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Original Article

Correlation of serum vitamin A and vitamin E levels with the occurrence and severity of preeclampsia

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Abstract: Objective: To investigate the correlation of serum vitamin A and vitamin E levels with the occurrence and severity of preeclampsia. Methods: The clinical data of 5,000 pregnant women in our hospital were retrospectively studied. Five hundred and sixty-five pregnant women with preeclampsia were divided into a mild group (259 cases) and a severe group (306 cases). The rest 4435 healthy pregnant women were classified as the healthy group. The concentrations of serum vitamin A and vitamin E in each group were compared to analyze the risk factors for preeclampsia. Results: The levels of vitamin A and vitamin E were negatively correlated with the severity of preeclampsia ($P<0.001$). The logistic regression analysis showed that older age (OR=1.674), vitamin A deficiency (OR=2.463) and vitamin E deficiency (OR=2.206) were independent risk factors for preeclampsia (all $P<0.05$). Conclusion: Older age, vitamin A deficiency and vitamin E deficiency are the risk factors for preeclampsia. The concentrations of vitamin A and vitamin E are negatively correlated with the severity of preeclampsia. Vitamin A and vitamin E deficiencies in preeclampsia can increase the risk of adverse pregnancy outcomes, which needs timely intervention.

Keywords: Vitamin A, vitamin E, pregnant woman, preeclampsia, correlation, pregnancy outcome

Introduction

Preeclampsia is a multi-organ and multi-system dysfunction syndrome that occurs after 20 weeks of pregnancy, manifested as hypertension, proteinuria and edema. It is an idiopathic disease during pregnancy, with an incidence of 2%-5% worldwide and about 9.4% in China [1, 2]. Vitamin A and vitamin E are fat soluble vitamins, participating in the metabolic processes. They are also non-enzymatic strong antioxidants, which have a scavenging effect on oxygen free radicals [3]. At present, the pathogenesis of preeclampsia has not been fully elucidated. It is generally believed that preeclampsia is related to the insufficient uterine spiral artery remodeling, genetic factors and excessive oxidative stress [4, 5]. Levels of vitamin A and E in preeclampsia patients have recent been found to be lower than those of healthy pregnant women. Therefore, it is speculated that vitamin A and vitamin E are closely related to the occurrence and development of preeclampsia [6, 7]. Vitamin A and vitamin E play an important role in antioxidation. Deficiency of vitamin A and vitamin E may lead to oxidative stress response, which mediates the endothelial damage involved in the basic pathophysiological process of preeclampsia [8-10]. However, the relationship between vitamin A, vitamin E and preeclampsia and whether deficiency of vitamin A or vitamin E causes preeclampsia remain elusive. In this study, 5,000 pregnant women in the Department of Obstetrics at our hospital were enrolled, so as to compare the serum vitamin A and vitamin E concentrations in healthy pregnant women and those with preeclampsia, and to analyze the correlation of vitamin A and vitamin E concentrations with preeclampsia.

Materials and methods

General information

The clinical data of 5,000 pregnant women admitted to our hospital from December 2017

to December 2019 were retrospectively studied. Five hundred and sixty-five pregnant women with preeclampsia were divided into a mild group (259 cases) and a severe group (306 cases). The remaining 4,435 healthy pregnant women were classified as a healthy group.

Diagnostic criteria for preeclampsia: Pregnant women met the diagnostic criteria for preeclampsia in *Obstetrics and Gynecology* [11]; pregnant women had a normal basic blood pressure before pregnancy, but experienced hypertension after 20 weeks of gestation (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg); pregnant women experienced 24 h urine protein ≥0.3 g or random urine protein (+); pregnant women experienced no urine protein but abnormal changes of vital organs, nervous system, blood system, etc., affecting the placenta and fetus. Patients with one or more of the following conditions was considered to have severe preeclampsia: systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg; 24 h urine protein ≥5.0 g or random urine protein (++); new-onset central nervous system abnormalities or visual impairment; platelet <100× 10^9/L; liver function damage; persistent epigastric pain; abnormal renal function; hypoproteinemia combined with pleural effusion or peritoneal effusion; fetal growth restriction or oligohydramnios; heart failure and pulmonary edema.

The inclusion criteria of preeclampsia group were: Pregnant women who were 18-40 years old; pregnant women whose serum vitamin A and vitamin E levels were detected at 12 weeks of gestation; pregnant women with a live singleton; pregnant women who underwent regular prenatal examination and delivery in our hospital; pregnant women who did not take multivitamins before enrollment; pregnant women without smoking or drinking history. The exclusion criteria of preeclampsia group were: pregnant women with gestational diabetes mellitus; pregnant women with combined with autoimmune diseases; pregnant women with a history of thrombosis; pregnant women with a history of malignant tumor; pregnant women combined with systemic acute and chronic infection; pregnant women combined with iron deficiency anemia. The inclusion criteria of healthy group were: pregnant women who were 18-40 years old; pregnant women whose serum vitamin A and vitamin E levels were detected at 12 weeks of gestation; pregnant women with a live singleton; pregnant women who underwent regular prenatal examination and delivery in our hospital; pregnant women who did not take multivitamins before enrollment; pregnant women without smoking or drinking history; pregnant women without other pregnancy complications. The exclusion criteria were: pregnant women with hypertension, diabetes, coronary heart disease, etc.; pregnant women with autoimmune diseases; pregnant women with a history of thrombosis; pregnant women with a history of malignant tumors; pregnant women with acute or chronic systemic infection. All selected candidates have signed the informed consent. This study was approved by the Ethics Committee of our hospital.

Methods

Detection of serum vitamin A and vitamin E concentrations: For all enrolled pregnant women, serum vitamin A and vitamin E concentrations were detected at 12-20 weeks of gestation. For pregnant women with preeclampsia, secondary detection of serum vitamin A and vitamin E concentrations were conducted after one month of treatment. The concentrations were detected by high performance liquid chromatography tandem mass spectrometry [12]. All subjects in the study were fasted for 8 hours before the blood collection. Fasting peripheral venous blood (3 mL) was collected, without anticoagulation treatment, and cryopreserved at -4°C. The blood sample was centrifuged at 3,000 rpm for 10 min with the centrifugation radius of 15 cm. The serum was collected, and the protein and impurities in the serum were removed. N-hexane was added to the sample, and the supernatant was collected and blown dry. The sample was added with methanol for re-dissolving. The concentrations of vitamin A and vitamin E were detected. The standard curve equation was made according to the instrument standard, with the relative standard deviation of <15%. The concentrations of vitamin A and vitamin E were calculated according to the standard curve equation, with the quality control range of $\bar{x} \pm 2$ standard deviation (sd).

Detection of urine protein and liver and kidney function: The morning urine was collected, and

Table 1. Comparison of general information between the preeclampsia group and healthy group ($\bar{x}$±sd, n (%))

Factor		Preeclampsia group (n=565)	Healthy group (n=4435)	χ^2/t	P
Age (years old)	<35	396 (70.09)	3902 (87.98)	132.953	<0.001
	≥35	169 (29.91)	533 (12.02)		
Pregnancy times	1 time	186 (32.92)	1,672 (37.70)	5.909	0.052
	2 times	170 (30.09)	1,313 (29.61)		
	≥3 times	209 (36.99)	1,450 (32.69)		
Labor times	0 time	315 (55.75)	2,561 (57.75)	0.901	0.637
	1 time	209 (36.99)	1,553 (35.02)		
	≥2 times	41 (7.26)	321 (7.24)		
Gestational weeks		14.3±0.7	14.2±0.6	0.718	0.473
BMI increase (kg/m^2)		6.03±1.55	5.34±1.53	10.081	<0.001

Note: BMI: body mass index.

the urine protein was detected by the wet chemical method. Three milliliters of peripheral venous blood were collected to detect liver and kidney function by the wet chemical method.

Data collection: The age, body mass index (BMI), gestational weeks, times of pregnancy, times of labor and pregnancy outcome of the enrolled women were collected. BMI increase equals to prenatal BMI minus pre-pregnancy BMI.

Treatment methods: According to the treatment principle of preeclampsia, the pregnant women in the preeclampsia group were given conventional treatment such as antihypertensive treatment and sedation. For pregnant women combined with vitamin A and vitamin E deficiency, they were additionally treated with drug adjustment. The specific dosage regimens were as follows. Vitamin A (Sinopharm Xingsha Pharmaceutical (Xiamen) Co., Ltd., China) 2,500 U/d, oral, once a day; vitamin E (Qingdao Shuangjing Pharmaceutical Co., Ltd., China) 10~100 mg/time, oral, twice or three times a day.

Evaluation criteria

The reference range of serum vitamin A concentration is 3~7 mg/dL [13]. The reference range of serum vitamin E concentration is 50~200 mg/L. A vitamin concentration lower than the reference range is considered deficiency [14].

Statistical analysis

SPSS 25.0 statistical software was used for statistical analysis. The measurement data were expressed as $\bar{x}$±sd and processed using t-test. Comparison for three or more groups was conducted using F test. The count data were expressed as percent, and conducted using chi-square test. Spearman rank correlation was used to analyze the correlation between vitamin A and vitamin E levels with preeclampsia. Univariate analysis was performed for each variable. The variables with statistical differences were entered into the multivariate logistic regression analysis. The test level is α=0.05. P<0.05 is considered statistically significant.

Results

Comparison of general information between the preeclampsia group and healthy group

There were significant differences in age and BMI increase between the preeclampsia group and healthy group (P<0.05). However, there were no significant differences in pregnancy times, labor times or gestational weeks between the two groups (all P>0.05). See **Table 1**.

Comparison of serum vitamin A and vitamin E levels among the preeclampsia groups with different degrees of severity and healthy groups

The levels of vitamin A and vitamin E in the severe group and mild group were lower than

Table 2. Comparison of serum vitamin A and vitamin E levels among the preeclampsia groups with different degrees of severity and healthy group ($\bar{x}$±sd, mg/dL)

Group	Vitamin A level	Vitamin E level	Vitamin A level after treatment	Vitamin E level after treatment
Healthy group (n=4,435)	6.05±1.31	45.01±5.15	-	-
Mild group (n=259)	1.64±0.28***	35.96±4.92***	3.82±1.21$^{\Delta\Delta\Delta}$	39.15±6.31$^{\Delta\Delta\Delta}$
Severe group (n=306)	0.93±0.24$^{***,\#\#\#}$	20.23±4.97$^{***,\#\#\#}$	2.79±1.29$^{\Delta\Delta\Delta}$	38.52±5.69$^{\Delta\Delta\Delta}$
F	2639.752	3601.968	1.659	1.247
P	<0.000	<0.000	0.102	0.213

Note: Compared with the healthy group, ***P<0.001; compared with the mild group, $^{\#\#\#}$P<0.001; compared with the same group before the treatment, $^{\Delta\Delta\Delta}$P<0.001.

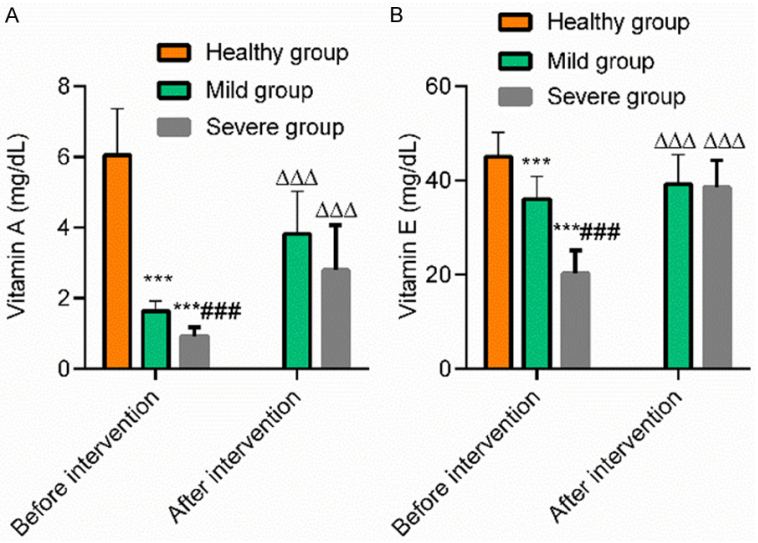

Figure 1. Comparison of serum vitamin A and vitamin E levels among the preeclampsia groups with different degrees of severity and healthy group. A: Vitamin A level; B: Vitamin E level. Compared with the healthy group, ***P<0.001; compared with the mild group, $^{\#\#\#}$P<0.001; compared with the same group before treatment, $^{\Delta\Delta\Delta}$P<0.001.

those in the healthy group, and the levels in the severe group were lower than those in the mild group before treatment (all P<0.001). With the exacerbation of preeclampsia, the levels of vitamin A and vitamin E showed decreasing trends. Spearman rank correlation analysis showed that the levels of vitamin A and vitamin E were negatively correlated with the severity of preeclampsia (vitamin A: r=-0.653, P<0.001; vitamin E: r=-1.105, P<0.001). The levels of vitamin A and vitamin E in two preeclampsia groups were increased after treatment (all P<0.001), but there was no significant difference between the mild group and severe group (both P>0.05). See **Table 2** and **Figure 1**.

Comparison of vitamin A and vitamin E deficiency rate among the preeclampsia group with different degrees of severity and healthy group

The deficiency rates of vitamin A and vitamin E in the mild group and severe group were higher than those in the healthy group, and were higher in the severe group than in the mild group (all P<0.05). See **Table 3**.

Logistic regression analysis of preeclampsia

Multivariate logistic regression analysis was performed with the occurrence of preeclampsia as the dependent variable, and with age, vitamin A deficiency, vitamin E deficiency and BMI increase as independent variables. For independent variables, $\alpha_{Entering}$=0.05 and $\alpha_{Exiting}$=0.05. The result showed that older age (OR=1.674), vitamin A deficiency (OR=2.463) and vitamin E deficiency (OR=2.206) were independent risk factors for preeclampsia (all P<0.05), as shown in **Table 4**.

Comparison of pregnancy outcomes among the preeclampsia group with different degrees of severity and healthy group

The incidences of neonatal asphyxia, fetal distress and preterm birth in pregnant women with vitamin A or vitamin E deficiency in each group were higher than those with normal vita-

Table 3. Comparison of vitamin A and vitamin E deficiency rate among the preeclampsia group with different degrees of severity and healthy group (n (%))

Group	n	Vitamin A deficiency	Vitamin E deficiency	Vitamin A and E deficiency
Healthy group	4,435	202 (4.55)	126 (2.84)	51 (1.15)
Mild group	259	67 (25.87)*	50 (19.31)*	15 (5.79)*
Severe group	306	125 (40.85)*,#	77 (25.16)*,#	32 (10.46)*,#
F		641.232	412.289	149.918
P		<0.001	<0.001	<0.001

Note: Compared with the healthy group, *P<0.05; compared with the mild group, #P<0.05.

Table 4. Logistic regression analysis of factors affecting preeclampsia

Index	B	S.E.	Wald χ^2	P	OR	95% CI	
						Upper limit	Lower limit
Older age	14.739	0.091	11.226	0.002	1.674	1.332	3.795
Vitamin A deficiency	25.033	0.032	61.139	0.007	2.463	1.554	12.049
Vitamin E deficiency	10.276	0.041	46.227	0.013	2.206	1.146	9.267
BMI increase	0.122	0.117	1.269	0.105	0.794	0.428	0.862

min A and vitamin E levels in each group, and the neonatal body weight and the neonatal Apgar score in pregnant women with vitamin A and vitamin E deficiencies were lower than those with normal vitamin A and vitamin E levels (all P<0.05). See **Table 5**.

Discussion

Vitamin A and vitamin E are microelements required to maintain the body's normal metabolism and physiological function, and they also serve as antioxidants. Vitamin A has the function of maintaining normal embryonic development and antioxidation and plays an important role in the growth and reproduction of normal cells [15]. In addition to the role of vitamins, vitamin E can also scavenge oxygen free radicals, play an antioxidant role and maintain the body's oxidative stress balance [16].

Foreign researchers conducted a comprehensive analysis of the oxidative stress markers and antioxidant status of preeclampsia, including 2,953 cases of patients with preeclampsia and 3,621 healthy pregnant women as the controls [17]. The study found that the vitamin E level in women with preeclampsia decreased significantly. Another researcher investigated 2,824 pregnant women and found that the abnormal rate of serum vitamin A concentrations was 12.3% [18]. A study found that vitamin E had a protective effect against preeclampsia. In the study, 400 IU/d vitamin E supplementation was given to pregnant women (within 20-40 weeks) with risk factors for preeclampsia. The results showed that the incidence of preeclampsia was 5.0%, lower than 17.5% in the control group without vitamin E supplementation [19]. The results of this study showed that the levels of vitamin A and vitamin E in the severe group and mild group were lower than those in the healthy group, and the deficiency rates of vitamin A and vitamin E in severe group and mild group were higher than those in healthy group, similar to the results reported above. After preeclampsia treatment, the levels of vitamin A and vitamin E increased in patients with preeclampsia. Further correlation analysis showed that the levels of vitamin A and E were negatively correlated with the severity of preeclampsia. Our results showed that the levels of vitamin A and E in patients with preeclampsia decreased significantly, and the levels of vitamin A and E were closely related to the severity of preeclampsia. The levels of vitamin A and E in patients with severe preeclampsia decreased more significantly than those with mild preeclampsia. It is speculated that the patients with preeclampsia consume a lot of antioxidants due to oxidative stress reaction, resulting in the decrease of vitamin A and vitamin E levels [20]. Vitamin A and vitamin E supplementation can improve the status of vitamin A and vitamin E deficiencies in patients with preeclampsia.

Table 5. Comparison of pregnancy outcomes among the preeclampsia group with different degrees of severity and healthy group ($\bar{x}$±sd, n (%))

Group		n	Neonatal asphyxia	Fetal distress	Premature delivery	Neonatal body weight (kg)	Neonatal Apgar score (scores)
Healthy group	Normal vitamin A and vitamin E	4056	51 (1.26)	63 (1.55)	192 (4.73)	3.69±0.52	9.30±0.59
	Vitamin A deficiency	202	10 (4.95)	15 (7.43)	20 (9.90)	3.57±0.50	9.13±0.51
	Vitamin E deficiency	126	6 (4.76)	12 (9.52)	13 (10.32)	3.60±0.53	9.09±0.56
	Vitamin A and E deficiency	51	6 (11.76)	9 (17.65)	10 (19.61)	3.49±0.51	9.01±0.54
χ^2/F			57.220	119.760	38.241	6.795	14.010
P			<0.001	<0.001	<0.001	<0.001	<0.001
Mild group	Normal vitamin A and vitamin E	127	5 (3.94)	8 (6.30)	9 (7.09)	3.41±0.40	9.02±0.47
	Vitamin A deficiency	67	10 (14.93)	12 (17.91)	11 (16.42)	3.13±0.37	8.79±0.45
	Vitamin E deficiency	50	7 (14.00)	11 (22.00)	9 (18.00)	3.15±0.39	8.82±0.43
	Vitamin A and E deficiency	15	3 (20.00)	5 (33.33)	4 (26.67)	3.02±0.35	8.63±0.49
χ^2/F			9.819	15.461	8.850	12.082	6.425
P			0.020	0.002	0.031	<0.001	<0.001
Severe group	Normal vitamin A and vitamin E	72	8 (11.11)	9 (12.50)	10 (13.89)	3.05±0.31	8.38±0.46
	Vitamin A deficiency	125	22 (17.60)	25 (20.00)	29 (23.20)	2.87±0.26	8.02±0.41
	Vitamin E deficiency	77	13 (16.88)	18 (23.38)	17 (22.08)	2.89±0.29	8.06±0.43
	Vitamin A and E deficiency	32	12 (37.50)	13 (40.62)	13 (40.62)	2.76±0.33	7.87±0.44
χ^2/F			10.649	10.800	9.119	9.228	15.264
P			0.014	0.013	0.028	<0.001	<0.001

We have shown that older age (OR=1.674), vitamin A deficiency (OR=2.463) and vitamin E deficiency (OR=2.206) were independent risk factors for preeclampsia. Yi et al. found that older age and vitamin A and vitamin E deficiencies were independent risk factors for preeclampsia through logistic regression analysis, which was consistent with the results of this study [21]. The possible reasons are listed as follows. (1) Older age. With the increase of age, the metabolic function of pregnant women over 35 years old changes, and there is a trend of metabolic disorder. The production of free radicals increases. The lower content of vitamin A and vitamin E leads to the relative increase of free radical content, leading to placental aging and vascular endothelial damage, thus increasing the incidence of preeclampsia [22, 23]. (2) Vitamin A and vitamin E deficiencies. During pregnancy, placental ischemia-hypoxia-reperfusion injury response stimulates the release of oxidative factors, leading to the damage of vascular endothelial cells, promoting inflammatory response and eventually leading to the development of preeclampsia [24]. Vitamin A and vitamin E not only participate in the body's normal metabolism and physiological function as essential microelements, but also maintain the body's oxidative stress balance as a non-enzymatic strong antioxidant, playing the role of antioxidant and scavenging oxygen free radicals. Vitamin A and vitamin E deficiencies can easily cause the imbalance of oxidative stress, increase the free radicals, cause endothelial damage, and increase the risk of preeclampsia [25, 26].

In addition, the results showed that for comparison within groups, the incidences of neonatal asphyxia, fetal distress and preterm birth in pregnant women with vitamin A and vitamin E deficiencies were higher than those with normal vitamin A and vitamin E levels, and the neonatal body weight and the neonatal Apgar score in pregnant women with vitamin A and vitamin E deficiency were lower than those with normal vitamin A and vitamin E levels. It suggests that in patients with preeclampsia, vitamin A and E deficiencies are more likely to develop adverse pregnancy outcomes such as neonatal asphyxia, fetal distress and premature delivery as well as lower neonatal body weight and neonatal Apgar score.

This is a retrospective study based on hospital cases from a single-center study. The sample size is small and the follow-up time is short, so there may be case selection bias. In the future,

we will do a multi-center study with expanded sample size and extended follow-up time, to further confirm the reliability of the research results. At the same time, we did not supplement pregnant women with different doses according to the degree of vitamin A and E deficiency in this study. There is no clinical research report on the supplement doses related to different vitamin deficiency levels. This is also a shortcoming of this study. The study will be further improved in the next step.

In conclusion, older age, vitamin A deficiency and vitamin E deficiency are risk factors for preeclampsia. The concentrations of vitamin A and vitamin E are negatively correlated with the severity of preeclampsia. Vitamin A deficiency and vitamin E deficiency in pregnant women with preeclampsia will increase the risk of adverse pregnancy outcomes. Therefore, during pregnancy, the levels of vitamin A and vitamin E should be closely monitored, and reasonable dietary guidance and nutritional supplements should be provided should vitamin A and vitamin E deficiencies occur, so as to avoid adverse pregnancy outcomes as of preeclampsia.

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Disclosure of conflict of interest

None.

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