Effect of vitamin E on Semen Quality Parameters: A Meta-Analysis of a Randomized Controlled Trial

Rui Wang[1]#, Shangren Wang[1]#, Yuxuan Song[2]#, Hang Zhou[1], Yang Pan[1], Li Liu[1], Shuai Niu[1], Xiaoqiang Liu[1]*

Purpose: To explore the effectiveness of vitamin E in male infertility, a systematic review and meta-analysis was conducted.

Materials and Methods: The retrieval time was from January 1947 to May 2021, without language restriction. Stata 12.0 was used for the meta-analysis.

Results: A total of 8 randomized controlled trials involving 459 patients were included. The results showed that after vitamin E treatment, semen volume was reduced (95% CI: - 0.55 to - 0.06, SMD = - 0.30, p = 0.015), total sperm count was increased (95% CI: 0.02-0.45, SMD = 0.23, p = 0.035), and the differences were statistically significant. There were no statistically significant differences in increasing sperm concentration (95% CI: -0.21-0.29, SMD = 0.04, p = 0.769), total sperm motility (95% CI: -0.01-0.42, SMD = 0.20, p = 0.061) or sperm forward motility rate (95% CI: -0.06-0.65, SMD = 0.29, p = 0.106). Subgroup analysis showed that vitamin E treatment for six months could improve sperm forward motility (95% CI: 0.46-1.14, SMD = 0.80, p <0.001).

Conclusion: Vitamin E could increase the total sperm count and reduce the volume of semen in male infertility patients, and long-term treatment could improve the forward motility rate of sperm. The decrease of semen volume may be the result of different abstinence time before and after the test.

Keywords: vitamin E; sperm quality; male infertility; sperm ; meta-analysis.

INTRODUCTION

Worldwide, infertility is becoming increasingly serious. At present, male infertility has received widespread attention. As a common clinical disease of the male reproductive system, the incidence of male infertility is increasing year by year.(1,2)Infertility is defined clinically as having a normal sexual life without contraception and failing to achieve clinical pregnancy for 12 months or more.(3) The incidence of infertility is approximately 15%, and male factors account for at least 50% of all infertility cases.(4)

The mechanism of male infertility is complex. One of the important causes of male infertility is the decline in semen quality, which leads to oligozoospermia or asthenospermia. These patients are prone to infertility.(5)There are many factors that can affect the quality of male semen, such as radiation, smoking, varicocele, urinary tract infection, oxidative stress, and other factors.(6) In recent years, people have gradually paid attention to the influence of oxidative stress on male infertility and how it affects the quality of semen. When oxidative stress occurs, reactive oxygen species (ROS) produced by organisms exceed the body's natural antioxidant defense. When the production of ROS is too high, it will exert toxic effects on many kinds of cells and tissues. Among them, male germ cell sperm are very sensitive to ROS. Excessive ROS can cause changes in sperm structure and function and affect sperm motility. Evidence shows that the semen antioxidant capacity of infertile men is lower than that of fertile men, and the level of ROS in the body is higher.(7,8)

The most common treatment for oxidative stress is antioxidants. Quite a few studies have started to explore whether the use of antioxidants improves semen quality, and antioxidants mainly include vitamin C, vitamin E, vitamin B12. Among them, the most commonly used is vitamin E, which is a fat-soluble antioxidant that can neutralize free radicals, prevent lipid peroxidation, and inhibit the production of ROS in infertile men. Previous studies have shown that vitamin E deficiency might lead to impaired human fertility.(9) However, the therapeutic effect of vitamin E on male infertility is controversial. Some studies have suggested that vitamin E is ineffective in the treatment of male infertility.(10,11) Therefore, in order to resolve these disputes, we conducted a meta-analysis to evaluate the effectiveness of oral vitamin E in improving semen quality .

MATERIALS AND METHODS

Search strategy

To formulate search strategies according to the requirements of the Cochrane Collaboration, we retrieved Pu-

[1]Department of Urology, Tianjin Medical University General Hospital, Tianjin, 300052, China.
[2]Department of Urology, Peking University People's Hospital, No. 11 Xizhimen South Street Xicheng District, Beijing, 100044, China.
#contributed equally to this work.
Xiaoqiang Liu, PHD;
Department of Urology, Tianjin Medical University General Hospital, 154 Anshan Road, Heping District, Tianjin 300052, China. Tel:+60361614 , E-mail: xiaoqiangliu1@163.com.
Received January 2022 & Accepted July 2022

Table 1. Criteria for Selecting Studies Based on PICO/PECO Statement.

	Inclusion Criteria	Exclusion Criteria
Population	patients with male infertility who were diagnosed according to the WHO and other diagnostic criteria	Studies performed on cells or animals
Intervention/exposure	the test group received vitamin E as the main treatment	The test group was mainly supplemented with other supplements, such as coenzyme Q10, folic acid, etc
Comparator/comparison	placebo	Antioxidants or drugs
Outcomes	sperm parameters and pregnancy rates	serum vitamin E levels in initial
Study design	Randomized controlled trial	No-control studies including single arm studies, case reports, meta-analyses, reviews, and comments. Study was not a randomized controlled trial.

Abbreviations: PICO/PECO,population-intervention/exposure-comparator-outcomes statement.

bMed, the Cochrane Library, Web of Science , Scopus , the VIP database, the Wanfang Database, and the China National Knowledge Infrastructure (CNKI). The used search strategy included the following :((((((((((male fertility) OR (sterility, male)) OR (male sterility)) OR (subfertility, male)) OR (male subfertility)) OR (subfertility, male)) OR (male subfertility)) OR (subfertility, male)) OR (infertility)) AND (semen quality)) OR (sperm)) AND (vitamin E) .The time of retrieval was from database building to May 2021, without language restriction. In addition, a manual search of relevant citations of the included studies was performed.

Literature selection criteria

We used PICO/PECO statement (population—intervention/exposure—comparator—outcomes statement) to set the inclusion criteria and exclusion criteria forfurther selecting eligible studies. The detailed criteria for selecting studies in the systematic review and meta-analysis are outlined in **Table 1**.

Data extraction

General information was extracted by two reviewers independently, including basic information of participants, interventions, the period of outcomes observed, the results and other information. Disagreements between the two authors were resolved by a third senior person.

Quality assessment

All included literature was evaluated for quality by 2 investigators independently referencing the modified Jadad scoring criteria and resolved after discussion with a third party if a disagreement arose. The scoring criteria included (1) random sequence generation; (2) allocation hiding; (3) blinding; and (4) follow-up. The total score is 1 to 7, of which 1 to 3 are low-quality research and 4 to 7 are high-quality research.[12]

Statistical analysis

Stata software (version 12.0) was used for statistical analysis. Standard statistical tables and charts were used to describe the characteristics of the respondents. The standardized mean difference (SMD) and 95% confidence interval (CI) were used to analyze the continuous data. The Q test and I^2 statistics were used to test the heterogeneity of the included results. When $I^2 > 50\%$ or $p < 0.05$, there was significant heterogeneity. If the heterogeneity between studies was obvious, the reasons for heterogeneity were analyzed, and subgroup analysis and sensitivity analysis were used. A *p* value of less than 0.05 for the difference was statistically significant. When $I^2 < 50\%$ or $p > 0.05$, the fixed effects model was used for meta-analysis. In this study, Begg's test and Egger's test were used to evaluate publication bias. If the p value of the above test was less than 0.05, it indicated that there was significant publication bias.[13]

RESULTS

Literature search results

A total of 545 studies were identified, including 265 from PubMed, 67 from Web of Science, 32 from Scopus, 26 from the Cochrane Library, 27 from CNKI, 118 from the Wanfang Database, and 23 from VIP. After reading titles and abstracts, 491 articles were excluded for animal experimentation, review, duplicate articles, and those that clearly did not meet the inclusion criteria. Then, the remaining 54 articles were searched for full-text reading, 46 articles were excluded that did not meet the inclusion criteria, and 8 articles[10,11,14-19] were finally included, with a total of 459 patients, including 238 cases in the experimental group and 221 cases in the control group. The literature screening flow is shown in Figure 1, and the basic information of the included studies is shown in **Table 2**.

Methodological quality assessment results

The modified Jadad score was used to evaluate the methodological quality of the included studies. Four articles[10,11,14,17] were high-quality literature, and four [15,16,18,19] were low-quality literature, as detailed in **Table 3**.

Meta-analysis results

1 Ejaculate volume

Five studies[10,14,16,17,19] reported the relationship between vitamin E treatment of male infertility and semen volume, for a total of 263 patients. There was no statistical heterogeneity among studies ($p = 0.697$, $I^2 = 0\%$), and the pooled effect size of the fixed-effect model was used for analysis. The results of the meta-analysis showed that patients in the test group had less semen volume than those in the control group, and the difference was statistically significant (95% CI: -0.55 to -0.06, SMD = -0.30, $p = 0.015$), as detailed in Figure 2. The sensitivity analysis showed that the results of the meta-analysis were robust, and the results of the funnel plot and Egger's test ($p = 0.422$) indicated the absence of publication bias, as shown in **Figure S1**.

2 Sperm concentration

Four studies[10,11,14,16] reported the relationship between vitamin E treatment of male infertility and sperm concentration in a total of 247 patients, as shown in Figure 3. After testing, there was no significant heterogeneity between the studies ($p = 0.604$, $I^2 = 0\%$). The fixed-effect model analysis showed that the difference between the treatment group and the control group was not sta-

Table2. Characteristics of included studies.

Author (year)	Country (mean ± sd)	Age recruited	Patients infertility	Case of male (T/C)	Intervention (T/C)	Duration of study	Outcomes
C.Rolf (1999)	Germany	36.1±5.0/35.2 ± 4.8	15/16	asthenospermia	800 mg vitamin E+1000 mg vitamin C daily/placebo	56 days	sperm parameters
Hussein Ghanem (2010)	Egypt	31.8±8.1	30/30	Oligoasthenozo-ospermia	400 mg vitamin E+25 mg clomiphene daily/ placebo	6 months	sperm parameters pregnancy rates
Ermanno Greco (2005)	European	unclear	32/32	men consulting for infertility	500 mg vitamin E+500 mg vitamin C twice daily/placebo	2 months	sperm parameters sperm DNA fragmentation
Suleiman SA (1996)	Saudi Arabia	unclear	52/35	Asthenozoospe-rmia	100 mg vitamin E three times a day/placebo	6 months	sperm parameters pregnancy rates
Ghazaleh Eslamian (2020)	Iran	32.80±4.13/33.04±4.08	45/45	idiopathic asthenozoosper-mia	600IU vitamin E+ placebo/ placebo+ placebo	12 weeks	sperm parameters
K. Ener (2016)	Turkey	25.8±4.6	22/23	varicocele	vitamin E capsules (300 mg×2)daily/nothing	12months	sperm parameters pregnancy rates
Rezvan Bahmyari (2021)	Iran	37.23±7.09/36.65±6.41	30/32	Oligo, astheno, teratozoospermia or oligoasthenozo-ospermia	vitamin E capsule (400 IU/day) + selenium tablet (200 µg/day) + folic acid tablet (5 mg/day)	3 months	sperm parameters
L. KESKES-AMMAR (2003)	Tunisie	unclear	12/8	unclear	400 mg vitamin E daily (Ephynal 100 mg, 2 tablets, twice daily) or 225 mg selenium (Bioselenium 35 mg, 2 capsules×3/day)/vitamin B	3months	sperm parameters

Abbreviations: IU,international unit; T/C, treatment group/control group; RCT, randomized controlled trial.

tistically significant (95% CI: -0.21-0.29, SMD = 0.04, p = 0.769).

3 Total sperm count

Five studies(10,14,15,17,19) reported the association between male infertility treated with vitamin E and total sperm count in 246 patients, as shown in Figure 4. After testing, there was no significant heterogeneity among the studies (I^2 = 39.0%, p = 0.132), and the fixed-effects model was used to combine the effect size. The results

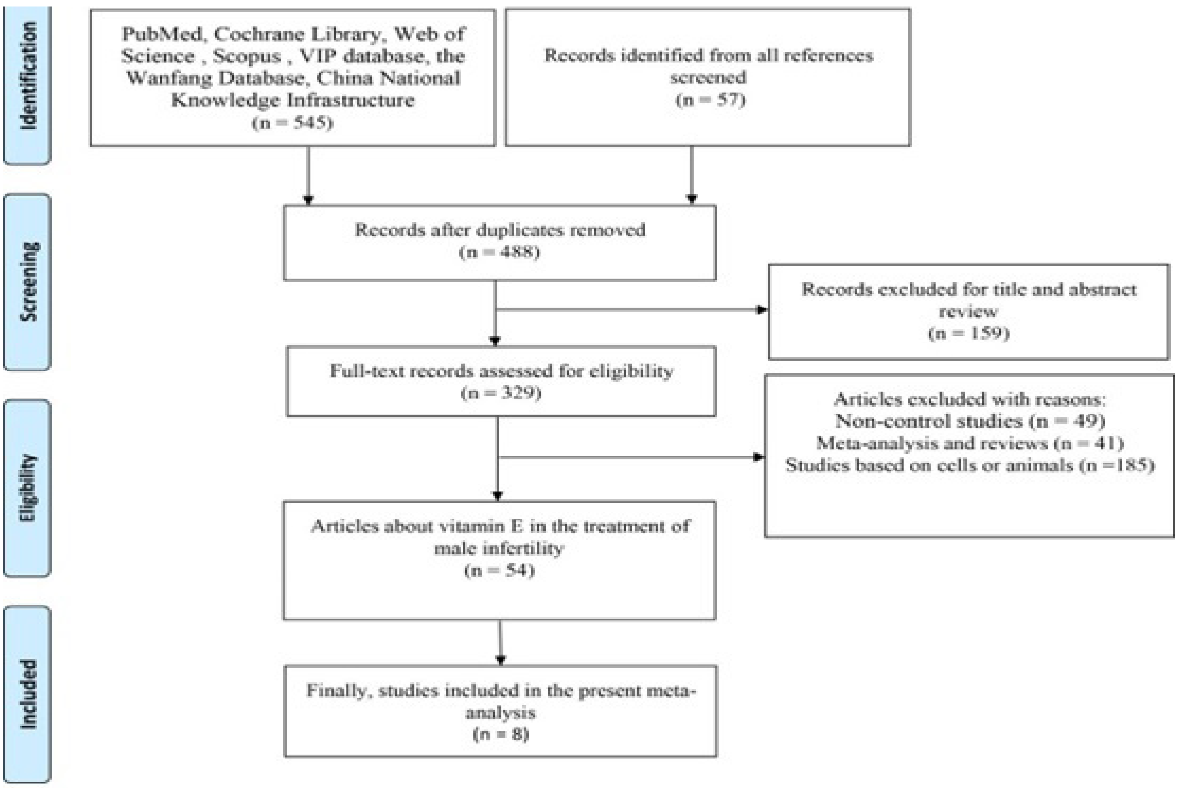

Figure 1. Flow chart of included studies

Table 3. Results of methodological quality evaluations of included studies (score).

Author (year)	Design	Random sequence generation	Concealment of randomization	Blinding	Sign out	Score
Ghazaleh Eslamian (2020)	RCTa	2	2	2	0	6
K. Ener (2016)	RCT	1	1	0	0	2
Rezvan Bahmyari (2021)	RCT	2	0	2	0	4
C.Rolf (1999)	RCT	2	2	2	1	7
Hussein Ghanem (2010)	RCT	1	2	2	0	5
Ermanno Greco (2015)	RCT	1	2	2	0	5
Suleiman SA (1996)	RCT	0	0	1	0	1
L. KESKES-AMMAR (2003)	RCT	2	1	0	0	3

Abbreviations: RCT:,randomized controlled trial.

showed that the total sperm count was significantly improved in the treatment group compared with the control group (95% CI: 0.02-0.45, SMD = 0.23, $p = 0.035$), as shown in **Figure 4**. Sensitivity analysis showed that the results of the meta-analysis were relatively robust, and no obvious publication bias was detected (Egger test: $p = 0.553$), as shown in **Figure S2**. Funnel plot found no significant publication bias in **Figure S6**.

4 Total sperm motility

Four studies with a total of 257 patients[14-17] reported the association between male infertility and total sperm motility with vitamin E treatment, as shown in Figure 5. After testing, there was no significant heterogeneity among the studies (I^2=49.9%, $p = 0.076$), and a fixed-effects model was used to combine the effect sizes. We identified a trend toward better total activity of sperm in treatment group than in control group.

5 Forward motility

Six studies[11,14,16-19] reported the association between male infertility treated with vitamin E and sperm forward motility rate in a total of 383 patients. After testing the heterogeneity between the studies (I^2 = 64.8%, $p = 0.014$), the random-effects model was used to combine the effect size. There was no statistically significant difference between the treatment group and the control group in terms of the sperm forward motility rate (95% CI: -0.06-0.65, SMD=0.29, $p = 0.106$), as shown in Figure 6. Subgroup analysis was performed according to the duration of vitamin E administration in the treatment group, as shown in Figure S3. The results showed that there was no statistical significance in terms of treatment duration of three months (95% CI: -0.31-0.29), SMD = -0.01, $p = 0.925$). The treatment duration was statistically significant at six months (95% CI: 0.46-1.14, SMD = 0.80, p = <0.001).

Sensitivity analysis and publication bias

Compared with the results after excluding one by one and rerunning the meta-analysis, the statistical results did not change significantly, as shown in Figure S4 and S5. These results confirmed that the results of the meta-analysis of vitamin E treatment for male infertility were reliable, as shown in **Figure S4** and Figure S5. Results of sensitivity analyses and publication bias Begg's test and Egger's test illustrated that no evidence of bias existed in this meta-analysis and the outcomes proved to be firm.

DISCUSSION

The aim of this meta-analysis was to assess whether oral vitamin E is effective in improving male infertility. Our meta-analysis found that oral vitamin E treatment could

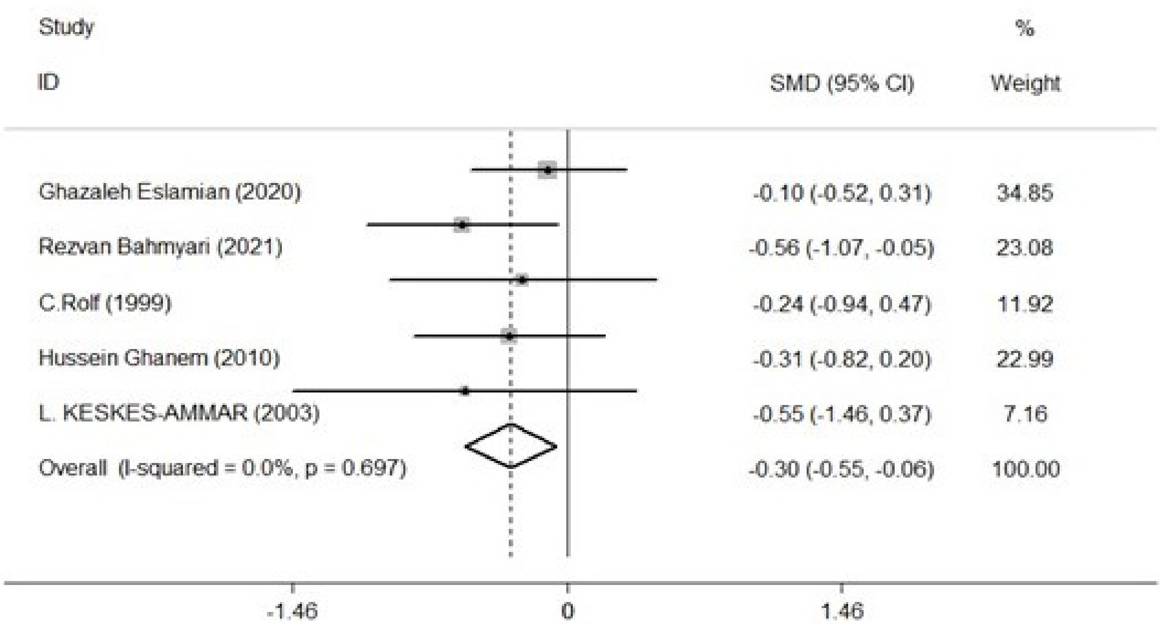

Figure 2. Forest plot of Meta-analysis of semen volume.

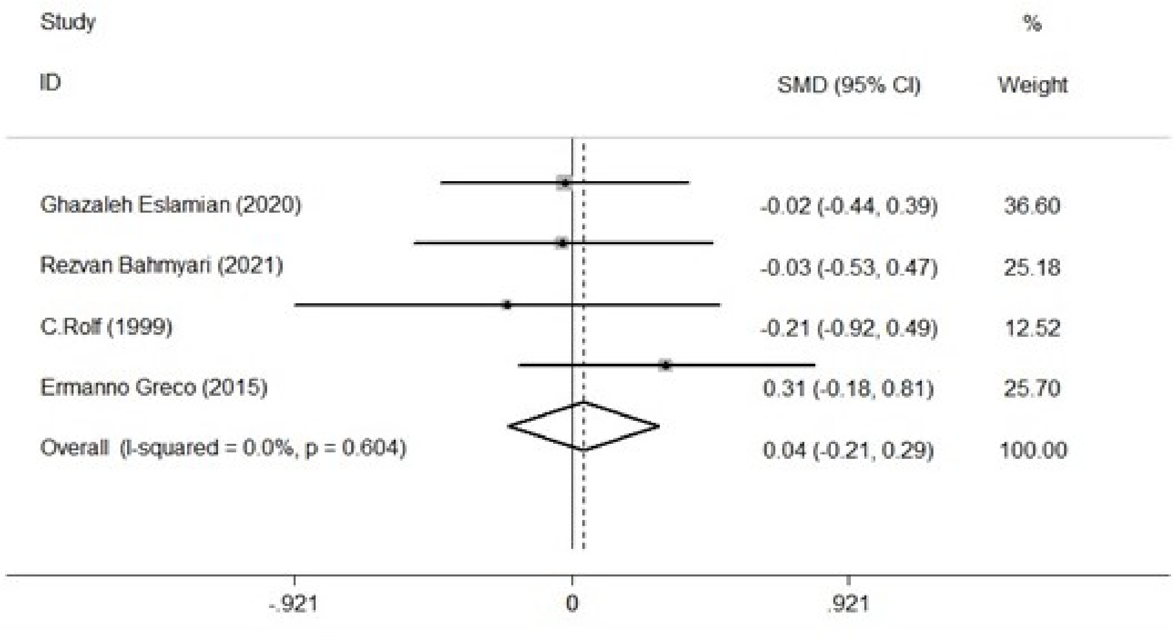

Figure 3. Forest plot of Meta-analysis of sperm concentration

significantly increase the total sperm count and reduce the volume of semen. It was further found that oral vitamin E treatment for up to 6 months could improve the forward motility of sperm but not for 3 months.

Eslamian et al. explored the separate effects of docosahexaenoic acid and vitamin E and showed that the effect of vitamin E alone on sperm concentration, total motility, and forward motility was significant, and the association was stronger than that of docosahexaenoic acid alone.[14]The study by Suleiman et al. reported that a 6-month vitamin E treatment can improve sperm motility.[18] A randomized double-blind controlled trial showed that oral administration of vitamin E could increase the levels of vitamin E in seminal plasma, and the levels of vitamin E in seminal plasma in the treatment group were significantly different from those in the control group.[20] Treatment with vitamin E was based on the fact that it could increase body vitamin E levels and decrease sperm ROS levels, thus protecting the function of sperm.

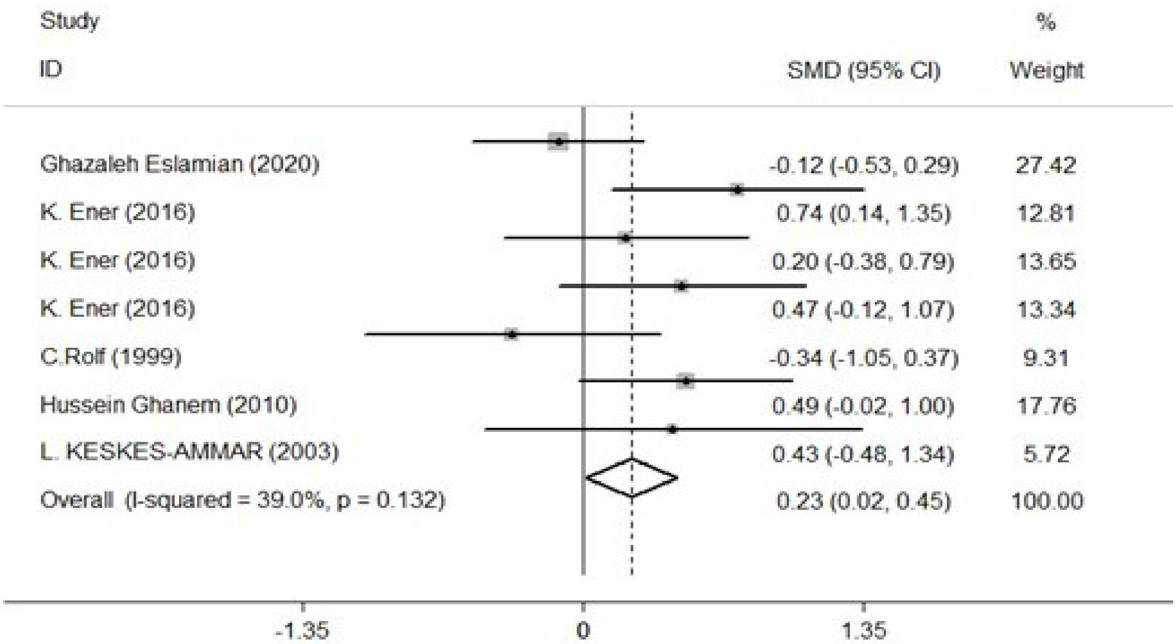

Figure 4. Forest plot of Meta-analysis of total sperm count

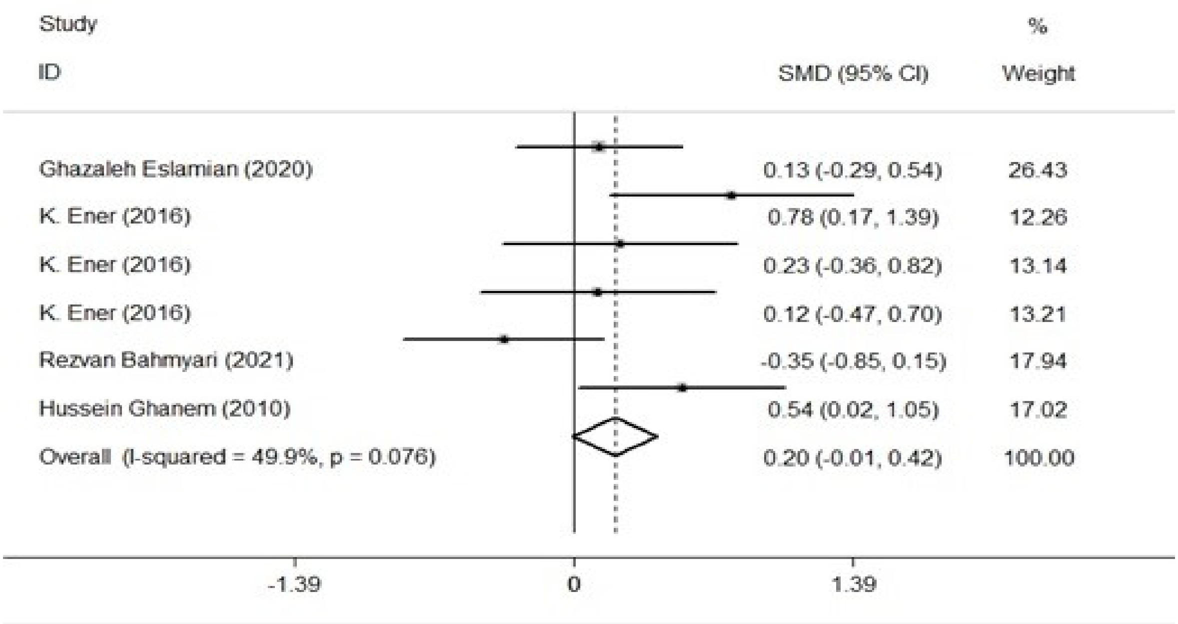

Figure 5. Forest plot of Meta-analysis of total sperm motility.

Furthermore, it was found in many preclinical studies that vitamin E supplementation could indeed improve semen quality. As an antioxidant, vitamin E has a special affinity for membrane phospholipids, and it can prevent lipid peroxidation and protect the integrity of the sperm membrane. The in vivo study showed that vitamin E can increase the total sperm count and sperm concentration of boars; the in vitro study was carried out with a nonenzymatic method for lipid peroxidation of boar seminal plasma using a vitamin E analog that could inhibit seminal plasma lipid peroxidation to control levels.[21] Another animal trial showed that oral administration of vitamin E improved sperm concentration, total sperm count, and percentage of normal sperm in infertile sires, and the plasma levels of vitamin E were also significantly increased.[22] Another animal experiment showed that vitamin E and vitamin C treatments can significantly improve the sperm quality of rabbits. After treatment with vitamins, rabbits significantly reduced the number of abnormally dead sperm, especially in the vitamin E supplement group.[23] The results also indicated that vitamin E was more effec-

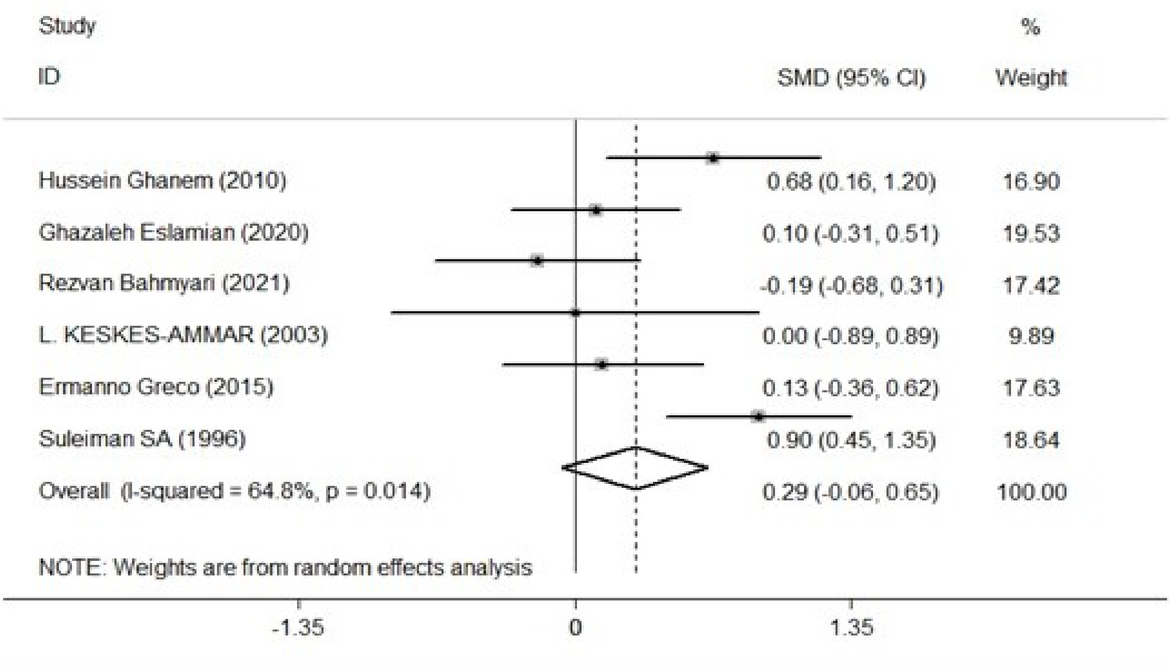

Figure 6. Forest plot of Meta-analysis of sperm forward motility

tive than vitamin C in inhibiting lipid peroxidation, and the results of Massaeli et al. supported this conclusion.[24] In contrast, Rolf et al.'s study found that no changes in any of the conventional ejaculatory parameters were observed during short- or long-term vitamin treatment when compared with the parameters before treatment and with the placebo group.[10] Several trials reported similar results to those of Rolf et al .[20,25,26] The duration of treatment in the study by Rolf et al. was 8 weeks, which is relatively short, perhaps explaining why it is in contrast to the results of Suleiman et al. The same finding was reported by Ermanno Greco et al. After 2 months of treatment, there was no significant change in concentration, vitality and morphology in either the treatment group or the placebo group[11]. However, the percentage of sperm with DNA fragmentation was significantly lower in patients treated for 2 months than in those treated with placebo. Only one of the studies we included reported that after vitamin E treatment, the proportion of sperm DNA fragments was significantly lower than that of the control group. Due to the lack of research data, no meta-analysis of sperm DNA fragments was performed.

Vitamin E can inhibit the formation of free radicals and prevent their induced membrane lipid peroxidation, thereby maintaining the integrity of the sperm acrosomal membrane and reducing the rate of sperm malformation. High levels of reactive oxygen species reduced the activity of acrosin[27] and impaired the binding of sperm and oocytes.[28] A prospective study showed that men with high levels of reactive oxygen species production had a sevenfold lower chance of conception than men with low levels of production.[7] Trials have shown that fertility is significantly improved by antioxidant treatment.[29] Vitamin E had a positive effect on testicular and sperm fertility, and the prescription of a supplement containing vitamin E could improve sperm function in vivo and in vitro by reducing oxidative stress damage.[23] The issue of pregnancy rate was addressed in two of our included articles. Suleiman et al. mentioned in a placebo-controlled double-blind study that vitamin E produced good effects in reducing the concentration of malondialdehyde and improving sperm motility; eleven of the 52 spouses in the treatment group became pregnant during the 6-month treatment period, and none became pregnant in the placebo group.[18] However, reasons for withdrawal or loss to follow-up were not described in this study, causing some degree of bias. Hussein Ghanem et al. showed four pregnancies in the placebo group and 11 pregnancies in the treatment group, with a significant increase in the cumulative number of pregnancies after treatment.[17] Kessopoulou et al. designed a double-blind randomized controlled crossover trial to treat male infertility caused by ROS using antioxidant vitamin E. The findings were not significant for semen parameters, but there was an improvement in sperm performance in the zona binding assay. Thirty patients completed the 2-year trial. As a result, 108 of the 120 semen samples recovered vitality, and there were 3 successful pregnancies.[25] It was concluded that oral administration of vitamin E had beneficial effects on sperm fecundity and improved IVF rates.[25,30] Because the study by Kessopoulou et al. was not an RCT trial, this article was not included in our review. Therefore, only two studies in the included literature mentioned pregnancy rates, with fewer data, so we did not perform a meta-analysis of pregnancy rates. We also included a study of vitamin E supplementation after varicocele surgery. The reason is that varicocele cause reflux of blood and other impaired microcirculation, and an increase in ROS levels will reduce the quality of semen and sperm function.[31] K. Ener et al. reported that vitamin E supplementation after varicocele surgery resulted in an improvement in sperm concentration and motility in both groups after varicocele resection compared to preoperative parameters, and the factor contributing to this improvement was merely varicocele surgery.[15] The findings from the data obtained above were controversial. This may be explained by the fact that antioxidant treatment may have been ineffective in some studies in which infertility was not a result of oxidative stress. The effects of vitamin E treatment depended strictly on its dosage. In the studies we included, the doses of vitamin E were different, but they were less than 1000 mg/d. The Food and Nutrition Committee of the Institute of Medicine has determined that the tolerable upper intake of vitamin E for adults is 1000 mg.[32] Common side effects of vitamin E supplementation include nausea, headache, visual changes, gastrointestinal discomfort, risk of hemorrhagic stroke, slightly elevated urinary creatinine, and necrotizing enterocolitis. There is a potential risk of increased bleeding during surgery because vitamin E is known to inhibit platelet aggregation and may increase the risk of anterior adenocarcinoma.[33,34]The dose of vitamin E used in several studies we included is within the safe range, which can show that our results are reliable. However, further research is needed to determine the optimal dose of oral vitamin E for infertile men. The treatment duration of these studies was 2 to 6 months. The data of our study showed that semen volume decreased after oral vitamin E treatment. This may be attributed to the difference in the number of days of abstinence before and after treatment and between groups. Long periods of abstinence can lead to increased semen volume. Similarly, prolonged abstinence resulted in a higher total sperm count, so we need more trials to confirm the above results.

The advantages of our meta-analysis included: 1) five of the included studies used the double-blind method, the results were robust, and 2) the subgroup analysis found more accurate and meaningful results. Despite these advantages, we acknowledged that this meta-analysis also had several limitations. We included only 8 articles, half of which were low-quality articles, and the number of patients was small. Due to the paucity of the included literature, there are certain limitations to the evaluation of publication bias. In several studies we included, vitamin E was combined with other drugs, which may confuse the results. The combined use of some antioxidants and vitamin E may increase or mask its own effects. The combination of drugs and vitamin E is used to treat semen quality. Drugs will interfere with the results of vitamin E treatment. It is impossible to determine whether the improvement of semen quality comes from the effect of vitamin E. Therefore, our conclusion needs to be verified by larger RCTs with strict designs and long-term follow-up to further evaluate the effectiveness of oral vitamin E treatment for male infertility.

CONCLUSIONS

Vitamin E could increase the total sperm count and reduce the volume of semen in male infertility patients. The decrease of semen volume may be the result of different abstinence time before and after the test. And long-term treatment could improve the forward motility rate of sperm.

SUMMARY

This article show that oral vitamin E can increase the total number of sperm in male infertility patients, reduce semen volume, and long-term treatment can improve the positive motility of sperm. In other word long-term oral vitamin E and dosage within a safe range can improve men's semen quality.

ACKNOWLEDGEMENT

This study was financially supported by National Natural Science Funds of China (No. 82171594) and Zhao Yi-Cheng Medical Science Foundation (No. ZYY-FY2018031).

CONFLICTS OF INTEREST

All authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in, or financial conflict with, the subject matter or materials discussed in the manuscript.

APPENDIX

https://journals.sbmu.ac.ir/urolj/index.php/uj/libraryFiles/downloadPublic/40

REFERENCES

1. Stahl P J, Schlegel P N.Genetic evaluation of the azoospermic or severely oligozoospermic male. Curr Opin Obstet Gynecolurnal.2012;24:221.
2. Marques-Pinto A, Carvalho D.Human infertility: are endocrine disruptors to blame? Endocr Connecturnal.2013;2:R15.
3. Zegers-Hochschild F, Adamson G D, de Mouzon J ,et al.International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology, 2009. Fertil Sterilurnal.2009;92:1520.
4. Sharlip I D, Jarow J P, Belker A M ,et al.Best practice policies for male infertility. Fertil Sterilurnal.2002;77:873.
5. Punab M, Poolamets O, Paju P ,et al.Causes of male infertility: a 9-year prospective monocentre study on 1737 patients with reduced total sperm counts. Hum Reprodurnal.2017;32:18.
6. Wong W Y, Thomas C M, Merkus J M, Zielhuis G A, Steegers-Theunissen R P.Male factor subfertility: possible causes and the impact of nutritional factors. Fertil Sterilurnal.2000;73:435.
7. Aitken R J, Irvine D S, Wu F C.Prospective analysis of sperm-oocyte fusion and reactive oxygen species generation as criteria for the diagnosis of infertility. Am J Obstet Gynecolurnal.1991;164:542.
8. Sukcharoen N, Keith J, Irvine D S, Aitken R J.Predicting the fertilizing potential of human sperm suspensions in vitro: importance of sperm morphology and leukocyte contamination. Fertil Sterilurnal.1995;63:1293.
9. Rengaraj D, Hong Y H.Effects of dietary vitamin E on fertility functions in poultry species. Int J Mol Sciurnal.2015;16:9910.
10. Rolf C, Cooper T G, Yeung C H, Nieschlag E.Antioxidant treatment of patients with asthenozoospermia or moderate oligoasthenozoospermia with high-dose vitamin C and vitamin E: a randomized, placebo-controlled, double-blind study. Hum Reprodurnal.1999;14:1028.
11. Greco E, Iacobelli M, Rienzi L ,et al.Reduction of the incidence of sperm DNA fragmentation by oral antioxidant treatment. J Androlurnal.2005;26:349.
12. Jadad A R, Moore R A, Carroll D ,et al.Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trialsurnal.1996;17:1.
13. Taouk Y, Spittal M J, LaMontagne A D, Milner A J.Psychosocial work stressors and risk of all-cause and coronary heart disease mortality: A systematic review and meta-analysis. Scand J Work Environ Healthurnal.2020;46:19.
14. Eslamian G, Amirjannati N, Noori N, Sadeghi M R, Hekmatdoost A.Effects of coadministration of DHA and vitamin E on spermatogram, seminal oxidative stress, and sperm phospholipids in asthenozoospermic men: a randomized controlled trial. Am J Clin Nutrurnal.2020;112:707.
15. 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. Andrologiaurnal.2016;48:829.
16. Bahmyari R, Ariafar A, Sayadi M, Hossieni S, Azima S.The Effect of Daily Intake of Selenium, Vitamin E and Folic Acid on Sperm Parameters in Males with Idiopathic Infertility: A Single-Blind Randomized Controlled Clinical Trial. Int J Fertil Sterilurnal.2021;15:8.
17. Ghanem H, Shaeer O, El-Segini A.Combination clomiphene citrate and antioxidant therapy for idiopathic male infertility: a randomized controlled trial. Fertil Sterilurnal.2010;93:2232.
18. Suleiman S A, Ali M E, Zaki Z M, el-Malik E M, Nasr M A.Lipid peroxidation and human sperm motility: protective role of vitamin E. J Androlurnal.1996;17:530.
19. Keskes-Ammar L, Feki-Chakroun N, Rebai T ,et al.Sperm oxidative stress and the effect of an oral vitamin E and selenium supplement on semen quality in infertile men. Arch Androlurnal.2003;49:83.
20. Moilanen J, Hovatta O, Lindroth L.Vitamin E levels in seminal plasma can be elevated by oral administration of vitamin E in infertile men. Int J Androlurnal.1993;16:165.
21. Brezezińska-Slebodzińska E, Slebodziński A B, Pietras B, Wieczorek G.Antioxidant effect of vitamin E and glutathione on lipid

peroxidation in boar semen plasma. Biol Trace Elem Resurnal.1995;47:69.
22. Domosławska A, Zdunczyk S, Franczyk M, Kankofer M, Janowski T.Selenium and vitamin E supplementation enhances the antioxidant status of spermatozoa and improves semen quality in male dogs with lowered fertility. Andrologiaurnal.2018;50:e13023.
23. Yousef M I, Abdallah G A, Kamel K I.Effect of ascorbic acid and Vitamin E supplementation on semen quality and biochemical parameters of male rabbits. Anim Reprod Sciurnal.2003;76:99.
24. Massaeli H, Sobrattee S, Pierce G N.The importance of lipid solubility in antioxidants and free radical generating systems for determining lipoprotein proxidation. Free Radic Biol Medurnal.1999;26:1524.
25. Kessopoulou E, Powers H J, Sharma K K ,et al.A double-blind randomized placebo cross-over controlled trial using the antioxidant vitamin E to treat reactive oxygen species associated male infertility. Fertil Sterilurnal.1995;64:825.
26. Giovenco P, Amodei M, Barbieri C ,et al.Effects of kallikrein on the male reproductive system and its use in the treatment of idiopathic oligozoospermia with impaired motility. Andrologiaurnal.1987;19 Spec No:238.
27. Zalata A A, Ahmed A H, Allamaneni S S, Comhaire F H, Agarwal A.Relationship between acrosin activity of human spermatozoa and oxidative stress. Asian J Androlurnal.2004;6:313.
28. Jedrzejczak P, Fraczek M, Szumała-Kakol A ,et al.Consequences of semen inflammation and lipid peroxidation on fertilization capacity of spermatozoa in in vitro conditions. Int J Androlurnal.2005;28:275.
29. Tremellen K.Oxidative stress and male infertility--a clinical perspective. Hum Reprod Updateurnal.2008;14:243.
30. Geva E, Bartoov B, Zabludovsky N ,et al.The effect of antioxidant treatment on human spermatozoa and fertilization rate in an in vitro fertilization program. Fertil Sterilurnal.1996;66:430.
31. Zini A, Dohle G.Are varicoceles associated with increased deoxyribonucleic acid fragmentation? Fertil Sterilurnal.2011;96:1283.
32. Hathcock J N, Azzi A, Blumberg J ,et al.Vitamins E and C are safe across a broad range of intakes. Am J Clin Nutrurnal.2005;81:736.
33. Brigelius-Flohé R, Kelly F J, Salonen J T ,et al.The European perspective on vitamin E: current knowledge and future research. Am J Clin Nutrurnal.2002;76:703.
34. Chan J M, Darke A K, Penney K L ,et al.Selenium- or Vitamin E-Related Gene Variants, Interaction with Supplementation, and Risk of High-Grade Prostate Cancer in SELECT. Cancer Epidemiol Biomarkers Prevurnal.2016;25:1050.