

Review Article

Correlation of vitamin E level during pregnancy with maternal and neonatal health outcomes: a meta-analysis and systematic review

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Abstract: Objective: To investigate maternal vitamin E (tocopherol) levels during pregnancy and maternal and neonatal health (MNH) outcomes by using meta-analysis and systematic review of literature. Methods: PubMed, Web of Science and Medline database were searched from database establishment to December 2022 to collect studies on the level of vitamin E (tocopherol) and pregnancy outcomes. Seven studies were finally included, after screening based on pre-specified eligibility and exclusion criteria. Included studies must have data on maternal vitamin E levels and maternal and infant pregnancy outcomes. Literature quality assessment was made using the Newcastle-Ottawa-Scale scoring standard, and meta-analysis was performed with the use of RevMan5.3. Results: Seven studies (involving 6247 normal women and 658 adverse pregnancy outcomes women, 6905 total), all with a quality evaluation score ≥ 6 points, were included. The meta-analysis of the 7 studies revealed the presence of statistical heterogeneity in vitamin E data ($P < 0.1$ and $I^2 > 50\%$), so a random-effects analysis was further carried out. Statistically lower serum vitamin E levels were determined in the adverse pregnancy outcome group compared with the normal group [SMD=4.44, 95% CI (2.44,6.43), $P < 0.001$]. Descriptive analysis of the correlation of vitamin E levels with maternal and neonatal general information showed no statistical difference in vitamin E levels among mothers of different ages (< 27 years, ≥ 27 years), $P = 0.214$; however, women with BMI < 18.5 kg/m² showed a higher incidence of vitamin E deficiency than those with BMI ≥ 18.5 kg/m² ($\chi^2 = 15.173$, $P < 0.05$). Maternal vitamin E level with neonatal weight Z-Score > 2 was [1.793 (0.08, 4.514) mg/L], which was significantly lower than that of maternal vitamin E level with neonatal weight Z-Score ≤ 2 [2.223 (0.899,6.958) mg/L], $P = 0.009$. Maternal vitamin E levels with neonatal length Z-Score > 2 [1.746 (0.08, 4.514) mg/L] were significantly lower than those with neonatal length Z-Score ≤ 2 [2.362 (1.380, 6.958) mg/L], $P = 0.006$. Conclusion: Maternal vitamin E level is lower in those with adverse pregnancy outcomes than that in those with non-adverse pregnancy outcomes. Still, given the limited research on the correlation of vitamin E during pregnancy with maternal BMI and neonatal body length and weight, a large-scale and well-designed cohort study is needed for further analysis.

Keywords: Vitamin E, pregnancy outcomes, meta-analysis

Introduction

The health care of pregnant women has received increasing attention from society with the improvement of the social economy and people's living standards as well as the comprehensive promotion of eugenics and prenatal care policies. The nutrient intake during pregnancy is not only important to maintain the body's own metabolism, but also to meet the needs of fetal growth and development, which makes pregnancy more prone to nutrient ab-

normalities [1]. In addition, some pregnant women have unbalanced intake of nutrients due to lack of nutritional knowledge, which in turn leads to abnormalities in some essential vitamins. The content of vitamins during pregnancy is closely related to the course of pregnancy, fetal growth and development, and delivery, and can affect the outcome of mothers and infants [2].

Vitamin E is a fat-soluble vitamin, with tocopherol as its hydrolyzed product, which has vari-

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ous effects such as maintaining fertility, anti-oxidation, anti-aging, and improving immunity [3-5]. The antioxidant effect of vitamin E mainly manifests in resisting the damage of harmful free radicals to phosphate fatty acids and keeping the cell membrane stable. Vitamin E, a fat-soluble vitamin, has a strong association with abnormal lipid metabolism in pregnant women and a certain correlation with oxidative stress, preeclampsia and other adverse pregnancy outcomes (APOs) [6, 7]. Vitamin E deficiency can lead to increased free radicals, enhanced lipid peroxidation, vascular endothelial cell damage, and aging of the placenta in pregnant women, and elevated risk of gestational hypertension, fetal distress, and premature rupture of fetal membranes [8-11]. Excessive vitamin E in pregnant women antagonizes other vitamins, and has anticoagulant activity, which increases the risk of neonatal hyperbilirubinemia [12].

Studies on associations between vitamin E level during pregnancy and maternal and infant outcomes have different conclusions. Some studies indicate that vitamin E in pregnant women is not associated with the high risk of cardiovascular malformations in children [13]. The discrepancies may be due to different sample sizes, populations, etc. Therefore, in this study, we searched the literature related to Vitamin E levels during pregnancy and maternal and infant outcomes, expanded the sample size, and conducted subgroup analysis on various confounding factors to comprehensively and carefully explore the correlation of pregnancy vitamin E level with maternal and infant outcomes, in order to provide guidance for vitamin E supplementation during pregnancy.

Materials and methods

Retrieval strategy

Two researchers independently searched the literature, and searched the relevant literature in databases such as PubMed, Web of Science and Medline. The search method was “primary keyword + secondary keyword”. Primary keyword: “Vitamin E”. Secondary keyword: “ α -tocopherol” and “pregnancy outcomes”, “maternal outcomes”, “neonatal outcomes”, “abortion”, “Caesarean section”, “premature delivery”, “stillbirth”, “neonatal death”, “fetal malformation”, “fetal distress”, “fetal growth restriction”, “neonatal jaundice”, and “low birth

weight infant”. The retrieval time was from database establishment to December 2022.

Literature eligibility and exclusion criteria

Eligibility criteria: (1) All included studies were published studies. (2) The study type was case-control study. (3) The subjects of the study were pregnant women. (4) Observation indicators included serum vitamin E level of pregnant women and maternal and neonatal pregnancy outcomes. (5) The language of the literature was English. Exclusion criteria: (1) Conference abstracts and review articles, duplicate articles, and unpublished articles. (2) Relevant and specific data were not available. (3) The grouping method was inconsistent with the inclusion criteria of this study design.

Data extraction process

The article screening process was as follows: firstly, the retrieved literature was initially screened by article titles and abstracts, then the full text was read for further screening, and the final decision for the literature inclusion was made strictly based on the literature eligibility and exclusion criteria. Two researchers jointly formulated the search strategy and independently completed the inclusion of the literature. The controversial literature was discussed and judged by the review group, and finally the data were integrated. Data were extracted, including the first author's name, year of publication, country where the research was conducted, ethnicity, number of cases included, maternal age, serum vitamin E levels, and maternal and infant pregnancy outcomes.

Literature quality evaluation

Literature quality evaluation was made independently by 2 researchers. The evaluation standard adopts the Newcastle-Ottawa-Scale (NOS) scoring standard (evaluated in 3 dimensions, namely selection, comparability and exposure), the score ranges from 0 (lowest) to 9 (highest) points, and a score ≥ 6 indicates that the quality of the article is relatively high. Articles with a score of ≥ 6 were included in this study.

Statistical analyses

The research data were meta-analyzed using Review Manager (RevMan5.3, Cochrane). The

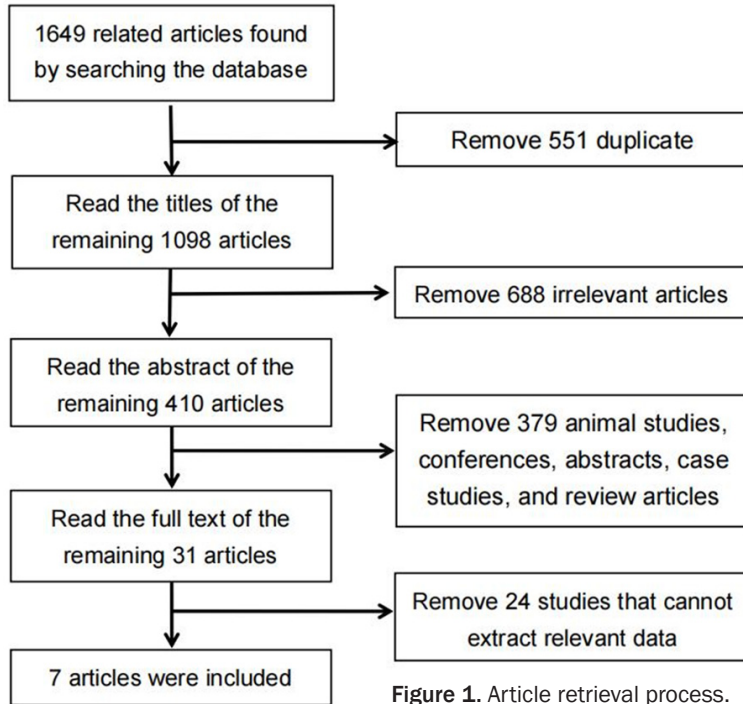


Figure 1. Article retrieval process.

heterogeneity of the results across studies was tested by Q test, with $P > 0.1$ and $I^2 < 50\%$ indicating no heterogeneity among the papers, in which case a fixed-effects model (FEM) was performed for further analysis. If statistical heterogeneity existed, the source of heterogeneity was analyzed, and subgroup analyses were conducted according to the source of heterogeneity. If clinical heterogeneity was excluded, a random-effects model (REM) analysis was applied. Sensitivity analysis was performed by excluding individual studies and recalculating their pooled effect sizes. The risk of bias was assessed by using funnel plot. The study data were continuous variables, with the results described in the form of the standardized mean difference (SMD) and its 95% confidence interval (CI). The formula for converting M (Q1, Q3) into the mean value was referred to McGrath S [14].

$$\bar{x} \approx \left(0.7 + \frac{0.39}{n}\right) \frac{Q1 + Q3}{2} + \left(0.3 - \frac{0.39}{n}\right) M$$

$$S = \frac{Q3 - Q1}{2\Phi^{-1}\left(\frac{0.75n - 0.125}{n + 0.25}\right)}$$

Results

Literature retrieval results

In the initial screening, 1,649 articles were obtained. Through title screening, abstract screening, and duplicate article screening, a total of 31 articles were screened. The full text of these 31 articles was read and further screened, and 7 articles were finally included, with a total of 6,905 cases (involving 6,247 normal women and 658 APO women). The article retrieval process is presented in Figure 1.

Basic characteristics and risk of bias assessment of included studies

The seven included articles, all of which were observational studies, had a quality evaluation score ≥ 6 . See Table 1 for the basic characteristics of each study.

Meta-analysis results

Serum vitamin E levels of pregnant women in APO and non-APO (normal) groups: A total of 7 studies [15-21] were included, and there was statistical heterogeneity across the study data ($P < 0.1$ and $I^2 > 50\%$), so a REM was used. The meta-analysis revealed statistically lower serum vitamin E levels in the APO group versus the normal group [SMD=4.44, 95% CI (2.44-6.43), $P < 0.001$] (Figure 2).

Risk assessment of bias: The 7 studies were further included for bias assessment. The funnel plot results showed that 4 studies fell outside the virtual 95% confidence interval line (Figure 3), indicating that the study may have some risk of bias, presumably due to the number of included studies.

Sensitivity analysis: In order to find the source of heterogeneity, each study was excluded one by one, and it was found that articles by Ajayi OO [15], Duan S [17], Kharb S [18], and Ma H [19] were the heterogeneity source. The direc-

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Table 1. The basic characteristics of each study

First author, year	Country	Rase	Study type	Object of study	Group	Sample size	Serum vitamin E	Age	NOS
Ajayi OO 2012 [15]	Nigeria	-	Case-control	Pregnant women with a history of recurrent spontaneous abortion	Case group	35	4.63±0.15 mg/L	30.50±0.88 years	7
		-		Pregnant women with no history of recurrent spontaneous abortion	Control group	34	9.13±0.27 mg/L	30.09±0.80 years	
Cave C 2018 [16]	America	-	cross-sectional	Caesarean Section	Caesarean Section group	63	12.48740 (2.26946, 20.19035) mg/L	28.7±5.6 years	6
		-		Vaginal delivery	Vaginal delivery group	114	12.33201 (0.17523, 34.68775) mg/L		
Cave C 2018 [16]	Nigeria	-	cross-sectional	Caesarean Section	Caesarean Section group	32	7.76652 (1.80104, 16.24840) mg/L	31.10±4.70 years	6
		-		Vaginal delivery	Vaginal delivery group	67	8.55584 (1.57659, 13.38237) mg/L		
Duan S 2021 [17]	China	-	Retrospective analysis	Severe pre-eclampsia	Preeclampsia group	306	20.23±4.97 mg/dL	<35 years: n=396 ≥35 years: n=169	8
		-		Healthy people	Health group	4435	45.01±5.15 mg/dL	<35 years: n=3902 ≥35 years: n=533	
Kharb S 1998 [18]	India	-	-	Preeclampsia pregnant woman	Preeclampsia	20	4.26±0.35 µg/ml	18-40 years	6
		-		Normal pregnant women	Normotensive pregnant	25	9.47±0.39 µg/ml	Age was matched 1:1 to the preeclampsia group	
Ma H 2021 [19]	China	-	Observational study	Adverse pregnancy Outcome (such as fetal macrosomia (greater than normal birth weight), neonatal hypoglycemia, premature rupture of membranes, placental abruption, premature delivery, fetal distress, threatened abortion, preeclampsia, threatened premature delivery, too much or too little amniotic fluid, fetal growth restriction, stillbirth, or severe fetal malformations)	Adverse pregnancy outcome group	43	22.54±1.02 mg/L	<27 years: n=23 ≥27 years: n=20	8
		-		Non-adverse pregnancy outcome	Non-adverse pregnancy outcome group	61	25.34±1.80 mg/L	<27 years: n=40 ≥27 years: n=21	
Medeiros JF 2016 [20]	Brazil	-	cross-sectional	<32 weeks of gestation	severe prematurity group	18	22.2±4.4 µmol/L	18-45 years, The mean age was 26 years	7
		-		≥32 weeks of gestation	moderate prematurity group	47	27.1±8.6 µmol/L		
Shamim AA 2015 [21]	Bangladesh	-	randomized controlled	Miscarriage	Miscarriage group	141	9.34 (7.55, 11.19) µmol/L	<20 years: n=65 20-29 years: n=51 ≥30 years: n=25	8
		-		Non-miscarriage	Non-miscarriage group	1464	10.07 (8.13, 12.48) µmol/L	<20 years: n=705 20-29 years: n=613 ≥30 years: n=145	

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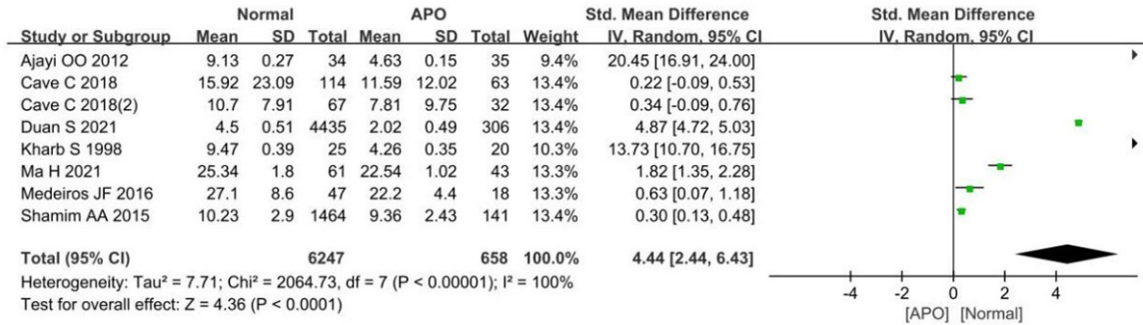


Figure 2. Forest plot of maternal serum vitamin E levels in adverse pregnancy outcome (APO) group and normal group.

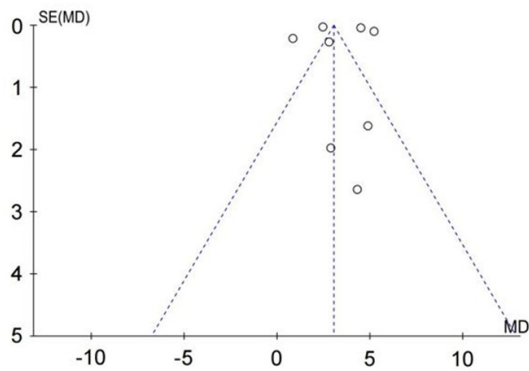


Figure 3. Funnel plot.

tion of the meta-analysis results did not change after excluding these 4 studies, that is, APO group showed statistically lower serum vitamin E levels than the normal group [SMD=0.31, 95% CI (0.17-0.45), $P < 0.001$] (**Figure 4**).

Correlation between maternal vitamin E level and maternal age during pregnancy

One [19] out of the 7 studies reported the correlation of age with vitamin E levels, which showed no significant difference in vitamin E levels among women in different age groups (<27 y, ≥27 y), $P = 0.214$.

Correlation of maternal vitamin E level with maternal body mass index (BMI) during pregnancy

One of the included studies reported the correlation between BMI and vitamin E levels. The study by Shamim AA et al. [21] showed that there were 546 cases of vitamin E deficiency (<12 μmol/L) in women with BMI <18.5 kg/m². Among them, miscarriage accounted for 10.4%

(57/546). There were 161 cases with normal vitamin E level (≥12 μmol/L), of which 8.7% (14/161) had miscarriage. Among the women with BMI ≥18.5 kg/m², there were 610 cases of vitamin E deficiency, of which 10.0% (61/610) had miscarriage. There were 281 cases with normal vitamin E level, of which 2.8% (8/281) had miscarriage. Pregnant women with BMI <18.5 kg/m² had a notably higher vitamin E deficiency rate than those with BMI ≥18.5 kg/m² ($\chi^2 = 15.173$, $P < 0.05$).

Correlation of maternal vitamin E level with neonatal length and weight during pregnancy

One of the included studies reported the correlation of serum vitamin E levels during pregnancy with neonatal length and weight. As reported by Cave C et al. [16], among neonates of the same age, the maternal vitamin E level was [1.793 (0.08, 4.514) mg/L] for those with neonatal weight Z-Score >-2, which was significantly lower than those with a neonatal weight Z-Score ≤-2 [2.223 (0.899, 6.958) mg/L], $P = 0.009$. Among the neonates of the same age, the maternal vitamin E level was [1.746 (0.08, 4.514) mg/L] for those with neonatal length Z-Score >-2, which was significantly lower than that in those with neonatal length Z-Score ≤-2 [2.362 (1.380, 6.958) mg/L], $P = 0.006$.

Discussion

Vitamin E, also known as tocopherol, was first found to be related to spermatogenesis and reproductive capacity [22]. It has an important impact on human reproductive capacity, and also has the effects of enhancing human immunity and improving human antioxidant capacity

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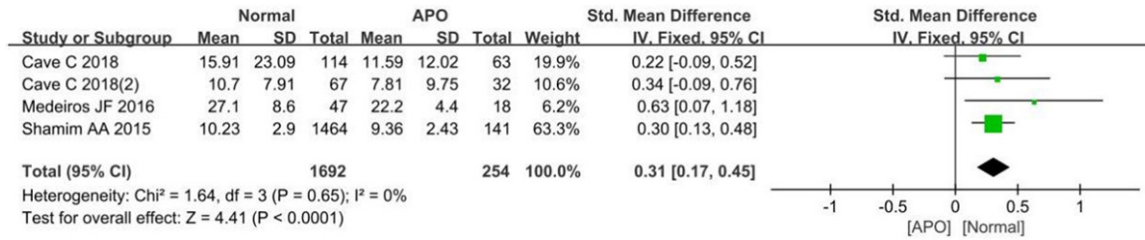


Figure 4. Forest plot of serum vitamin E levels of pregnant women in the adverse pregnancy outcome group (APO) and the normal group after removing heterogeneity.

[23]. There is a certain connection between vitamin E intake during pregnancy and pregnancy outcomes [24]. However, the Bastani [25] study showed that vitamin E supplementation in the second trimester did not seem to affect pregnancy outcomes and the occurrence of preeclampsia, and Szilasi et al. [13] also showed no association of maternal vitamin E intake with higher risk of cardiovascular malformations in children. At present, most reports focus on investigating the influence of vitamin E therapy on pregnancy outcomes, without systematic review on the correlation of maternal vitamin E levels with pregnancy outcomes. In view of this, we systematically evaluated the association of maternal vitamin E level with maternal and neonatal health outcomes.

Herein, a meta-analysis was performed to compare vitamin E levels in mothers with APOs (pre-eclampsia, miscarriage, low birth weight infant) and normal mothers. Seven studies were finally included, and the vitamin E level was found to be statistically lower in the APO group than in the normal group; however, there was heterogeneity among the studies. In order to find the source of heterogeneity, we excluded each study one by one and found that four of them were the source of heterogeneity. The direction of the meta-analysis results did not change after removal of the 4 studies with heterogeneity, that is, the vitamin E level was still significantly lower in the APO group than in the normal group. It can be seen that women with APOs have lower vitamin E level than the normal group, which is more reliable. In a multicenter retrospective cohort study conducted in China, the pre-eclampsia risk elevated dramatically when vitamin E concentrations were less than 7.3 mg/L during early pregnancy [26], suggesting that vitamin E supplementation may help reduce the occurrence of pre-eclampsia

when its concentration during pregnancy was <7.3 mg/L. Vitamin E is known to have antioxidant effects, and the occurrence of pre-eclampsia is closely related to oxidative stress, so the decrease of vitamin E is closely related to the increased risk of pre-eclampsia. However, in a review article, taking any vitamin supplements before or during early pregnancy did not prevent women from miscarriage [27].

In the studies on the correlation of vitamin E with the clinical characteristics of pregnant women, only descriptive analysis and evaluation can be performed due to the lack of included studies and inconsistent grouping methods. Ma H et al. [19] investigated the correlation between age and vitamin E levels and found no marked difference in vitamin E among women of different ages (<27 y, ≥27 y). Shamim et al. [21] reported the correlation between BMI and vitamin E levels and concluded that the vitamin E deficiency rate was significantly higher in mothers with BMI <18.5 kg/m² than in those with BMI ≥18.5 kg/m². This suggests that there is no significant correlation between vitamin E deficiency during pregnancy and maternal age, but the rate of vitamin E deficiency is higher in women with a smaller BMI index. Due to the small number of included studies, more experimental studies are still needed for further confirmation. In addition, there is still limitation of this study, that is, only a few articles reported the effect of age and BMI on pregnancy outcomes, so the forest plot could not be drawn, only descriptive analysis could be carried out.

Conclusion

This study determined lower maternal vitamin E levels in the APO group compared with the non-APO group. Due to the limited research on the correlation of vitamin E levels during pregnancy with maternal BMI and neonatal body length

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and weight, a large-scale and well-designed cohort study is still needed for discussion and confirmation.

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Disclosure of conflict of interest

None.

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