

The effect of oral vitamin E supplementation on infertile women: a systematic review and meta-analysis

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This study was aimed to investigate the effect of vitamin E (Vit E) supplementation on endometrial thickness and pregnancy outcomes in infertile women. The literature was screened by two researchers and the data was extracted by searching published literature from 1999 to 2020 in the Cochrane library, PubMed, and Embase database. Seven clinical trials were included, with a total of 652 subjects. Here we found the mean endometrium was thicker in Vit E treatment group than that in the control group [SMD = 0.57, 95% CI (0.26, 0.87), $P = 0.0002$]. Subgroup analysis showed that no significant effect between administration of 400 IU (267 mg) or 100 mg Vit E per day. There was no significant difference between with or without Vit E on ongoing pregnancy rate [OR = 1.08, 95% CI (0.72, 1.62), $P = 0.70$]. The current evidence demonstrates that Vit E supplementation may increase endometrial thickness in women of reproductive age.

Keywords

Vitamin E supplementation; Endometrial thickness; Ongoing pregnancy; Systematic review

1. Introduction

Successful embryo implantation requires two conditions: a well-developed embryo and a well-tolerated endometrium. Although assisted reproductive technology (ART) has been widely used in infertile couples, the failure of implantation resulted from poor endometrial receptivity is still an important factor which could not be underestimated [1]. There are different parameters to evaluate the endometrial receptivity such as endometrial morphology and endometrial blood supply, while endometrial thickness is most commonly used as compared to the other indexes. At present, there are various strategies to enhance endometrial thickness, such as surgical therapy (endometrial biopsy and curettage) [2], prolonged hormone therapy [3], intrauterine perfusion [4], vasoactive medicine therapy (low-dose aspirin and Sildenafil) [5, 6], and regenerative medicine (stem cell therapy) [7].

The above methods of improving endometrial receptivity are more or less invasive, difficult to perform, or expensive. In recent years, some investigators have proposed a simple, safe and economical strategy, namely taking a certain dose of Vit E in women of reproductive age to increase the thick-

ness of endometrium [8–11]. Vit E is an exogenous lipid-soluble molecule, acts as a peroxy radical scavenger *in vivo* and is metabolized through the liver and kidney. Vit E is not only a kind of exogenous lipid soluble antioxidant molecule but also a direct scavenger of free radicals. According to research reports, Vit E may improve endometrial thickness by anti-oxidation and increase endometrial secretion activity [11]. As showed by some studies, Vit E can increase capillary blood flow in a wide variety of organs, thereby generating favorable endometrium [12]. On the contrary, Levent *et al.* pointed out that the methods such as taking vitamin E to increase endometrial thickness are inefficient or even useless [13]. Until now, whether vitamin E Supplementation can help increase endometrial thickness and even improve pregnancy outcomes remains controversial.

Infertility is mostly a result of complex interplay of various factors, such as uterine, fallopian tubes, ovarian and male. Increasing endometrial thickness itself will not enable an infertile woman to get pregnant, but still has a positive effect on pregnancy outcomes. Therefore, the objective of this systematic review was to investigate whether Vit E is beneficial to endometrial thickness and pregnancy outcomes, we reviewed the previous publications and analyzed the effects of Vit E on endometrial thickness and pregnancy outcomes.

2. Methods

2.1 Search strategy and study selection

The Cochrane library, PubMed, and Embase data bank were searched by computer to collect clinical research on the effect of Vit E supplementation on endometrium and pregnancy outcomes in women from 1999 to 2020. The search was conducted on November 15, 2019 and updated on April 16, 2020, two authors independently screened citations. Meanwhile, this study carefully reviewed the reference list of known related articles to ensure that there are no potential publications missing from the electronic search. The following key words were searched: “IVF”/“infertile woman” and “Vit E”/“tocopherol”/“endometrial thickness”/“pregnancy outcome”.

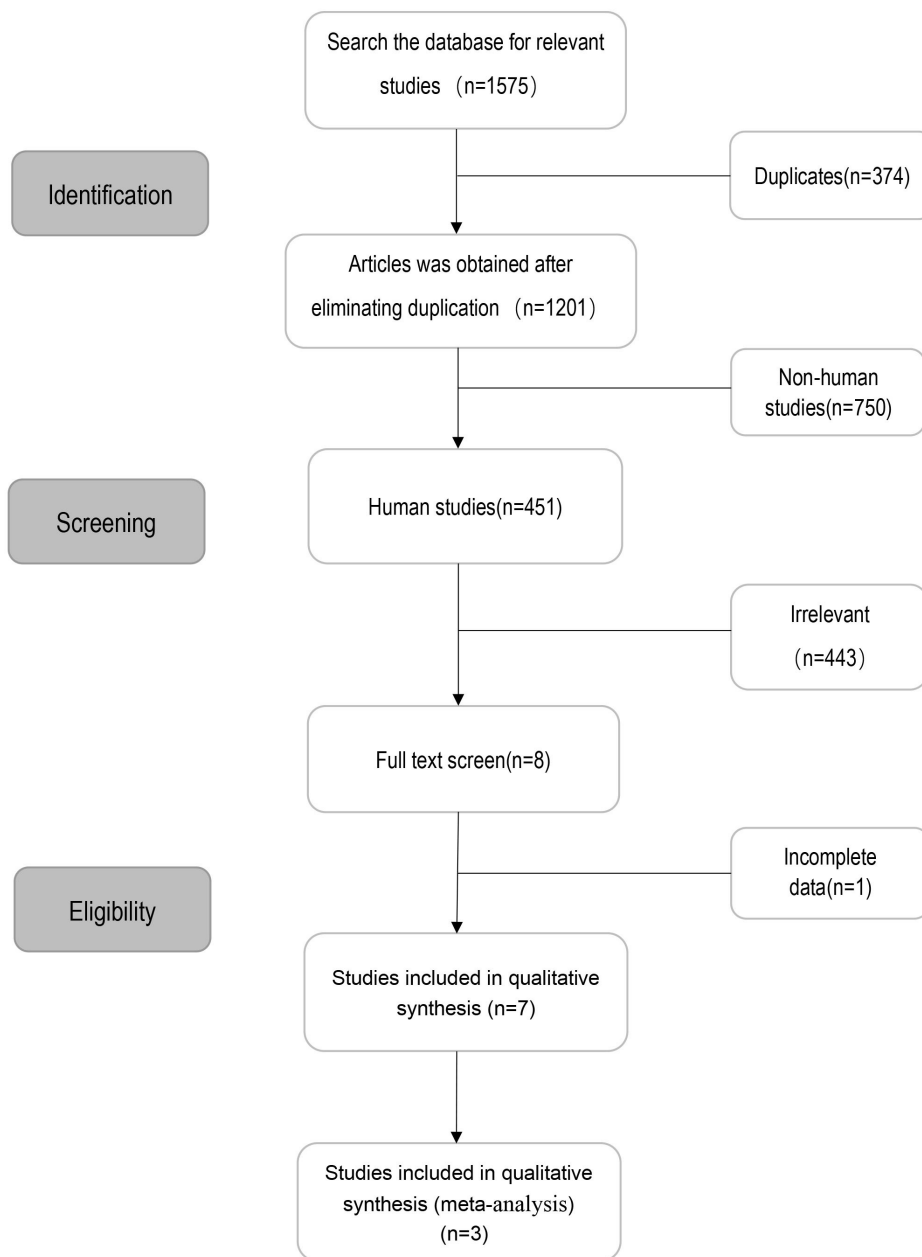


Fig. 1. Flow chart.

2.2 Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) the original study, (2) the full text of the study, (3) publication of the study report in English, (3) intervention group taking Vit E, (4) the change of endometrial thickness before and after intervention, (5) pregnancy outcome was reported. Exclusion criteria: (1) incomplete data; (2) inconsistent with inclusion criteria.

2.3 Literature screening and data extraction

Two researchers independently screened the literature, extracted the data and made cross-checking. When the opinions were inconsistent, the solution was discussed or negotiated with a third party. Besides, the researchers read the topic

first and then screened the abstract and the full text to determine whether the article was included. Lead author, year of publication, country, sample size, age, study type, BMI, endometrial thickness, ongoing pregnancy, dose and type of supplement, duration were included in the data extraction.

2.4 Statistical analysis

Revman 5.3 software was used for statistical analysis. The mean difference (MD) was adopted as the effect analysis statistics and the 95% confidence interval (CI) was used as the standard mean difference (SMD) to evaluate the effect of Vit E on the endometrial thickness in women. Dichotomous data were expressed as odds ratio (OR). Moreover, the het-

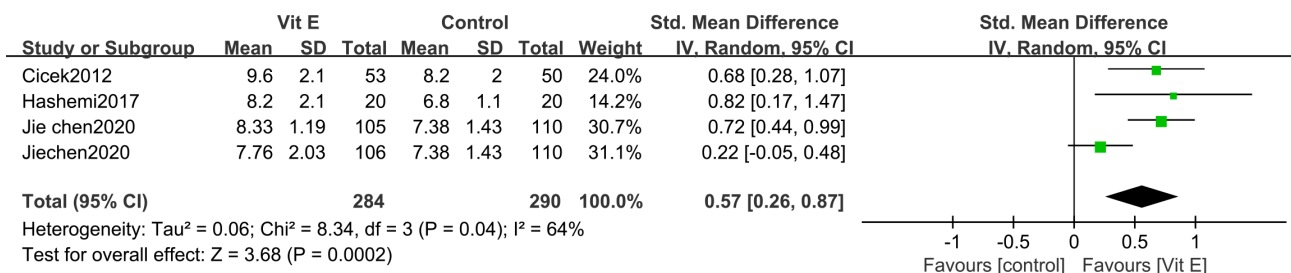


Fig. 2. Vitamin E Supplementation for endometrial thickness.

erogeneity was analyzed by χ^2 test ($\alpha = 0.1$) and the size of heterogeneity was determined by I quantitative analysis. If there was no statistical heterogeneity among the results, the fixed effect model was used for meta-analysis. If there was statistical heterogeneity among the results, the source of heterogeneity would be further analyzed. After the obvious clinical heterogeneity was excluded ($I^2 > 50\%$), the random effect model was used for meta-analysis. Apart from that, the test level of meta-analysis was $\alpha = 0.05$. Subgroup analysis was performed based on possible clinical heterogeneity, including different doses of Vit E.

3. Results

3.1 Search results

The document retrieval and inclusion process are shown in Fig. 1. A total of 1575 related articles were retrieved from the Cochrane library, PubMed and Embase databases, 1124 of which were screened and repeated without full text and animal experiments. After irrelevant literature was excluded according to the inclusion criteria, eight relevant papers were retained, of which one was not complete data and the remaining seven were included in qualitative synthesis [8–11, 14–16] and three were included in quantitative synthesis (meta-analysis) [8, 10, 15] (Fig. 1).

3.2 Characteristic of included studies

Our analysis included seven trials, one of which could be split into four groups, to explore the effects of Vit E supplements on endometrial thickness and pregnancy outcomes. The methods included case report (self-control), randomized control and retrospective cohort study. The population were composed of patients with thin endometrium, infertility, failure of embryo implantation and infertile women with polycystic ovary syndrome (PCOS). The administration dose was mainly 100 mg, 400 IU (267 mg) or 1000 IU daily. The duration of intervention during the trial ranged from weeks to months. The basic features of inclusion in the study are presented in Table 1.

3.3 Endometrial thickness

A total of three clinical studies were included [8, 10, 15], one of which could be divided into four comparison groups with a total of 574 subjects. Two randomized controlled studies (RCTs) and a retrospective cohort study were included. The results of random-effect model meta-analysis showed

that the endometrium was thicker in Vit E supplementation group than that in the control group. [SMD = 0.57, 95% CI (0.26, 0.87), $P = 0.0002$] (Fig. 2). Besides, three case reports and a prospective observational study showed that oral Vit E supplementation may increase endometrial thickness [3, 9, 11, 17] (Table 1).

Subgroup analysis revealed: There was no significant effect between the administration of 400 IU (267 mg) or 100 mg per day of vitamin E on endometrial thickness (Fig. 3).

3.4 Pregnancy outcomes

Due to fewer related studies, two clinical studies were included ultimately [8, 15], one of which could be divide into four comparison groups. A total of 534 subjects were included. The results of random-effect model meta-analysis indicated that there was no significant difference between the two groups on ongoing pregnancy rate [OR = 1.08, 95% CI (0.72, 1.62), $P = 0.70$] (Fig. 4).

3.5 Publication bias analysis

Publication bias estimation was shown in Fig. 5. Due to the asymmetry of the funnel plot, there may be publication bias in our study.

4. Discussion

This analysis mainly reports the effects of Vit E on the endometrium. As shown by the current meta-analysis, oral Vit E supplementation contributes to endometrial growth in women of reproductive age, especially for patients with thin endometrium. There was no significant difference between Vit E group and control group on ongoing pregnancy rate.

The successful implantation of an embryo requires the simultaneous development of the endometrium and the embryo [18]. Histologically, the endometrium consists of two layers of tissue: the basal layer and the functional layer [19]. Endometrial growth is a hormone-dependent process that requires proper blood supply to the uterus [20]. The high impedance of uterine arterial blood flow may promote the growth of epithelial cells, lead to a decrease in the expression of vascular endothelial growth factor (VEGF) in the endometrial vessels, and inhibit the formation of endometrial vessels, thus reducing the blood supply of the endometrium, which is not conducive to the formation of satisfactory endometrium for embryo implantation [21, 22].

Table 1. Characteristics of including.

Author (year)	Location	Study design	Object	Vitamin E group						Placebo group number			Intervention (type and dosage)		Duration
				Age (year)	BMI	Number	Endometrial thickness Mean \pm SD (mm)	Ongoing pregnancy	Age (year)	BMI	Number	Endometrial thickness Mean \pm SD (mm)	Ongoing pregnancy		
Cicek [8] 2012	Turkey	RCT	Unexplained infertile women	25.3 \pm 4.8	23.8 \pm 2.7	53	9.6 \pm 2.1	10	26.4 \pm 5.3	22.7 \pm 2.9	50	8.2 \pm 2.0	7	400 IU Vit E/day	From the 3rd to the 5th day of the menstrual cycle until the hCG injection day
ACHARYA 2009 [11]	UK	Case report	Women with a thin endometrium	Not provided	Not provided	19	6.05 \pm 1.83	Not provided	Not provided	Not provided	Not provided	Not provided	Not provided	800 mg pentoxifylline (PTX) & 1000 IU Vit E/day	Mean duration of treatment was 8.1 months
Hashemi 2017 [10]	Iran	RCT	Women with implantation failure	32.2 \pm 2.3	25.0 \pm 3.7	20	8.2 \pm 2.1	Not provided	31.5 \pm 2.3	26.0 \pm 2.7	20	6.8 \pm 1.1	Not provided	400 IU Vit E/day	12 weeks
Takasaki 2010 [14]	Japan	Prospective observational study	Women with a thin endometrium	23–44	Not provided	25	8.3	Not provided	23–44	Not provided	10	6.8	Not provided	600 mg Vit E/day	Throughout the menstrual cycle
He le'ne 2002 [16]	France	Case report	Women with a thin endometrium	31.0 \pm 4.0	Not provided	6	6.2 \pm 0.6	Not provided	Not provided	Not provided	Not provided	Not provided	Not provided	800 mg PTX/day, 1000 IU Vit E/day	At least 12 months
Bataille 2002 [9]	France	Case report	Women with a thin endometrium	28–45	Not provided	18	6.2 \pm 1.4	Not provided	Not provided	Not provided	Not provided	Not provided	Not provided	800 mg PTX, 1000 IU Vit E/day	6 months
Jie Chen 2020 [15]	China	Retrospective cohort study	Infertile women	PCOS 26.88 \pm 2.84	23.80 \pm 3.69	105	8.33 \pm 1.19	29	25.87 \pm 2.63	22.91 \pm 4.05	110	7.38 \pm 1.43	27	Vit E 100 mg/day	From the 3rd day of the menstrual cycle to 14th day of luteal phase
Jie Chen 2020 [15]	China (2)	Retrospective cohort study	Infertile women	PCOS 26.81 \pm 2.64	23.57 \pm 3.89	106	7.76 \pm 2.03	24	25.87 \pm 2.63	22.91 \pm 4.05	110	7.38 \pm 1.43	27	Vit E 100 mg/day	Started when ovulation was confirmed, and lasted for 14 consecutive days

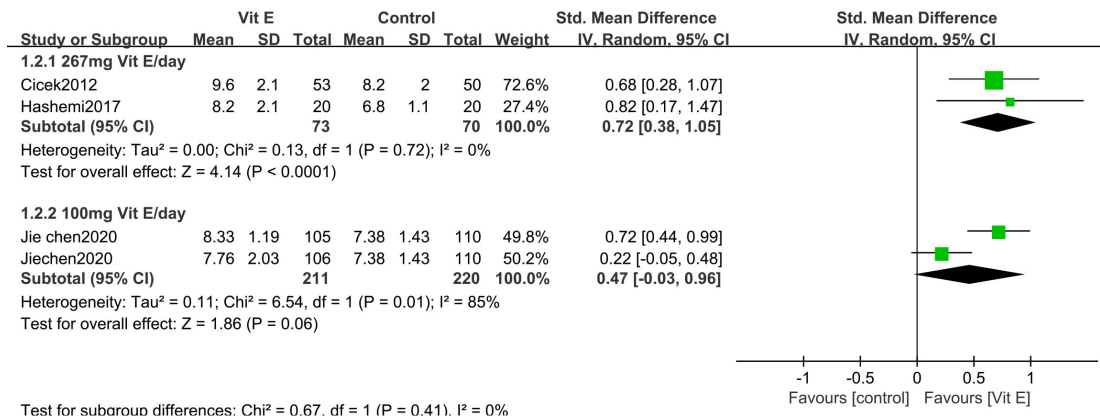


Fig. 3. Subgroup analysis.

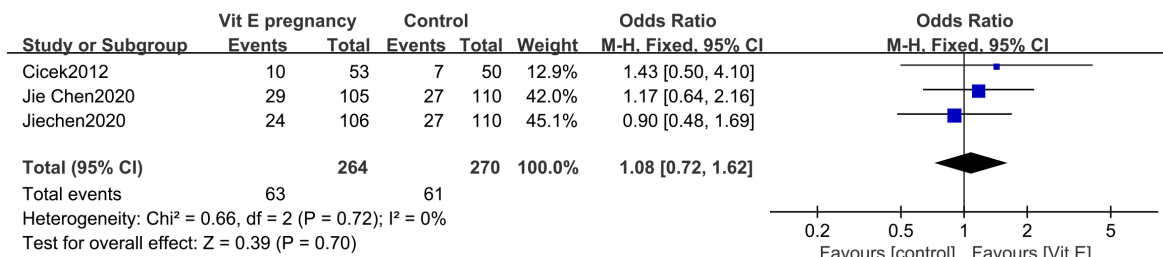


Fig. 4. Oral Vitamin E Supplementation for ongoing pregnancy.

The probable mechanism by which Vit E enhances endometrial thickness could be as following: Firstly, reactive oxygen species (Ros) can cause oxidative damage to cellular macromolecules (such as lipids, proteins and nucleic acids) in tissues [17]. Vit E scavenges Ros produced during oxidative stress and protects cell membrane from lipid peroxidation, thereby reducing the damage of Ros to endometrium at biochemical level [23]. Secondly, Vit E has an anticoagulant effect, which could increase the blood supply of follicles and granulosa cells, promote the production of estrogen, and thus produce favorable endometrium [8]. Thirdly, Vit E may improve vascular resistance, and the increase of endometrial glands, vascular development and VEGF protein expression in endometrium can be observed in patients who take Vit E [24], the increase of uterine blood supply provides sufficient nutrition for endometrial formation [14].

Previous findings toward Vit E have mainly focused on men's semen quality, gestational diabetes and hypertension [25–27], while less attention has been given to the endometrial thickness. Our analysis showed that oral Vit E supplementation increased endometrial thickness in fertile women, especially for those who were suffered from the thin endometrium. Endometrial thickness may be critical to successful pregnancy. Some scholars suggest that the minimum intimal thickness should be 7 mm (preferably more than 9 mm) to achieve the highest pregnancy rate [28]. Although there are various schemes to improve endometrial thickness in patients with infertility due to endometrial causes, which

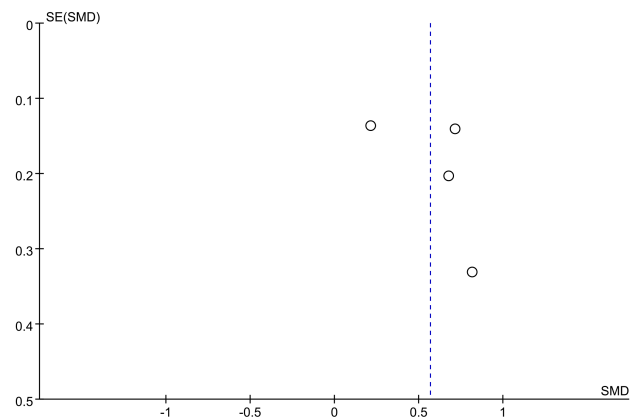


Fig. 5. Funnel plot.

are difficult to implement and have traumatic defects. Oral Vit E supplements provide an economical, convenient, and safe strategy for improving endometrial thickness. However, there was no significant difference between Vit E group and the control group on ongoing pregnancy rate in this analysis. Since less result was found to report the effect of Vit E on the pregnancy rate, live birth rate and miscarriage rate apart from endometrial thickness and ongoing pregnancy rate in these publications, we could not make an explicit conclusion of the effect of Vit E in the other pregnancy outcome. We expect that in the future multicenter randomized prospective study and a larger sample size would be performed in order to

confirm the further outcome of the Vit E in pregnancy rate, live birth rate and miscarriage rate especially in the thin endometrium patients.

To the best of our knowledge, this meta-analysis is the first meta-analysis of the effects of oral Vit E supplementation on endometrial thickness and pregnancy outcome. However, there is still limitation, such as small amount of data, inclusion of only studies published in English journals, the failure to determine the effective duration and the most suitable population of Vit E to increase endometrial thickness. Limited by the quantity and quality of the included studies, these conclusions need to be verified by the further multicenter randomized prospective studies which require larger sample size. Prospective trials or randomized controlled trials could be designed to study the effects of different doses of vit E on endometrial thickness and pregnancy outcomes in infertile women.

5. Conclusions

In summary, current evidence suggests that oral Vit E supplementation may increase endometrial thickness. Further, due to few available studies, there is no clear evidence that oral Vit E supplementation is beneficial for pregnancy outcomes.

Author contributions

JW and DY made major contributions to data analysis, article conception and writing. JL and LC were responsible for data analysis. WQ and WM contributed to data collection and verification. XX contributed to the research and design, critical discussion and review of manuscripts.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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