both control and intervention groups pre- and post-varicocelelectomy. A variety of supplementations were used as intervention, that is, oral l-carnitine 250 mg (for 24 weeks), oral VIT E 300 mg (50 weeks), oral VIT C 250 mg for 12 weeks, oral Korean ginseng 500 gm (12 weeks), oral saffron capsules 60 mg (24 weeks), Oral melatonin 400 mg (12 weeks), VIT C 10 mg of ZnO 200 µg folic acid 50 µg and vitamin B12 (VIT B12) for (24 weeks) and 1 mg ketotifen for 12 weeks. Details are described in Table 2.

Overall, in comparison to the baseline parameter, a very substantial increase in sperm count was observed at the end-point assessment for the groups consuming l-carnitine and VIT E supplementation. It was observed that the increase in sperm count for the l-carnitine users as a post-varicocelelectomy intervention was 37.82×10^6 from the baseline values; for VIT E, it is observed to 22.1×10^6 from the baseline values.

Impact of Interventions on Sperm Motility

The number of studies measuring the outcome percentage of sperm motility pre- and post-varicocelelectomy in both control and interventional groups was $n = 11$. The most common parameter measured in all studies was the percentage of motile sperm cells. A comparison of the percentage of motile sperm cells between the baseline and end values of both the control and interventional groups showed that the percentage of motile spermatozoa was markedly increased in the interventional group than in the control. This shows that like sperm count, the percentage of motile sperm cells also had a marked effect of that adjunct pharmacotherapeutic intervention.

A study performed by Azizollahi et al.³⁴ divided the participants into three groups: group A received zinc sulfate 66 mg, 1 capsule for 6 months; group B received folic acid 5 mg, 1 capsule for 6 months; group C received zinc sulfate plus folic acid 66 mg plus 5 mg, 1 capsule for 6 months, all of these interventional groups had same controls, that is, only varicocelelectomy. The study performed by Zaazaa et al.³⁶ divided the groups into two groups: group A received 1 mg ketotifen twice daily for 3 months, and group B received varicocelelectomy followed by 1 mg ketotifen twice daily for 3 months. These two studies had five subgroups randomized and assessed adjunct pharmacotherapeutic intervention's efficacy. These studies confirmed the results of nine other studies in improving the percentage of motile sperm. The summary is shown in Table 3.

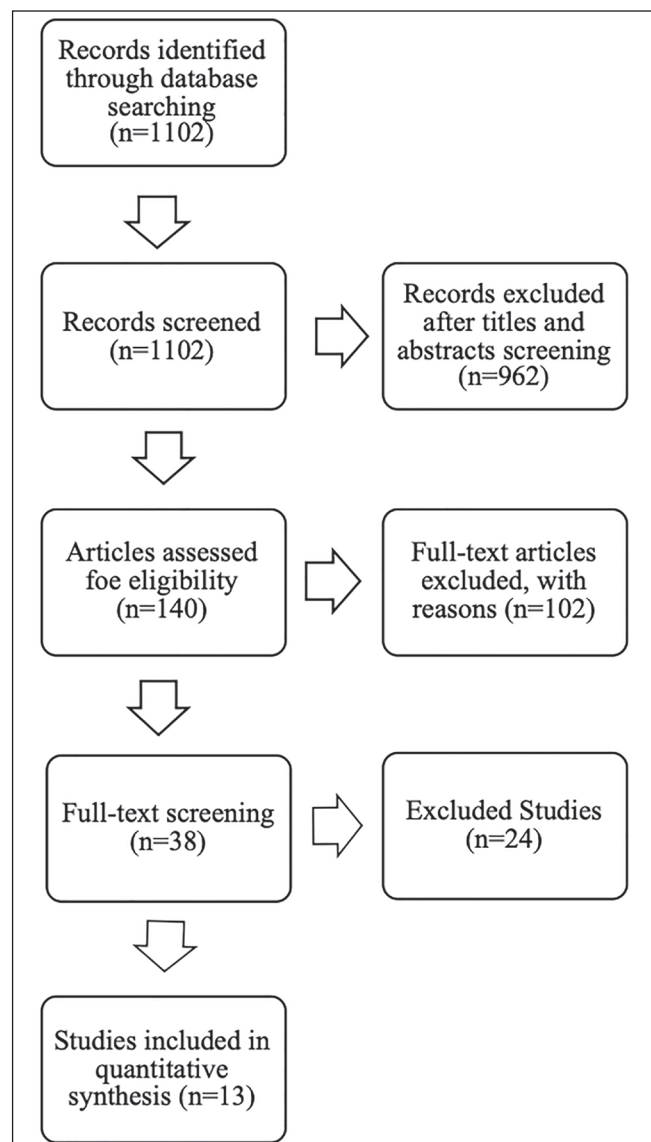


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram.

Table 1. Characteristics of Included Studies.

Author (Year)	Intervention	Comparator	Sample Size/Group	Age Range	Outcomes Measured	Grading of Disease	Duration of Study
Azadi et al. (2011) ²⁴	Ketotifen 1 mg	Varicocelectomy only	103/2	NA	Semen parameters and pregnancy rate	Grades 2 and 3	36 weeks
Pourmand et al. (2014) ²⁵	L-Carnitine 250 mg	Varicocelectomy only	50/2	NA	Semen parameters and DNA damage assessment of spermatozoa	Grades 1, 2, and 3	24 weeks
Ener et al. (2016) ²⁶	Vitamin E	Varicocelectomy plus placebo	45/2	NA	Semen parameters and pregnancy	NA	50 weeks
Cyrus et al. (2015) ²⁷	Vitamin C 250 mg	Varicocelectomy plus placebo	115/2	18–50	Semen parameters	Grades 2 and 3	12 weeks
Park et al. (2016) ²⁸	Korean red ginseng 1.5 g	Varicocelectomy plus placebo	77/4	25–45	Semen parameters	NA	12 weeks
Qu et al. (2017) ²⁹	Xuanju three grains (0.42 g/grain)	Varicocelectomy only	88/2	24–39	Semen parameters and serum hormone levels	NA	36 weeks
Asr Badr et al. (2017) ³⁰	60 mg edible saffron capsules	Varicocelectomy plus placebo	45/2	20–35	Semen parameters	Grades 1, 2, and 3	24 weeks
Lu et al. (2018) ³¹	400 mg melatonin	Varicocelectomy only	54/2	NA	Semen parameters, hormonal profile, and seminal oxidative stress	NA	12 weeks
Kızılay and Altay (2019) ³²	Oral antioxidant sachet	Varicocelectomy only	90/2	NA	Semen parameters and pregnancy rate	Grades 1, 2, and 3	24 weeks
Amirzargar et al. (2012) ³³	HCG vs. HMG vs. rhFSH	Varicocelectomy only	113/4	22–49	Pregnancy rate	NA	12 weeks
Azizollahi et al. (2013) ³⁴	Zinc sulfate vs. folic acid vs. zinc sulfate/folic acid	Varicocelectomy plus placebo	112/4	20–43	Semen parameters	Grade 3	24 weeks
Nematollahi et al. (2014) ³⁵	Zinc sulfate/folic acid vs. folic acid vs. zinc sulfate	Varicocelectomy plus placebo	160/4	NA	Serum hormone level	Grade 3	24 weeks
Zaazaa et al. (2018) ³⁶	Ketotifen only vs. ketotifen after varicocelectomy	Varicocelectomy only	120/3	NA	Semen parameters	Grades 1, 2, and 3	12 weeks

Note: HCG: Human chorionic gonadotropin; HMG: Human menopausal gonadotropin; rhFSH: Recombinant human follicle-stimulating hormone.

Table 2. Quantitative Parameters of the Included Studies on Sperm Count.

Author (Year)	Comparator Sperm Count in Millions						Intervention Sperm Count in Millions						Comparator and Intervention De- tails and Duration
	Baseline			Endpoint			Baseline			Endpoint			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Pour- mand et al. (2014) ²⁵	50	108.7	87.6	50	207.7	76.74	50	102.57	87.6	50	140.39	74.21	Varicocelectomy/oral L-carnitine 250 mg TID for 24 weeks
Ener et al. (2016) ²⁶	23	28.2	25.7	23	47.2	19	22	36.5	29.8	22	58.6	20.2	Varicocelectomy/ Oral VIT E 300 mg BD for 50 weeks

(Table 2 continued)

(Table 2 continued)

Author (Year)	Comparator Sperm Count in Millions						Intervention Sperm Count in Millions						Comparator and Intervention De- tails and Duration
	Baseline			Endpoint			Baseline			Endpoint			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Cyrus et al. (2015) ²⁷	69	37.5	28.1	69	44.9	21.4	46	42.5	28.4	46	54.5	18.3	Varicocelectomy/oral VIT C 250 mg for 12 weeks
Park et al. (2016) ²⁸	19	13.7	6.1	19	7.5	3.4	18	13.4	4.2	18	8.1	4.3	Varicocelectomy/oral Korean ginseng 500 g TID for 12 weeks
Asr Badr et al. (2017) ³⁰	21	46.38	40.7	21	65.62	12.6	27	43.93	26.16	27	46.29	5.77	Varicocelectomy/oral saffron capsules 60 mg OD for 24 weeks
Lu et al. (2018) ³¹	27	14.1	2.5	27	28.4	4.6	27	12.8	1.9	27	33.8	5.2	Varicocelectomy/oral melatonin 400 mg OD for 12 weeks
Kızılay and Altay (2019) ³²	28	21.64	4.41	28	27.44	5.24	62	22.09	3.89	62	32.22	6.11	VIT C 10 mg of ZnO 200 µg folic acid 50 µg and VIT B12 for 24 weeks
Zaazaa et al. (2018) ³⁶	40	52	11.1	40	75.6	15.8	40	69.4	16.3	40	90.7	19.3	Varicocelectomy/ group A 1 mg ketoti- fen BD for 12 weeks

Note: BD: Two times a day; OD: Once a day; TID: Thrice a day; VIT B12: Vitamin B12; VIT C: Vitamin C; VIT E: Vitamin E; ZnO: Zinc oxide.

Sperm with Normal Morphology %

Out of all the included studies, $n = 14$, only $n = 10$ studies assessed the outcome of sperms with normal morphology % pre- and post-varicocele/ectomy in both control and interventional groups. All the studies assessed the percentage of sperm with normal morphology in control groups with only surgical intervention and the interventional group with the adjunct pharmacotherapeutic intervention post-varicocele/ectomy. Results confirmed the previous results as the percentage of normal sperms increased significantly in interventional groups than in controls. The study performed by Nematollahi-Mahani et al.³⁵ further divided the interventional groups into three groups: group A received zinc sulfate 66 mg 1 capsule for 6 months, group B received folic acid 5 mg 1 capsule for 6 months, and group C received zinc sulfate plus folic acid 66 mg plus 5 mg 1 capsule for 6 months as described in sperm motility as well. The study performed by Zaaza et al.³⁶ divided the interventional group into further two subgroups. The summary is shown in Table 4.

Impact of Interventions on Semen Volume

Among the finalized studies, $n = 3$ discussed and compared semen volume as a main outcome.^{29,33} Findings from the study of Qu et al. showed a statistically non-significant increase in the semen volume in comparison to the baseline results.²⁹ However, results from Amirzargar et al.³³ showed inconclusive results for the use of adjunct supplementation of HCG, and semen volume decreased in both control and interventional groups pre- and post-varicocele/ectomy. This showed that

adjunct pharmacotherapeutic interventions had no significant effect on semen volume. The summary is shown in Table 5.

Impact of Interventions on Sperm Density

Only two studies discussed sperm density as an outcome assessed pre- and post-varicocele/ectomy in both the control and interventional groups. Studies discussing sperm density were the result from these two studies have shown a significant increase in sperm density in both groups.^{24,29} However, the increase in sperm density in the interventional group was more significant than in the control, showing that adjunct pharmacotherapeutic intervention markedly affected sperm density. The summary is shown in Table 6.

Impact of Interventions on the Hormonal Profile of Patients

Exploration in this regard has shown the main three hormones that were investigated in the selected studies: testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH).^{28,29,35} Three studies have investigated the impact of the intervention on testosterone. Two studies have shown an increase in the level of testosterone in both the control and interventional groups.^{28,29} However, the increase was not significant, and the last study assessed zinc sulfate and folic acid as adjunct pharmacotherapeutic interventions and showed a decrease in the testosterone level. This reveals that the adjunct pharmacotherapeutic intervention did not affect the level of testosterone pre- and post-varicocele/ectomy.

Table 3. Quantitative Data on Sperm Motility for the Intervention and Comparator.

Author/ Year	Comparator						Intervention						Intervention
	Baseline			End			Baseline			End			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Azadi et al. (2011) ²⁴	52	40	2.38	45	50	1.86	51	34.5	2.03	38	55.05	2.07	Zaditen 1 mg BD after varicocelec- tomy for 3 months
Pourmand et al. (2014) ²⁵	50	33	17.9	50	38	—	50	33.2	18.2	50	46.33	—	Oral L-carnitine 250 mg TID for 6 months
Ener et al. (2016) ²⁶	23	45	24.6	23	57	20.2	22	54.1	20.4	22	59.3	16.2	Oral vitamin E 300 mg BD for 12 months
Cyrus et al. (2015) ²⁷	69	32	14.3	69	45	21.4	46	33.8	15.5	46	54.5	18.3	Oral vitamin C 250 mg BD for 3 months
Park et al. (2016) ²⁸	19	21	7.7	19	19	7.7	18	20.6	8.4	18	24.2	8.1	Oral Korean red ginseng 500 mg TID for 3 months
Qu et al. (2017) ²⁹	44	28	17.2	44	37	16.2	44	27.6	17.8	44	53.21	13	Oral Xuanju capsules 3 grains (0.42 g/grain) once TID for 3 months
Asr Badr et al. (2017) ³⁰	21	20	12.6	21	22	11.5	27	18.1	10.1	27	30	14.5	Oral saffron cap- sule 60 mg OD every other day post-varicocelec- tomy for 6 months
Lu et al. (2018) ³¹	27	51	7.8	27	59	7.6	27	49.3	8.8	27	64.3	7.2	Oral melatonin 400 mg OD post- varicocelectomy for 3 months
Kızılay and Altay (2019) ³²	28	26	4.89	28	31	8.34	62	30.2	5.16	62	38.83	10.4	Oral two sachets of antioxidant BD containing
Azizol-lahi et al. (2013) ³⁴ A	25	38	7.4	25	50	4.8	32	55	4.3	32	49.8	2	Zinc sulfate 66 mg 1 capsule for 6 months
Azizol-lahi et al. (2013) ³⁴ B	25	38	7.4	25	50	4.8	26	48.8	4	26	51.5	2	Folic acid 5 mg 1 capsule for 6 months
Azizol-lahi et al. (2013) ³⁴ C	25	38	7.4	25	50	4.8	29	42.6	5.1	29	52.4	3.3	Zinc sulfate plus folic acid 66 mg plus 5 mg 1 cap- sule for 6 months
Zaazaa et al. (2018) ³⁶ A	40	24	10.8	40	32	12.1	40	28.7	14.7	40	37.6	18.4	1 mg ketotifen twice daily for 3 months
Zaazaa et al. (2018) ³⁶ B	40	24	10.8	40	32	12.1	40	19.5	11.5	40	30.5	14.2	Varicocelectomy followed with 1 mg ketotifen twice daily for 3 months

Note: BD: Two times a day; OD: Once a day; TID: Thrice a day.

Table 4. Quantitative Data on Sperm Morphology for the Intervention and Comparator.

Author/ Year	Comparator							Intervention					Intervention
	Baseline			End				Baseline		End			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Azadi et al. (2011) ²⁴	52	4.23	0.65	45	5.46	0.67	51	5.29	0.56	38	15.2	1.3	Zaditen 1 mg BD after varicocelectomy for 3 months
Pourmand et al. (2014) ²⁵	50	21.75	15.32	50	24.4		50	21.6	9.38	50	28.6		Oral L-carnitine 250 mg TID for 6 months
Cyrus et al. (2015) ²⁷	69	57	18.2	69	67.5	16.4	46	52.2	16.1	46	75.3	13.1	Oral vitamin C 250 mg BD for 3 months
Park et al. (2016) ²⁸	19	5.6	3.7	19	1.9	0.3	18	5.31	3.6	18	2.8	0.5	Oral Korean red ginseng 500 mg TID for 3 months
Qu et al. (2017) ²⁹	44	26.95	1.53	44	27.19	3.67	44	27.41	2.42	44	53.7	59.2	Oral Xuanju capsules 3 grains (0.42 g/grain) once TID for 3 months
Asr Badr et al. (2017) ³⁰	21	29.9	5.4	21	34.14	5.59	27	23.48	3.48	27	25.6	3.96	Oral saffron capsule 60 mg OD every other day post-varicocelectomy for 6 months
Lu et al. (2018) ³¹	27	2.6	0.2	27	5.1	0.3	27	2.8	0.4	27	6.2	0.6	Oral melatonin 400 mg OD post-varicocelectomy for 3 months
Kızılay and Altay (2019) ³²	28	2.13	0.66	28	2.98	0.21	62	1.89	0.45	62	3.32	0.3	Oral two sachets of antioxidant BD containing
Azizol-lahi et al. (2013) ³⁴ A	25	42.1	4.8	25	48.4	9.9	32	40	3.2	32	53.2	2.7	Group A received zinc sulfate 66 mg 1 capsule for 6 months
Azizol-lahi et al. (2013) ³⁴ B	25	42.1	4.8	25	48.4	9.9	26	52.1	2.8	26	53.7	1.7	Group B received folic acid 5 mg 1 capsule for 6 months
Azizol-lahi et al. (2013) ³⁴ C	25	42.1	4.8	25	48.4	9.9	29	46.7	2.7	29	56.6	2.2	Group C received zinc sulfate plus folic acid 66 mg plus 5 mg 1 capsule for 6 months
Zaazaa et al. (2018) ³⁶ A	40	1.5	0.5	40	2.2	0.9	40	1.5	0.5	40	1.9	0.6	Group A received 1 mg ketotifen twice daily for 3 months
Zaazaa et al. (2018) ³⁶ B	40	1.5	0.5	40	2.2	0.9	40	1.4	0.5	40	2.3	0.7	Group B received varicocelectomy followed with 1 mg ketotifen twice daily for 3 months

Note: BD: Two times a day; OD: Once a day; TID: Thrice a day.

Table 5. Sperm Volume at Baseline and Endpoint of the Intervention and Comparator.

Author/Year	Comparator						Intervention						Intervention
	Baseline			End			Baseline			End			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Qu et al. (2017) ²⁹	44	3.62	0.28	44	3.66	0.37	44	3.51	0.31	44	3.62	0.34	Oral Xuanju capsules 3 grains (0.42 g/grain) once TID for 3 months
Asr Badr et al. (2017) ³⁰	21	3.17	1.63	21	4	2.13	27	2.77	1.1	27	3.3	1.84	Oral saffron capsule 60 mg OD every other day post-varicocelectomy for 6 months
Amirzargar et al. (2012) ³³ A	35	3.59	1.8	35	3.41	1.52	25	3.38	1.85	25	2.86	1.63	HCG 5,000 IU weekly human chorionic
Amirzargar et al. (2012) ³³ B	35	3.59	1.8	35	3.41	1.52	21	2.96	1.08	21	3.02	1.42	HMG 75 IU 3 times a week
Amirzargar et al. (2012) ³³ C	35	3.59	1.8	35	3.41	1.52	32	3.48	1.61	32	2.93	1.54	rhFSH 75 IU 3 times a week

Note: BD: Two times a day; HCG: Human chorionic gonadotropin; HMG: Human menopausal gonadotropin; OD: Once a day; rhFSH: Recombinant human follicle-stimulating hormone; TID: Thrice a day.

Table 6. Sperm Density at Baseline and Endpoint of the Intervention and Comparator.

Author/ Year	Comparator						Intervention						Intervention
	Baseline			End			Baseline			End			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Azadi et al. (2011) ²⁴	52	37.05	5.21	45	44.45	5.62	51	35.02	3.88	38	67.52	5.35	Zaditen 1 mg BD after varicocelelectomy for 3 months
Qu et al. (2016) ²⁹	44	15.73	5.67	44	29.32	3.48	44	15.82	3.73	44	35.24	6.73	Oral Xuanju capsules 3 grains 0.42 g/grain) once TID for 3 months

Note: BD: Two times a day; TID: Thrice a day.

Interventions having oral Korean red ginseng 500 mg TID for 3 months and oral Xuanju capsules 3 grains (0.42 g/grain) once TID for 3 months post-varicocelelectomy interestingly showed a decrease in FSH level after surgery in the interventional group.³⁵ Two studies assessed the levels of LH in both control and interventional groups.^{28,29} Both studies displayed a decrease in the levels of LH post-varicocelelectomy interestingly in both groups. The decrease was significant in the interventional group compared to the control group. Furthermore, a decrease in LH levels is considered a factor in improving fertility status in males.

Quality of Studies

Cochrane risk of bias criteria was used to assess the risk of bias among the included studies. It was observed that overall, the blinding of personnel and the blinding of outcomes were observed to be the main areas with a higher risk of bias among the selected studies. Details are shown in Figure 2.

Discussion

One of the most contentious issues surrounding male infertility is varicocele. While the majority of international fertility societies concur that virtual reality (VR) should be used when a man is infertile and has a clinically detectable varicocele and abnormal semen parameters,^{37–39} some medical professionals continue to have doubts about varicocelelectomy's positive effects on semen parameters and reproductive status.^{40–42} The present study is primarily assessing the impact of supportive pharmacological and supplemental care among post-varicocelelectomy patients.

In summation of the results, it was observed that ketotifen supplementation has shown significant improvement in semen parameters, chromatin integrity, and pregnancy rates. Cumulative pregnancy significantly improved in the treatment group compared to the control group, except for DNA integrity.²⁴ For the improvement of the DNA damage, it was observed that 750 mg of L-carnitine and mast cell stabilizers improved the semen analysis and DNA integrity compared to

Author (Year)	Random Sequence Generation	Allocation Concealment	Blinding of Personals	Blinding of Outcomes	Incomplete Outcome Data	Selective Reporting	Other Bias
Azadi et al. (2011) ²⁴	?	?	—	—	—	+	?
Pourmand et al. (2014) ²⁵	+	—	?	?	?	?	?
Ener et al. (2016) ²⁶	?	?	+	+	—	—	?
Cyrus et al. (2015) ²⁷	+	+	+	?	+	?	?
Park et al. (2016) ²⁸	+	?	+	?	+	+	?
Qu et al. (2017) ²⁹	?	?	—	—	+	+	?
Asr Badr et al. (2017) ³⁰	+	?	—	—	+	+	?
Lu et al. (2018) ³¹	?	?	?	?	?	?	?
Kızılçay and Altay (2019) ³²	+	—	?	?	?	?	?
Amirzargar et al. (2012) ³³	?	?	—	—	+	+	?

(Figure 2 continued)

(Figure 2 continued)

Azizollahi et al. (2013)³⁴	?	?	—	—	—	+	?
Nematollahi et al. (2014)³⁵	?	?	—	—	+	+	?
Zaazaa et al. (2018)³⁶	?	?	—	—	+	?	?

Figure 2. Quality of the Selected Studies.

the comparator; however, the improvement in DNA integrity was not statistically significant.^{25,36} However, due to the limited number of studies, it remains challenging to recommend any of the measures above as a first-line regimen for the post-varicocele surgery management of patients.

A variety of supplements, that is, VIT E and VIT C, were also investigated among post-varicocele surgery patients. It was observed that these supplements were found to have a positive impact on parameters like sperm count, percentage of change in sperm count, motile sperm count, and percentage of change in motile sperm count.^{26,27} However, antioxidant treatment increases the likelihood of getting pregnant and has a significant impact on varicocele surgery results.³² One may draw the conclusion that co-administering folic acid and zinc greatly enhanced sperm parameters and improved varicocele surgery results. Therefore, following surgery, medical therapy with appropriate medications may be beneficial for getting satisfactory results on hormonal and sperm parameters.^{34,35}

Korean ginseng was also investigated for its effect on the serum levels of testosterone, LH, and FSH did not differ significantly between the groups though. Korean ginseng may be a helpful treatment for male infertility; however, its impact on spermatogenesis may need to be clarified.²⁸ Xuanju capsule and the effect of the therapy on levels of sex hormone and anti-sperm antibody (AsAb) was also assessed in comparison to the control group. The group receiving Xuanju had a substantially higher rate of clinical efficacy, 84.09%. In addition, sperm density, percentage, and sperm survival rate were all significantly greater in the Xuanju supplementation group. Conclusions: Xuanju capsules were observed to have a significantly higher semen quality and level of sexual hormones as well as lower serum AsAb levels in comparison to the control group.²⁹ Similar assessment was performed among infertile males with clinical varicocele following varicocele surgery using saffron as

a herbal supplement. Saffron improves sperm motility but does not affect other semen parameters.³⁰ When comparing the melatonin group to the placebo group, there were statistically significant improvements in the post-operative parameters of semen analyses (sperm concentration, motility, and proportions of normally produced spermatozoa), peripheral blood inhibin B, and total antioxidant capacity. Thus, can be used as a recommended regimen in the post-varicocele surgery patients.³¹

The effect of rhFSH, HCG, and HMG was also assessed. It is proven that these hormones may shorten the period needed to induce spermatogenesis and fertility when compared to varicocele surgery alone. Compared to other medications, rhFSH is more useful for these objectives.³³ When comparing the melatonin group to the placebo group, there were statistically significant improvements in the post-operative parameters of semen analyses (sperm concentration, motility, and proportions of normally produced spermatozoa), peripheral blood inhibin B, and total antioxidant capacity. Thus, it can be used as a recommended regimen in the post-varicocele surgery patients.³¹

There was no evidence of publication bias in the analyzed papers on sperm volume, total sperm count, total sperm motility, and normal morphology. No investigation was sensitive enough to affect the conclusion of our findings regarding sperm concentration and progressive motility. Researchers who are against using varicocele surgery to treat male infertility primarily fear that, even in the absence of treatment, semen quality may naturally increase. A lack of a suitable control group resulted in poor analysis, which prevented several researchers from taking this issue into account.⁴¹ Results of the current systematic review have shown a significant improvement after varicocele surgery, specifically in the case when various supplements and anti-inflammatory agents had a very fruitful effect on sperm count and motility, but this was not statistically significant. Furthermore, keeping in view the

current evidence-based synthesis guidelines, there is an immediate need for more well-planned studies with selective control groups so that the entire effect of the intervention can be assessed scientifically.

Conclusion

Selected studies in the review have revealed improvements in the various physical and morphological markers associated with sperm and other parameters associated with fertility among men. However, the main limitation observed in the published scientific data is the limited studies on the supplements that are used in the post-varicocelectomy. To begin with, not all RCTs met the requirements to be included in the analysis. Second, all tested outcomes showed high heterogeneity. Third, research examining the effect of VR on sperm concentration and progressive sperm motility showed notable results, but several studies are lacking to conclude using the effect size of the selected intervention.

Limitations and Implications of This Research

One of the main limitations of this study is the lack of quantitative comparison, which was unfortunately not possible due to differences and deficiencies across the different studies and the parameters they measured as an outcome. The rest of this study has given the researchers a new perspective on exploring the impact of various pharmacotherapy regimens as adjunct therapies for managing varicoceles.

Abbreviations

AsAb: Anti-sperm Antibody; **BD:** Two times a day; **FSH:** Follicle-stimulating hormone; **HCG:** Human chorionic gonadotropin; **HMG:** Human menopausal gonadotropin; **LH:** Luteinizing hormone; **MeSH:** Medical Subject Headings; **PICOT:** Population, intervention, comparator, outcome; **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **RCTs:** Randomized clinical trials; **ROS:** Reactive oxygen species; **TID:** Thrice a day; **VIT B12:** Vitamin B12; **VIT C:** Vitamin C; **VIT E:** Vitamin E; **VR:** Virtual reality; **WHO:** World Health Organization; **ZnO:** Zinc oxide.

Acknowledgments

None.

Declaration of Conflicting Interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval and Informed Consent

Not applicable.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Mohammad Akbar Hossain  <https://orcid.org/0000-0001-8990-9875>

References

1. Hafeez M, Ahmed A, Usmanhane K, et al. Clinical evaluation of herbal medicine for oligospermia. *Pak J Nutr* 2011; 10(3): 238–240. doi: 10.3923/pjn.2011.238.240
2. Rahim R and Majeed SS. Aetiology factors of infertility. *J Postgrad Med Inst* 2004; 18(2).
3. Irfan M, Shabbir A, Raja GK, et al. Sperm disorders and aetiologies of male infertility in Pakistan: meta-analyses and review. *Austin J Reprod Med Infertil* 2015; 2(6): 1034.
4. Cooper TG, Noonan E, Von Eckardstein S, et al. World Health Organization reference values for human semen characteristics. *Hum Reprod Update* 2010; 16(3): 231–245. doi: 10.1093/humupd/dmp048, PMID 19934213.
5. Misurale F, Cagnazzo G, and Storace A. Asthenospermia and its treatment with HCG. *Fertil Steril* 1969; 20(4): 650–653. doi: 10.1016/s0015-0282(16)37092-3, PMID 5795044.
6. Kumar R. Medical management of non-obstructive azoospermia. *Clinics (Sao Paulo)* 2013; 68 Suppl 1: 75–79. doi: 10.6061/clinics/2013(sup01)08, PMID 23503956.
7. Grimes DA and Lopez LM. “Oligozoospermia,” “azoospermia,” and other semen-analysis terminology: the need for better science. *Fertil Steril* 2007; 88(6): 1491–1494.
8. Saypol DC. Varicocele. *J Androl* 1981; 2(2): 61–71.
9. Will MA, Swain J, Fode M, et al. The great debate: varicocele treatment and impact on fertility. *Fertil Steril* 2011; 95(3): 841–852. doi: 10.1016/j.fertnstert.2011.01.002, PMID 21272869.
10. Baigorri BF and Dixon RG. Varicocele: a review. *Semin Intervent Radiol* 2016; 33(3): 170–176. doi: 10.1055/s-0036-1586147, PMID 27582603.
11. World Health Organization. The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. *Fertil Steril* 1992; 57(6): 1289–1293. doi: 10.1016/S0015-0282(16)55089-4, PMID 1601152.
12. Eisenberg ML and Lipshultz LI. Varicocele-induced infertility: newer insights into its pathophysiology. *Indian J Urol* 2011; 27(1): 58–64. doi: 10.4103/0970-1591.78428, PMID 21716891.
13. Akbay E, Cayan S, Doruk E, et al. The prevalence of varicocele and varicocele-related testicular atrophy in Turkish children and adolescents. *BJU Int* 2000; 86(4): 490–493. doi: 10.1046/j.1464-410x.2000.00735.x, PMID 10971279.
14. Al-Ali BM, Marszalek M, Shamloul R, et al. Clinical parameters and semen analysis in 716 Austrian patients with varicocele. *Urology* 2010; 75(5): 1069–1073. doi: 10.1016/j.urology.2009.11.042, PMID 20138656.
15. 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, PMID 17683466.
16. Pauroso S, Di Leo N, Fulle I, et al. Varicocele: ultrasonographic assessment in daily clinical practice. *Eur J Ultrasound* 2011; 14(4): 199–204. doi: 10.1016/j.jus.2011.08.001.

17. Kupis L, Dobroński PA, and Radziszewski P. Varicocele as a source of male infertility—current treatment techniques. *Cent Eur J Urol* 2015; 68(3): 365–370. doi: 10.5173/cej.2015.642, PMID 26568883.
18. Andò S, Giacchetto C, Colpi G, et al. Plasma levels of 17-OH-progesterone and testosterone in patients with varicoceles. *Eur J Endocrinol* 1983; 102(3): 463–469. doi: 10.1530/acta.0.1020463.
19. Sakamoto Y, Ishikawa T, Kondo Y, et al. The assessment of oxidative stress in infertile patients with varicocele. *BJU Int* 2008; 101(12): 1547–1552. doi: 10.1111/j.1464-410X.2008.07517.x, PMID 18294306.
20. Damsgaard J, Joensen UN, Carlsen E, et al. Varicocele is associated with impaired semen quality and reproductive hormone levels: a study of 7035 healthy young men from six European countries. *Eur Urol* 2016; 70(6): 1019–1029. doi: 10.1016/j.eururo.2016.06.044, PMID 27423503.
21. Younes AK. Low plasma testosterone in varicocele patients with impotence and male infertility. *Arch Androl* 2000; 45(3): 187–195. doi: 10.1080/01485010050193968, PMID 11111867.
22. Porth CJ, Bamrah VS, Tristani FE, et al. The Valsalva maneuver: mechanisms and clinical implications. *Heart Lung* 1984; 13(5): 507–518. PMID 6565684.
23. Cochrane. *Cochrane handbook for systematic reviews of interventions*. Available from: <https://training.cochrane.org/cochrane-handbook-systematic-reviews-interventions>
24. Azadi L, Abbasi H, Deemeh MR, et al. Zaditen (Ketotifen), as mast cell blocker, improves sperm quality, chromatin integrity and pregnancy rate after varicocelectomy. *Int J Androl* 2011; 34(5 Pt 1): 446–452. doi: 10.1111/j.1365-2605.2010.01112.x, PMID 20874726.
25. Pourmand G, Movahedin M, Dehghani S, et al. Does l-carnitine therapy add any extra benefit to standard inguinal varicocelectomy in terms of deoxyribonucleic acid damage or sperm quality factor indices: a randomized study. *Urology* 2014; 84(4): 821–825. doi: 10.1016/j.urology.2014.07.006, PMID 25260444.
26. Ener K, Aldemir M, Işık E, et al. The impact of vitamin E supplementation on semen parameters and pregnancy rates after varicocelectomy: a randomised controlled study. *Andrologia* 2016; 48(7): 829–834. doi: 10.1111/and.12521, PMID 26780969.
27. Cyrus A, Kabir A, Goodarzi D, et al. The effect of adjuvant vitamin C after varicocele surgery on sperm quality and quantity in infertile men: a double blind placebo controlled clinical trial. *Int Braz J Urol* 2015; 41(2): 230–238. doi: 10.1590/S1677-5538.IBJU.2015.02.07, PMID 26005963.
28. Park HJ, Choe S, and Park NC. Effects of Korean red ginseng on semen parameters in male infertility patients: a randomized, placebo-controlled, double-blind clinical study. *Chin J Integr Med* 2016; 22(7): 490–495. doi: 10.1007/s11655-015-2139-9, PMID 25967606.
29. Qu X, Shan Z, Zhang N, et al. Curative effect of surgery in combination with compound Xuanju capsule in treating subclinical varicocele induced infertility. *Biomed Res* 2017; 28(3): 1247–1250.
30. Asr Badr YA, Sepehran E, Del Azar A, et al. The effect of saffron on semen analysis in infertile men with clinical varicocele after varicocelectomy. *Nephrourol Mon* 2017; 9(5): e59939. doi: 10.5812/numonthly.59939.
31. Lu XL, Liu JJ, Li JT, et al. Melatonin therapy adds extra benefit to varicocelectomy in terms of sperm parameters, hormonal profile and total antioxidant capacity: a placebo-controlled, double-blind trial. *Andrologia* 2018; 50(6): e13033. doi: 10.1111/and.13033, PMID 29740842.
32. Kızılay F and Altay B. Evaluation of the effects of antioxidant treatment on sperm parameters and pregnancy rates in infertile patients after varicocelectomy: a randomized controlled trial. *Int J Impot Res* 2019; 31(6): 424–431. doi: 10.1038/s41443-018-0109-4, PMID 30659292.
33. Amirzargar MA, Yavangi M, Basiri A, et al. Comparison of recombinant human follicle stimulating hormone (rhFSH), human chorionic gonadotropin (HCG) and human menopausal gonadotropin (HMG) on semen parameters after varicocelectomy: a randomized clinical trial. *Iran J Reprod Med* 2012; 10(5): 441–452. PMID 25246910.
34. Azizollahi G, Azizollahi S, Babaei H, et al. Effects of supplement therapy on sperm parameters, protamine content and acrosomal integrity of varicocelectomized subjects. *J Assist Reprod Genet* 2013; 30(4): 593–599. doi: 10.1007/s10815-013-9961-9, PMID 23435530.
35. Nematollahi-Mahani SN, Azizollahi GH, Baneshi MR, et al. Effect of folic acid and zinc sulphate on endocrine parameters and seminal antioxidant level after varicocelectomy. *Andrologia* 2014; 46(3): 240–245. doi: 10.1111/and.12067, PMID 23356505.
36. Zaazaa A, Adel A, Fahmy I, et al. Effect of varicocelectomy and/or mast cells stabilizer on sperm DNA fragmentation in infertile patients with varicocele. *Andrology* 2018; 6(1): 146–150. doi: 10.1111/andr.12445, PMID 29195028.
37. Colpi GM, Francavilla S, Haidl G, et al. European Academy of Andrology guideline: management of oligo-astheno-teratozoospermia. *Andrology* 2018; 6(4): 513–524. doi: 10.1111/andr.12502, PMID 30134082.
38. Marmar JL, Agarwal A, Prabakaran S, et al. Reassessing the value of varicocelectomy as a treatment for male subfertility with a new meta-analysis. *Fertil Steril* 2007; 88(3): 639–648. doi: 10.1016/j.fertnstert.2006.12.008, PMID 17434508.
39. 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, PMID 33295258.
40. Silber SJ. The varicocele dilemma. *Hum Reprod Update* 2001; 7(1): 70–77. doi: 10.1093/humupd/7.1.70, PMID 11212078.
41. Kantartzi PD, Goulis ChD, Goulis GD, et al. Male infertility and varicocele: myths and reality. *Hippokratia* 2007; 11(3): 99–104. PMID 19582201.
42. Silber S. The varicocele argument resurfaces. *J Assist Reprod Genet* 2018; 35(6): 1079–1082. doi: 10.1007/s10815-018-1160-2, PMID 29589295.