DOI: *10.4081/aiua.2026.15165*

REVIEW

Effect of adjuvant vitamin E supplementation on sperm parameters after varicocelectomy: A systematic review and meta-analysis

Nafis Audrey Febriansyah, Agustin J. Nanda De Niro, Fikri Rizaldi

Department of Urology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

Summary ***Introduction and objectives: Varicocele is associated with oxidative stress and impaired semen quality. Vitamin E is a lipid-soluble antioxidant that may augment postoperative recovery after varicocelectomy, but clinical evidence remains inconsistent. This study evaluated the effect of adjuvant vitamin E-based supplementation on semen parameters and pregnancy outcomes after varicocelectomy.***

Materials and methods: This systematic review and meta-analysis followed PRISMA 2020 and was registered in PROSPERO (CRD420261309544). PubMed, ScienceDirect, Cochrane, Springer, and Scopus were searched through February 16, 2026. Studies evaluating vitamin E, alone or in antioxidant combinations, after varicocelectomy were included. Primary outcomes were sperm concentration and motility; secondary outcomes included morphology, sperm DNA fragmentation, pregnancy, and safety. Risk of bias was assessed using RoB 2.0 for randomized trials and the Newcastle-Ottawa Scale for the cohort study.

Results: Five studies involving 408 participants were included. Pooled analysis of two randomized trials showed no significant additional benefit of vitamin E versus control for sperm concentration (SMD 0.09, 95% CI-0.59 to 0.76; p = 0.80) or sperm motility (SMD 0.15, 95% CI-0.19 to 0.49; p = 0.39). Morphology and pregnancy outcomes were reported heterogeneously. Comparative studies suggested that varicocelectomy was superior to antioxidant-only regimens for morphology, sperm DNA fragmentation, and natural pregnancy, whereas vitamin E as a postoperative adjuvant did not show a consistent incremental benefit.

Conclusions: Current evidence does not demonstrate a consistent improvement in key semen parameters with adjuvant vitamin E supplementation after varicocelectomy. Larger trials with standardized regimens and clinically relevant outcomes are needed.

KEY WORDS: Varicocelectomy; Vitamin E; Male infertility; Sperm motility; Meta-analysis.

Submitted 21 March 2026; Accepted 29 March 2026

INTRODUCTION

Infertility remains a major global health issue, and current prevalence estimates vary across regions (1). Male factor infertility contributes substantially to the burden of infertile couples, and several potentially treatable causes can be addressed with targeted interventions (2). Varicocele is one of the most common causes of male infertility and is reported in approximately 15% of healthy men and 35% of men with primary infertility (3). Varicocele is associated with oxidative stress and oxidative damage to sperm. Clinical evidence links varicocele to increased reactive oxygen species and impaired sperm function (4). Varicocelectomy can improve semen parameters, although the magnitude of benefit varies across studies; meta-analytic evidence suggests improvements in sperm count and motility, whereas effects on pregnancy are less consistent (5).

The biological rationale for antioxidant therapy after varicocelectomy is strong, yet clinical findings remain heterogeneous across compounds, doses, durations, and patient populations. Guideline-oriented reviews and evidence syntheses emphasize this heterogeneity and underline the need for higher-quality, condition-specific trials rather than broad, untargeted supplementation (2, 6, 7). Vitamin E is a fat-soluble antioxidant that may protect sperm membranes from oxidative damage. Several randomized clinical trials have evaluated vitamin E, alone or in combination, as an adjunct after varicocelectomy, with variable effects on semen parameters and limited or inconsistent data on pregnancy outcomes (8-10).

Therefore, a focused systematic review and meta-analysis was undertaken to evaluate the effects of vitamin E supplementation after varicocelectomy on sperm parameters and pregnancy outcomes, while also considering heterogeneity across vitamin E-based and other antioxidant regimens.

MATERIALS AND METHODS

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (11) and was registered in PROSPERO (CRD420261309544).

Eligibility criteria

1. *Population*: adult patients undergoing varicocelectomy.
2. *Intervention*: treatment with vitamin E as adjuvant therapy, either alone or as part of an antioxidant regimen.
3. *Study design*: randomized controlled trials and observational studies, including cohort, case-control, and cross-sectional designs.
4. Outcomes: reporting of at least one prespecified out-

come measure, including sperm concentration, motility, morphology, pregnancy, sperm DNA fragmentation, or safety outcomes.

Search strategy and study selection

PubMed, ScienceDirect, Cochrane, Springer, and Scopus were searched on February 16, 2026, without language restrictions. The search strategy used the terms [(varicocelectomy) OR (varicocele)] AND [(vitamin E) OR (tocopherol)]. Supplemental searches included hand-searching the reference lists of eligible studies, medRxiv, and clinical trial registries. Two independent investigators performed study selection using a standardized screening protocol, and disagreements were resolved by consensus.

Data extraction and quality assessment

A piloted, standardized extraction form captured study characteristics, demographic data, details of supplementation and comparator regimens, and efficacy and safety outcomes. Risk of bias in randomized trials was assessed with the Cochrane Risk of Bias 2.0 tool, while the cohort study was assessed with the Newcastle-Ottawa Scale. Disagreements were resolved by discussion until consensus.

Statistical analysis

Review Manager 5.4 and R (version 4.3.1) were used for all analyses. Dichotomous outcomes were pooled as risk ratios with 95% *confidence intervals* (CIs) using Mantel-Haenszel random-effects models. Continuous outcomes were analyzed as *standardized mean differences* (SMDs) with 95% CIs using inverse-variance weighting. Statistical heterogeneity was quantified with the I^2 statistic, with values greater than 50% indicating substantial heterogeneity. Small-study effects were planned to be assessed, when feasible, using Begg's rank correlation test and visual inspection of funnel plot asymmetry. Leave-one-out sensitivity analysis was planned to evaluate the influence of individual studies. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Study selection

A total of 1,405 records were identified from databases and four additional records were identified from other sources. After removal of 26 duplicates, 1,379 titles and abstracts were screened. Twenty-five database records and four additional records underwent full-text assessment, and five studies met the inclusion criteria for the review. The study selection process is shown in Figure 1. Among the included studies, four randomized controlled trials were judged to be at low risk of bias according to RoB 2, whereas the single cohort study was considered to be of good quality according to the Newcastle-Ottawa Scale.

Study characteristics

The five included studies comprised four randomized controlled trials and one cohort study conducted in Iran, Turkey, and Egypt (8-10, 12, 13). Across all studies, 408 participants were included (209 in intervention arms and 199 in control arms). Interventions included vitamin E

Figure 1.
PRISMA 2020 flow diagram of study selection,

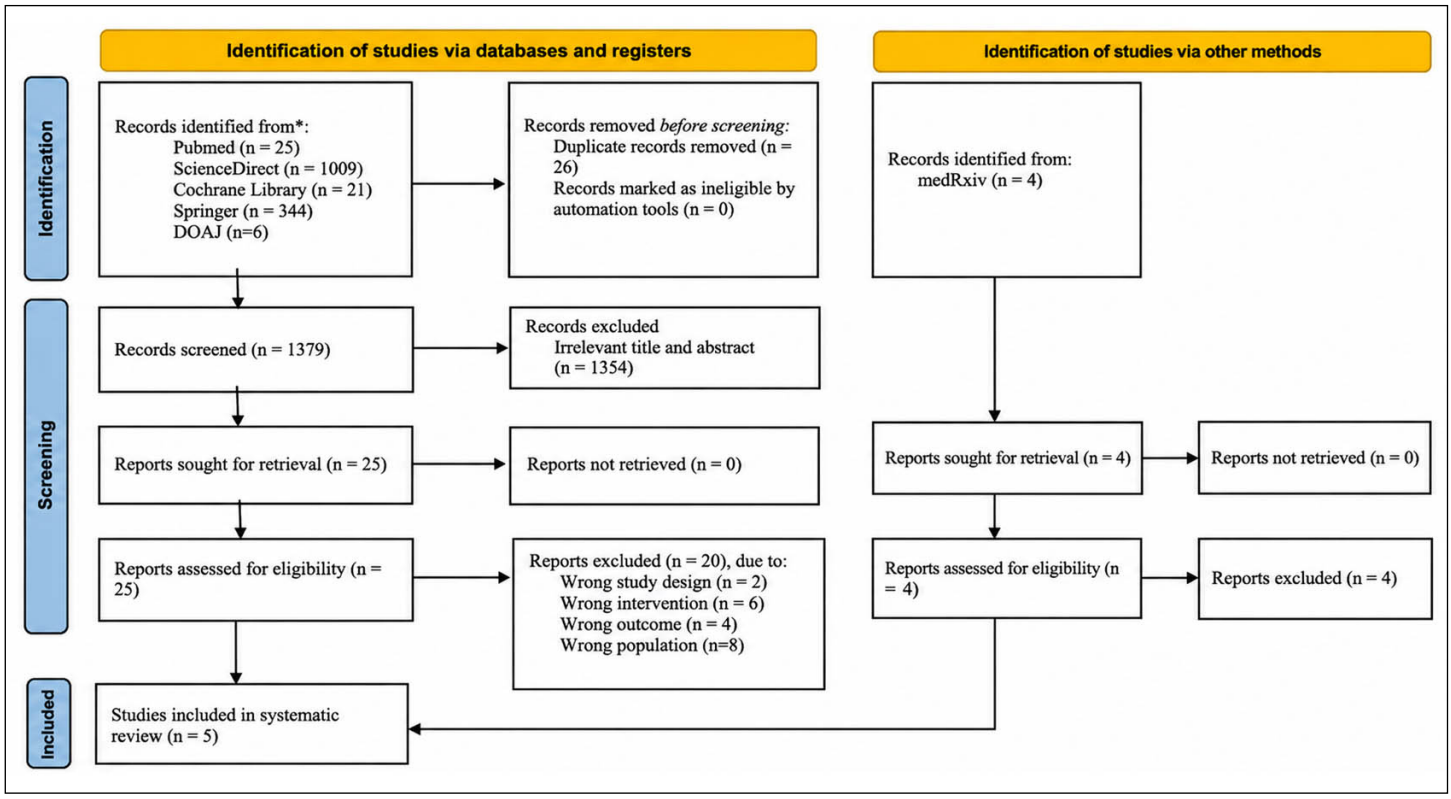


Table 1.
Characteristics of the included studies. Values are reported as presented in the original studies.

No.	Study	Design/country	N (I/C)	Age, y (I/C)	Intervention	Comparator	Main outcomes
1	Saeedian et al., 2025	RCT/Iran	45/45	30.37 ± 6.18/31.0 ± 6.49	Vitamin E 400 units/day orally for 3 months after varicocelectomy.	Placebo for 3 months.	Endpoint count, motility, and morphology reported; no significant morphology difference.
2	Ener et al., 2016	RCT/Turkey	22/23	26.5 ± 5.0/25.2 ± 4.3	Vitamin E 300 mg twice daily (600 mg/day) orally for 12 months after varicocelectomy.	No supplementation after varicocelectomy.	Endpoint count, motility, and 12-month pregnancy reported.
3	Ardestani Zadeh et al., 2019	RCT/Iran	30/30	30.27 ± 4.67/30.47 ± 6.09	Vitamin E 400 IU/day + selenium 200 µg/day + folic acid 5 mg/day orally for 6 months after varicocelectomy.	No supplementation after varicocelectomy.	Pre- and post-treatment count, motility, and morphology reported; no significant morphology difference.
4	Saber-Khalaf et al., 2026	RCT/Egypt	40/41	32.4 ± 4.01/32.78 ± 5.46	L-carnitine 1 g + vitamin C 1 g + vitamin E 400 mg daily for 6 months.	Microsurgical subinguinal varicocelectomy without antioxidant therapy.	Count, motility, morphology, SDF, and 12-month pregnancy reported; surgery favored over antioxidants.
5	Fathi et al., 2021	Cohort/Egypt	72/60	34.5 (24-43)/33 (24-41)	L-carnitine 1 g (2 tablets/day) + vitamin C 1 g/day + vitamin E 400 mg/day for 6 months.	Microsurgical subinguinal varicocelectomy without antioxidant therapy.	Progressive motility, morphology, SDF, and pregnancy reported; surgery favored over antioxidants.

I/C: intervention/control; RCT: randomized controlled trial; SDF: sperm DNA fragmentation.

alone for 3 to 12 months after varicocelectomy, vitamin E combined with selenium and folic acid, and combination antioxidant regimens containing L-carnitine, vitamin C, and vitamin E. Primary study outcomes focused on semen parameters, particularly sperm concentration and motility, whereas secondary outcomes included morphology, sperm DNA fragmentation, and natural pregnancy. A summary of study characteristics is provided in Table 1.

Sperm analysis parameters

Sperm count

Meta-analysis of the two post-varicocelectomy vitamin E trials by *Ener et al.* (8) and *Saeedian et al.* (10) showed no statistically significant improvement in sperm concentration compared with varicocelectomy alone (SMD 0.09, 95% CI -0.59 to 0.76; p = 0.80; random-effects model). One study slightly favored vitamin E and the other slightly favored control, resulting in an inconsistent overall direction of effect. These findings suggest no clear additional benefit of adjuvant vitamin E supplementation on sperm concentration after varicocelectomy. The corresponding forest plot is provided in Figure 2.

Motility analysis

The pooled analysis of the same two randomized trials (8,10) also showed no statistically significant improvement in sperm motility with adjuvant vitamin E compared with varicocelectomy alone (SMD 0.15, 95% CI -

Figure 2.
Forest plot for sperm concentration.

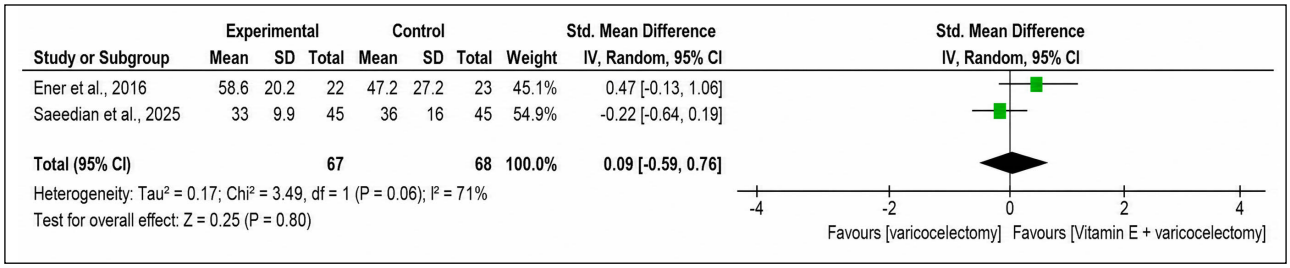
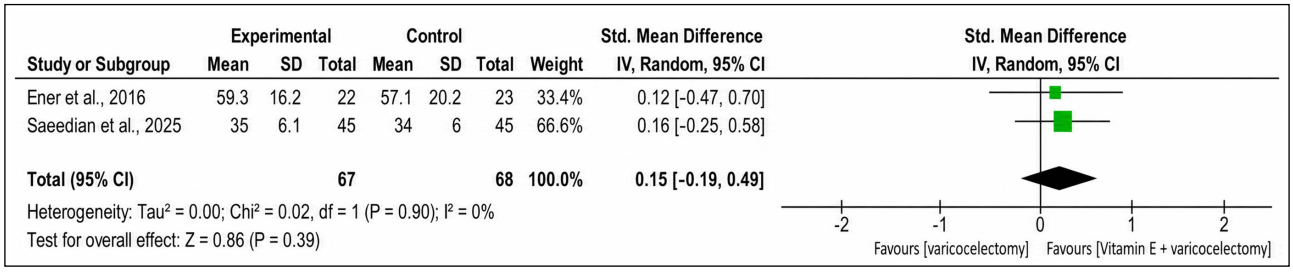


Figure 3.
Forest plot for sperm motility.



0.19 to 0.49; p = 0.39). Statistical heterogeneity was not detected (Tau² = 0.00; Chi² = 0.02, df = 1; p = 0.90; I² = 0%), indicating consistent results across the two studies. Nevertheless, the evidence base remains limited, and the pooled estimate does not demonstrate a clear incremental benefit of vitamin E on postoperative sperm motility. The corresponding forest plot is provided in Figure 3.

Morphology analysis

Four studies reported morphological changes after treatment. In the triple-blind randomized trial by *Saeedian et al.* (10), morphology improved within both arms after varicocelectomy, but the between-group difference at follow-up was not significant (p = 0.30). Ardestani *Zadeh et al.* (9) likewise found no significant difference in sperm morphology between the supplementation group and control group at baseline or after 6 months.

In contrast, the comparative studies by *Saber-Khalaf et al.* (13) and *Fathi et al.* (12) favored varicocelectomy over antioxidant-only regimens. In the randomized trial by *Saber-Khalaf et al.* (13), both groups improved, but the increase in normal forms was greater after varicocelectomy than after antioxidants alone (p = 0.007).

In the retrospective cohort by *Fathi et al.* (12), morphology also improved in both groups at 6 months, but the improvement and the proportion of patients achieving normal forms were significantly higher after varicocelectomy.

Pregnancy rates

Pregnancy outcomes were reported in three studies (8, 12, 13). In the randomized trial by *Ener et al.* (8), all participants underwent varicocelectomy and were randomized to vitamin E or control; at 12 months, pregnancy rates were similar between groups (5/22 *vs* 5/23). In contrast, studies comparing varicocelectomy with antioxidant-only regimens favored surgery: *Fathi et al.* (12) reported natural pregnancy in 22/72 (30.5%) after varicocelectomy *versus* 10/60 (16.7%) after antioxidants, and *Saber-Khalaf et al.* (13) reported natural pregnancy in 9/40 (22.5%) *versus* 5/41 (12.5%), respectively.

Discussion

Principal findings

This review evaluated vitamin E-based antioxidant regimens used after varicocelectomy in infertile men with clinical varicocele. Across five eligible studies (8-10, 12, 13), the pooled evidence from the two direct post-varicocelectomy vitamin E trials did not show a consistent additional benefit for sperm concentration or motility beyond surgery alone (8, 10). Findings for morphology were inconsistent, and clinically meaningful outcomes such as pregnancy were reported sparsely and heterogeneously. Comparative studies suggested that varicocelectomy was superior to antioxidant-only regimens for morphology, sperm DNA fragmentation, and natural pregnancy, but these studies do not establish a postoperative adjuvant effect of vitamin E itself (12, 13).

These patterns are consistent with previous syntheses reporting substantial heterogeneity and uncertain clinical benefit of antioxidants in varicocele-associated infertility, particularly in unselected patients (14, 15).

Potential role of adjuvant vitamin E after varicocelectomy

Vitamin E remains a biologically plausible adjunct because it is a lipid-soluble, chain-breaking antioxidant that limits membrane lipid peroxidation (16). Varicocele has been closely linked to oxidative stress pathways that may impair spermatogenesis and increase sperm DNA damage (4, 17). However, varicocelectomy itself may reduce oxidative burden, so any additional effect from vitamin E may be modest and perhaps confined to subgroups with persistent oxidative stress or elevated sperm DNA fragmentation. Current guideline documents and reviews emphasize the need for selective rather than routine antioxidant use and for better patient stratification in future trials (2, 15, 18).

Comparison with existing evidence

Evidence specifically addressing vitamin E after varicocelectomy is limited and methodologically heterogeneous. The two direct randomized trials used different doses and durations, and one recent study used a triple-blind placebo-controlled design (8, 10). Other studies have examined combination regimens that included vitamin E together with selenium, folic acid, L-carnitine, and vitamin C, but those results cannot be attributed to vitamin E alone (9, 12, 13). Broader reviews of male subfertility and post-varicocelectomy antioxidant therapy suggest that some semen parameters may improve at early follow-up, but benefits for pregnancy remain inconsistent and the overall certainty of evidence is limited (14, 19).

Effect of adjuvant antioxidant therapy after varicocelectomy

Our findings can be compared with the meta-analysis by *Wang et al.* (14), which reported significant improvements in several semen parameters at 3 months after varicocelectomy, although these benefits were less consistent at 6 months and pregnancy rates did not differ significantly.

Similarly, *Azizollahi et al.* (20) found that postoperative zinc sulfate plus folic acid supplementation improved several semen-related outcomes. Taken together, these data suggest that some antioxidant regimens may benefit selected semen parameters after varicocelectomy, particularly at early follow-up or when combination therapy is used, whereas the additional effect of vitamin E alone appears smaller and more variable.

Comparison of vitamin E with varicocelectomy

In the present review, vitamin E used as an adjuvant after varicocelectomy did not demonstrate consistent superiority over varicocelectomy alone (8, 10). This contrasts with studies of conservative vitamin E-based therapy for varicocele without surgery, where multinutrient antioxidant formulations improved sperm DNA integrity more clearly than conventional semen parameters (21). Similarly, tocopherol nicotinate-containing regimens have shown potential benefit in selected varicocele subgroups (22). By comparison, randomized evidence for varicocele repair itself shows more consistent benefit for fertility-related outcomes than observation alone (23).

Limitations

This review has several limitations. First, the available evidence base was small, with only five eligible studies and only two randomized trials contributing to pooled estimates for the primary semen outcomes, which limits statistical power and precision. Second, there was substantial clinical heterogeneity in antioxidant regimens, including differences in formulations, doses, and treatment durations, and some studies used multi-ingredient combinations, limiting attribution of effects specifically to vitamin E. Third, follow-up schedules and semen analysis methods varied across studies, and clinically meaningful outcomes such as pregnancy were inconsistently reported, precluding robust conclusions on reproductive endpoints. Finally, adverse events and biomarkers of oxidative stress or sperm DNA fragmentation were rarely and non-uniformly measured, restricting subgroup analyses and limiting assessment of which patients might benefit most.

Conclusions

Current evidence suggests that vitamin E supplementation as adjuvant therapy after varicocelectomy does not provide consistent additional benefit for key semen parameters compared with varicocelectomy alone. Evidence for clinical outcomes, including pregnancy and safety, remains limited. Larger, methodologically rigorous trials with standardized regimens and a greater focus on clinically meaningful endpoints are needed.

Declarations

Ethical approval and consent for participate: *Not applicable. This study is a systematic review and meta-analysis of previously published data.*

Consent for publication: *Not applicable.*

Availability of data and material: *All data generated or analyzed during this study are included in this manuscript.*

Competing interests: *The authors declare that they have no competing interests.*

Funding: *The authors received no specific funding for this work.*

Authors' contributions: *NAF contributed to the study conception and design, literature search, data extraction, data analysis, and drafting of the manuscript. AJNDN contributed to study selection, data extraction, methodological assessment, and critical revision of the manuscript. FR contributed to the study conception and supervision, interpretation of data, critical revision of the manuscript, and final approval of the version to be published. All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work. All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.*

Acknowledgments: *Not applicable.*

Further information: *PROSPERO registration number CRD420261309544.*

References

1. Cox CM, Thoma ME, Tchangalova N, et al. Infertility prevalence and the methods of estimation from 1990 to 2021: a systematic review and meta-analysis. Hum Reprod Open 2022; 2022:hoac051.

2. Minhas S, Boeri L, Capogrosso P, et al. European Association of Urology guidelines on male sexual and reproductive health: 2025 update on male infertility. Eur Urol 2025; 87:601-16.

3. Alsaikhan B, Alrabeeah K, Delouya G, Zini A. Epidemiology of varicocele. Asian J Androl 2016; 18:179-81.

4. Finelli R, Leisegang K, Kandil H, et al. Oxidative stress: a comprehensive review of biochemical, molecular, and genetic aspects in the pathogenesis and management of varicocele. World J Mens Health 2022; 40:87-103.

5. Schauer I, Madersbacher S, Jost R, et al. The impact of varicocelectomy on sperm parameters: a meta-analysis. J Urol 2012; 187:1540-7.

6. Agarwal A, Leisegang K, Majzoub A, et al. Utility of antioxidants in the treatment of male infertility: clinical guidelines based on a systematic review and analysis of evidence. World J Mens Health 2021; 39:233-90.

7. Amorini AM, Listorti I, Bilotta G, et al. Antioxidant-based therapies in male infertility: do we have sufficient evidence supporting their effectiveness? Antioxidants (Basel) 2021; 10:220.

8. Ener K, Aldemir M, Isik E, et al. The impact of vitamin E supplementation on semen parameters and pregnancy rates after varicocelectomy: a randomised controlled study. Andrologia 2016; 48:829-34.

9. Ardestani Zadeh AA, Arab D, Kia NS, et al. The role of vitamin E, selenium and folic acid supplementation in improving sperm parameters after varicocelectomy: a randomized clinical trial. Urol J 2019; 16:495-500.

10. Saeedian K, Davaryar S, Emadzadeh M, et al. The impact of vitamin E supplementation on sperm analysis in varicocelectomy patients: a triple-blind randomized controlled trial. Trials 2025; 26:36.

11. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.

12. Fathi A, Castiglione F, Mohamed O, et al. Varicocelectomy versus antioxidants in infertile men with isolated teratozoospermia: a retrospective analysis. Turk J Urol 2021; 47:279-84.

13. Saber-Khalaf M, Mohamed O, Mahmoud O, et al. Varicocelectomy versus antioxidants in infertile men with isolated teratozoospermia: a randomized controlled trial. Clin Exp Reprod Med 2026; 53:47-53.

14. Wang J, Wang T, Ding W, et al. Efficacy of antioxidant therapy on sperm quality measurements after varicocelectomy: a systematic review and meta-analysis. Andrologia 2019; 51:e13396.

15. Pyrgidis N, Sokolakis I, Palapelas V, et al. The effect of antioxidant supplementation on operated or non-operated varicocele-associated infertility: a systematic review and meta-analysis. Antioxidants (Basel) 2021; 10:1067.

16. Niki E. Role of vitamin E as a lipid-soluble peroxyl radical scavenger: in vitro and in vivo evidence. Free Radic Biol Med 2014; 66:3-12.

17. Wang K, Gao Y, Wang C, et al. Role of oxidative stress in varicocele. Front Genet 2022; 13:850114.

18. European Association of Urology (EAU) Guidelines Office. EAU

guidelines on sexual and reproductive health: limited update April 2024. Arnhem: EAU Guidelines Office; 2024.

19. de Ligny W, Smits RM, Mackenzie-Proctor R, et al. Antioxidants for male subfertility. Cochrane Database Syst Rev 2022; 5:CD007411.

20. 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; 30:593-9.

21. Gual-Frau J, Abad C, Amengual MJ, et al. Oral antioxidant treatment partly improves integrity of human sperm DNA in infertile grade I varicocele patients. Hum Fertil (Camb) 2015; 18:225-9.

22. Takeshima T, Karibe J, Saito T, et al. Effect of keishibukuryogan combined with tocopherol nicotinate on sperm parameters in patients with a varicocele. Int J Urol 2022; 29:165-9.

23. Abdel-Meguid TA, Al-Sayyad A, Tayib A, Farsi HM. Does varicocele repair improve male infertility? An evidence-based perspective from a randomized, controlled trial. Eur Urol 2011; 59:455-6.

Correspondence

Nafis Audrey Febriansyah
nafisaudreyf.28@gmail.com

Agustin J. Nanda De Niro
deniro_nanda@yahoo.co.id

Department of Urology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

Fikri Rizaldi (Corresponding Author)
fikririz@gmail.com

Department of Urology, Dr. Soetomo General Academic Hospital, Jl. Mayjen Prof. Dr. Moestopo No. 6-8, Airlangga, Gubeng, Surabaya, East Java 60286, Indonesia