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Association between Dietary Total Antioxidant Capacity and Odds of Preeclampsia: A Case-control Study

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ABSTRACT

Background: Preeclampsia may cause maternal and child morbidity and mortality. Evidence suggests that oxidative stress may be involved in the development of preeclampsia; however, the role of dietary total antioxidant capacity (DTAC) on preeclampsia risk has not yet been elucidated. Thus, this study aims to assess the relationship between DTAC and odds of preeclampsia. **Methods:** This case-control study was conducted on 240 pregnant women (preeclampsia, n=60; controls, n=180) in Qazvin, Iran. Controls were 3:1 ratio matched with cases in terms of participants' age and gestational age. Dietary intakes were assessed using a validated food frequency questionnaire evaluating the preceding year. DTAC was measured by two methods: ferric reducing antioxidant potential (FRAP) and oxygen radical absorbance capacity (ORAC). Multivariable logistic regression was employed to evaluate the association between preeclampsia and DTAC and also selected antioxidants. **Results:** After controlling for potential confounders, a significant inverse relationship was found between ORAC and preeclampsia; individuals in the highest tertile of ORAC were 67% less likely to have preeclampsia than those in the lowest tertile of ORAC (OR: 0.33; 95% CI: 0.11-0.97; P-trend<0.05). There was no significant relation between FRAP and preeclampsia. The risk of preeclampsia was 70% lower among subjects with the highest tertile of vitamin C intake compared to the lowest tertile of it. **Conclusion:** Pregnant women with the highest tertile of ORAC and vitamin C intake were at lower risk of preeclampsia. Therefore, prospective studies are needed to confirm the protective effects of dietary anti-oxidants on preeclampsia incidence.

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Introduction

Preeclampsia is a pregnancy complication, occurring after the 20th week of gestational age with increased blood pressure and proteinuria in women who previously had normal blood pressure (Ghulmiyyah and Sibai, 2012). Preeclampsia occurs in approximately 2% to 8% of pregnancies worldwide (Henderson et al., 2017). Prevalence is slightly higher in Iran, (about 4% to 10%) (Omani-Samani et al., 2019). Moreover, this disorder is one of the main reasons of maternal, fetal, and neonatal mortality and morbidity (Henderson et al., 2017).

Recent studies indicated an opposite association between Dietary Total Antioxidant Capacity (DTAC) and the odds of chronic diseases like type 2 diabetes (Mancini *et al.*, 2018), breast cancer (Pantavos *et al.*, 2015), gestational diabetes mellitus (Daneshzad *et al.*, 2020), and fatty liver (Salavatizadeh *et al.*, 2022).

Some studies showed maternal diet plays a significant role in incidence of preeclampsia (Cao *et al.*, 2020, Grum *et al.*, 2018). Moreover, according to previous studies, supplementation with folic acid (Wang *et al.*, 2015), vitamins E, and C reduce incidence of preeclampsia (Lorzadeh *et al.*, 2020). Other studies demonstrated that lower intake of vitamins E and C, fruits, fiber, carotenoids, and excessive intake of carbohydrates, fat, saturated fat, sodium, and calories may be associated with high risk of preeclampsia (Kang *et al.*, 2022, Saputra *et al.*, 2017, Yusuf *et al.*, 2019). However, evidence is varied and inconsistent in this respect (Christiansen *et al.*, 2022, Eshriqui *et al.*, 2016, Kalpdev *et al.*, 2011).

We consume different groups of food in our diet containing numerous nutrients and antioxidants that may have cumulative or synergic effects on each other (Mancini *et al.*, 2018). Investigation of them individually may be misleading (Liu *et al.*, 2022). Studies indicated that DTAC, as a summary of dietary anti-oxidants intake, is an effective tool for assessing odds of chronic diseases (Nascimento-Souza *et al.*, 2018). This indicator represents the capacity of food antioxidants to neutralize free radicals (Mancini *et al.*, 2018).

Pro-inflammatory diets corresponded to high inflammatory biomarkers that play critical role in incidence of preeclampsia (Liu *et al.*, 2022). Evidence demonstrated that primary reduction of antioxidants and increases in oxidative stress products may induce a situation that plays an important role in pathogenesis of this disorder (Taravati and Tohidi, 2018). Unusually, high levels of free radicals and also a decline in enzymatic and non-enzymatic antioxidant defense can lead to damage of cellular organelles and enzymes, and an increase in lipid peroxidation products can promote endothelial cell dysfunction (Shehu *et al.*, 2020, Taravati and Tohidi, 2018). Furthermore, some previous studies suggested adequate antioxidant intake may reduce the odds of preeclampsia by neutralizing free radicals and protecting endothelial cells from oxidative stress damage (Aminuddin *et al.*, 2021, Lorzadeh *et al.*, 2020).

According to the researchers' knowledge, only one study analyzed the relationship between DTAC and preeclampsia (Sheikhi *et al.*, 2017), while no study investigated this relationship using the Ferric Reducing Antioxidant Potential (FRAP) method. The Iranian traditional dietary pattern has specific features such as large size of food portion containing refined carbohydrates. Thus, examining the relationship between DTAC and the odds of preeclampsia in the Middle Eastern countries with their specific dietary patterns might add further information to the researchers' knowledge. Therefore, the association between DTAC and preeclampsia was investigated by using the two most common methods (Oxygen Radical Absorbance Capacity (ORAC) and FRAP).

Materials and Methods

Study design and sample

This case-control study was conducted in two

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referral hospitals in Qazvin, Iran. Participants were selected from pregnant women whose gestational age was more than 20 weeks (Magee *et al.*, 2022, Mol *et al.*, 2016) by convenience sampling method between January and September 2021. A total of 240 pregnant women were examined and who had high blood pressure before pregnancy, incomplete Food Frequency Questionnaire (FFQ), and energy intake more than mean±3 standard deviation (SD) were excluded. Eventually, 218 participants remained (57 cases, 161 controls); the case-to-control ratio of 1:3 was considered.

Cases were chosen from pregnant women with blood pressure greater than 140/90 mmHg and presence of protein in urine (Mol *et al.*, 2016). Controls were selected from outpatients or those who were referred for delivery. Furthermore, all controls were matched to cases in terms of age and gestational age at the same time to avoid bias.

Dietary assessment

The authors employed a semi-quantitative, valid, and reliable FFQ with 168 food items in an in-person interview to assess individuals' dietary consumption over the previous year (Mirmiran *et al.*, 2010). An expert interviewer completed all questionnaires and asked participants about food items consumption frequency (daily, weekly or monthly). Participants who could not declare their dietary consumption based on standard serving size were asked based on their own portion size, and then, a dietitian converted these data to grams per day. The authors computed energy and nutrient composition of foods with the United States Department of Agriculture (USDA) food composition database. For some Iranian food items like traditional bread that did not exist in USDA database, the Iranian Food Composition Table (FCT) was used.

DTAC calculation

Two methods for DTAC measurement was used. FRAP estimates the capacity of dietary antioxidants to reduce ferric to ferrous ions (Carlsen *et al.*, 2010), and ORAC evaluates inhibitory effect of dietary antioxidants on peroxy-radical-induced oxidation (Haytowitz and Bhagwat, 2010). The daily intake of each food item was multiplied by its related corresponding value, and then was used to calculate overall DTAC. The supplements in the DTAC calculation were not considered because the researchers did not access detailed data about them (frequency and dosage of supplements were not evaluated, and supplements that were used sporadically were not considered).

Assessment of other variables

Required data including age, gestational age, pre-pregnancy weight, gravidity, primiparous, abortion, pregnancy interval, oral contraceptive use, smoking, education, occupation, previous preeclampsia history, and family history of preeclampsia were gathered by structured questionnaire in a face-to-face interview. Additionally, participants were asked about dietary supplements (yes/no) commonly used in pregnancy and before pregnancy including folate, iron, multivitamins plus minerals, and vitamin D.

Anthropometric measures like weight and height were measured with accuracy of 0.1 kg and 0.1 cm, respectively. pre-pregnancy Body Mass Index (BMI) was calculated by dividing pre-pregnancy weight (kg) by square of height (m^2), and gestational weight gain by the difference between current and pre-pregnancy weight. Measuring tape was placed between acromial process and olecranon in non-dominant hand for measurement of middle upper arm circumference with an accuracy of 0.1 cm. The hand flexed 90° from the elbow.

The authors used a reliable and valid questionnaire for estimation of physical activity levels (Klishadi *et al.*, 2001). This questionnaire consisted of different physical activity levels, from resting or sleeping (Metabolic Equivalent (Mets)= 0.9) to heavy activities (Mets > 6). All participants were asked about the duration of all these activities in a day. These numbers were multiplied by the related Met coefficient. Finally, all numbers were

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added to calculate physical activity level (Met-h/day).

Ethical considerations

The study was conducted according to Helsinki declaration. The Ethics Committee of the Zahedan University of Medical Sciences authorized protocols of this study. (Approval ID: IR.ZAUMS.REC.1399. 438) All participants signed written knowledgeable consent.

Data analysis

Characteristics of participants were summarized using descriptive statistics. Kolmogorov-Smirnov test was employed for assessment of normal distribution of continuous variables. Student's t-test and Mann–Whitney U test were used for comparing two groups in continuous variables with normal and non-normal distribution, respectively. For comparing more than two groups, the authors employed Analysis of Variance (ANOVA) for continuous variables and Kruskal-Wallis test for non-normal continuous variables. Then, Chi-square test and Fisher exact test were employed to assess categorical variables. Finally, binary logistic regression was used to estimate odds ratio (OR) and 95% confidence interval (CI) in different models that adjusted for multiple covariates. P-values less than 0.05 were considered significant. Additionally, all tests were two sides. IBM SPSS statistical package (version 21) was employed for all analyses.

Results

General characteristics and dietary intake of participants are summarized in **Table 1**. Cases had higher pre-pregnancy weight, pre-pregnancy BMI, mid-upper arm circumference (MUAC), pregnancy interval, and previous preeclampsia history (P<0.05). In assessment of dietary intake between cases and controls, controls reported higher intake of fruits and nuts. Moreover, caffeine intake was lower in control group (P<0.05). ORAC and FRAP scores did not indicate significant differences between cases and controls (P>0.05). Additionally, not significant difference was found between cases and controls regarding the use of supplements (data not shown).

Table 2 presents general characteristics of study participants across tertiles of DTAC. There were significantly more primiparous individuals in the lowest tertile of FRAP compared to the highest tertile of it. Additionally, individuals in the highest tertile of ORAC had lower percentage of family history of preeclampsia (P<0.05) in comparison to the lowest tertile of it.

Table 3 indicated dietary intake of study participants across tertiles of DTAC. Pregnant women in the highest tertile of FRAP had significantly higher intakes of whole grains, fruits, nuts, energy, carbohydrate, protein, total fat, polyunsaturated fatty acid, vitamin C, caffeine, and fiber compared with individuals in the lowest tertile of it. Subjects in the top tertile of ORAC had higher consumption of whole grains, vegetables, fruits, dairy products, legumes, nuts, energy, carbohydrate, protein, total fat, polyunsaturated fatty acids, vitamin C, sodium, caffeine, and fiber (P<0.05) compared to the lowest tertile of it.

ORs and 95% CIs for the risk of developing preeclampsia across tertiles of DTAC are reported in **Table 4**. Results from modeling of FRAP did not show any significant relationship among cases and controls. A significant inverse association was found between ORAC and risk of preeclampsia; individuals in the highest ORAC tertile were 0.77 times less likely to have preeclampsia compared with those in the lowest tertile after controlling for potential confounders ($OR_{T3–T1}$=0.33, 95% CI:0.11–0.97; P=0.04). The contribution of food groups in the FRAP score was as follows: tea (41%), fruit (26%), and vegetable (10%). While for ORAC scores, the most alteration was explained by consumption of fruits (49%), vegetables (22%), and tea (8%) (data not shown).

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Table 1. General characteristics and dietary intake of preeclampsia cases and controls.

Variables	Case (n=57)	Control (n=161)	P-value[a]
Quantitative variables	**Mean ± SD**	**Mean ± SD**	
Age (y)	29.93 ± 6.83	29.02 ± 6.52	0.37
Pre-pregnancy weight (kg)	71.74 ± 14.48	62.90 ± 10.79	<0.001
Gestational weight gain (kg)	12.20 ± 5.98	10.89 ± 5.15	0.11
Height (cm)	161.82 ± 6.84	160.49 ± 6.09	0.17
MUAC (cm)	29.65 ± 3.70	27.62 ±3.03	<0.001
Pre-pregnancy body mass index (kg/m^2)	27.33 ± 4.84	24.44 ± 4.12	<0.001
Physical activity (Met.h/day)	29.65 ± 3.35	29.48 ± 3.33	0.74
DTAC by ORAC (mmol/day)	14.08 ± 3.86	15.21 ± 4.45	0.09
Energy (kcal/day)	2512.17 ± 546.06	2536.23 ± 493.25	0.75
Carbohydrate (% of energy)	56.49 ± 5.42	57.62 ± 5.52	0.18
Protein (% of energy)	12.80 ± 1.79	12.78 ± 1.61	0.94
Fat (% of energy)	33.06 ± 5.89	31.90 ± 5.95	0.20
Fiber (g/day)	29.73 ± 9.39	29.73 ± 8.56	0.99
Refine grains (g/day)	367.38 ± 151.38	385.84 ± 124.77	0.36
Fruits (g/day)	304.03 ± 130.81	374.87 ± 143.56	0.001
Legumes (g/day)	36.99 ± 20.82	40.37 ± 25.77	0.37
	Median (IQR)	**Median (IQR)**	
Nuts (g/day):	5.22 (13.27)	10.58 (13.50)	0.004
Vegetables (g/day)	315.81 (213.29)	323.27 (237.32)	0.81
Red meat (g/day)	13.19 (23.21)	11.85 (19.54)	0.37
Caffeine (mg/day)	89.06 (72.04)	47.14 (66.0)	0.01
DTAC by FRAP (mmol/day)	10.07 (3.88)	9.24 (3.83)	0.14
Qualitative variables	**n (%)**	**n (%)**	
Primiparous (yes)	16 (28.1)	41 (25.5)	0.70
Abortion history (yes)	12 (29.3)	46 (38.3)	0.29
Pregnancy interval (y)			
≤4	12 (29.3)	61 (50.8)	0.01
>4	29 (70.7)	59 (49.2)	
Oral contraceptive use (yes)	11 (19.3)	23 (14.3)	0.37
Smoking (present smoker)	1 (1.8)	1 (0.6)	0.45
Education level			0.80
Secondary school and less	25 (43.9)	75 (46.6)	
High school	23 (40.4)	66 (41.0)	
University	9 (15.8)	20 (12.4)	
Occupation (yes)	3 (5.3)	11 (6.8)	1.00
Previous preeclampsia history[b]	9 (22.0)	10 (8.3)	0.02
Family history of preeclampsia	11 (19.3)	17 (10.6)	0.09

*[a]: Student t-test or Mann–Whitney U test was used for quantitative variables; and Chi-square or fisher exact test was used for qualitative variables; **[b]:** Among the 161 (73.8%) women with a previous pregnancy; **MUAC**: Mid upper arm circumference; **DTAC**: Dietary total antioxidant capacity; **ORAC**: Oxygen radical absorbance capacity; **IQR**: interquartile range.*

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Table 2. General characteristics of participants across tertiles of dietary total antioxidant capasity.

Variable	Tertiles of DTAC by FRAP			P-value[a]	Tertiles of DTAC by ORAC			P-value[a]
	I	II	II		I	II	II	
	<8.31 (n = 67)	8.31-10.78 (n = 74)	>10.78 (n = 77)		<12.98 (n =79)	12.98-16.76 (n=72)	>16.76 (n=67)	
Age (y)	28.15 ± 6.92[b]	30.11 ± 6.64	29.42 ± 6.19	0.20	28.32 ± 6.54	29.72 ± 6.79	29.88 ± 6.41	0.27
Gestational age (weeks)	35.73 ± 4.19	36.04 ± 3.68	36.51 ± 3.24	0.54	36.11 ± 3.46	36.31 ± 3.77	35.90 ± 3.93	0.72
Pre pregnancy weight (kg)	64.66 ± 13.13	64.51 ± 12.71	66.37 ± 11.64	0.60	66.82 ± 13.31	64.56 ± 12.04	64.00 ± 11.81	0.34
Pre pregnancy BMI (kg/m^2)	25.24 ± 4.75	25.21 ± 4.76	25.14 ± 4.02	0.99	25.81 ± 4.66	25.21 ± 4.53	24.46 ± 4.18	0.19
Physical activity (Met-h/day)	28.82 ± 2.73	29.63 ± 3.77	30.03 ± 3.28	0.08	29.79 ± 3.44	29.32 ± 3.37	29.41 ± 3.18	0.66
Primiparous (yes)	26 (38.8)	16 (21.6)	15 (19.5)	0.01	23 (29.1)	19 (26.4)	15 (22.4)	0.65
Family history of preeclampsia (yes)	11 (16.4)[c]	7 (9.5)	10 (13.0)	0.46	16 (20.3)	5 (6.9)	7 (10.4)	0.04
Education level								
Secondary school and less	35 (52.2)	29 (39.2)	36 (46.8)	0.37	39 (49.4)	32 (44.4)	29 (43.3)	0.92
High school	25 (37.3)	36 (48.6)	28 (36.4)		29 (36.7)	31 (43.1)	29 (43.3)	
University	7 (10.4)	9 (12.2)	13 (16.9)		11 (13.9)	9 (12.5)	9 (13.4)	

[a]*: ANOVA-test or Kruskal-Wallis test was used for quantitative variables; Chi-square test was used for qualitative variables;* [b]*: Mean±SD;* [c]*: n (%);* ***DTAC****: Dietary total antioxidant capacity;* ***ORAC****: Oxygen radical absorbance capacity;* ***FRAP****: Ferric reducing antioxidant potential;* ***BMI****: Body mass index.*

Table 3. Dietary intake of participants across tertiles of dietary total antioxidan capacity.

Variable	Tertiles of DTAC by FRAP			P-value[a]	Tertiles of DTAC by ORAC			P-value[a]
	I	II	II		I	II	II	
Whole grains (g/day)	72.87 ± 92.04[b]	112.91 ± 105.93	133.23 ± 122.24	0.001	81.15 ± 100.10	107.61 ± 102.87	139.38 ± 122.57	<0.001
Refined grains (g/day)	379.48 ± 129.94	404.50 ± 138.43	359.77 ± 125.64	0.11	395.27 ± 129.40	387.23 ± 134.43	357.52 ± 131.63	0.20
Vegetables (g/day)	347.90 ± 162.44	352.70 ± 156.84	376.26 ± 195.91	0.74	293.47 ± 136.87	381.62 ± 185.34	413.74 ± 174.57	<0.001
Fruits (g/day)	289.76 ± 100.34	362.86 ± 139.01	408.03 ± 157.53	<0.001	252.22 ± 88.87	357.06 ± 98.27	478.36 ± 140.97	<0.001
Dairy products (g/day)	328.49 ± 196.54	332.33 ± 183.46	354.56 ± 213.38	0.69	259.55 ± 179.40	352.64 ± 157.66	418.04 ± 223.27	<0.001
Red meat (g/day)	17.42 ± 15.57	16.06 ± 13.37	17.48 ± 17.96	0.90	15.82 ± 15.01	14.52 ± 13.19	20.98 ± 18.30	0.08
Legumes (g/day)	34.49 ± 20.58	41.64 ± 22.03	41.76 ± 29.29	0.13	30.86 ± 19.42	39.52 ± 22.72	49.63 ± 28.11	<0.001
Nuts (g/day)	9.65 ± 8.04	11.67 ± 12.24	15.72 ± 15.29	0.04	6.00 ± 6.45	11.44 ± 8.08	21.24 ± 16.49	<0.001
Energy (kcal)	2254.22 ± 396.92	2542.05 ± 428.94	2758.20 ± 546.57	<0.001	2231.88 ± 419.58	2524.77 ± 427.08	2886.93 ± 450.74	<0.001
Carbohydrate (g/day)	316.92 ± 62.37	367.93 ± 70.25	395.48 ± 78.58	<0.001	315.25 ± 64.35	362.66 ± 63.66	416.37 ± 70.69	<0.001

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Protein (g/day)	71.93 ± 15.25	82.10 ± 15.99	86.84 ± 19.92	<0.001	69.82 ± 15.26	80.25 ± 14.67	93.84 ± 16.51	<0.001
Total fat (g/day)	82.53 ± 23.45	88.79 ± 23.54	100.33 ± 28.27	0.001	81.12 ± 24.48	90.04 ± 24.74	103.50 ± 24.89	<0.001
Polyunsaturated fatty acid (g/day)	21.58 ± 7.73	22.57 ± 7.94	24.99 ± 8.60	0.03	21.35 ± 7.96	23.22 ± 8.62	25.10 ± 7.68	0.01
Vitamin E (mg/day)	20.13 ± 10.00	19.55 ± 9.01	21.69 ± 10.53	0.51	18.82 ± 9.41	21.68 ± 10.51	21.16 ± 9.56	0.10
Vitamin C (mg/day)	117.80 ± 39.94	149.03 ± 50.40	161.29 ± 66.26	<0.001	109.67 ± 37.58	141.02 ± 42.45	186.91 ± 60.32	<0.001
Sodium (mg/day)	3747.58 ± 1225.95	3958.46 ± 1037.97	4191.57 ± 1524.35	0.07	3844.82 ± 1273.53	3862.17 ± 1377.84	4252.94 ± 1185.84	0.01
Caffein (mg/day)	33.82 ± 25.72	62.34 ± 28.53	135.64 ± 67.68	<0.001	71.06 ± 48.60	68.18 ± 54.88	101.51 ± 78.83	0.01
Fiber (g/day)	24.99 ± 6.68	30.56 ± 7.67	33.05 ± 9.60	<0.001	23.45 ± 5.61	29.84 ± 6.78	37.01 ± 8.05	<0.001
Partially hydrogenate vegetable oils (g/day)	9.59 ± 14.39	9.82 ± 17.13	11.47 ± 18.61	0.78	13.14 ± 17.72	8.86 ± 16.50	8.60 ± 15.94	0.08

[a]: *ANOVA-test or Kruskal-Wallis test was used for quantitative variables; Chi-square test was used for qualitative variables;* [b]: *Mean±SD;* ***DTAC****: Dietary total antioxidant capacity;* ***ORAC****: Oxygen radical absorbance capacity;* ***FRAP****: Ferric reducing antioxidant potential.*

Table 4. Odds ratios and 95% confidence intervals for the association between dietary total antioxidant capacity and preeclampsia.

Variable	I	II		III		P_{trend}
		OR	95% CI	OR	95% CI	
Tertiles of FRAP						
Crude	Reference	1.19	0.55-2.60	1.47	0.69-3.13	0.31
Model 1	Reference	1.23	0.55-2.77	1.62	0.71-3.71	0.24
Model 2	Reference	0.96	0.36-2.52	0.59	0.15-2.27	0.47
Tertiles of ORAC						
Crude	Reference	0.67	0.33-1.38	0.49	0.22-1.05	0.06
Model 1	Reference	0.58	0.27-1.24	0.36	0.14-0.92	0.03
Model 2	Reference	0.74	0.31-1.75	0.33	0.11-0.97	0.05

Model 1*: Adjusted for age and energy;* ***Model 2****: Further adjusted for gestational age, pre-pregnancy body mass index, primiparous, gravidity, abortion history, pregnancy interval, education, previous preeclampsia history, family history of preeclampsia, caffeine, gestational weight gain, status of physical activity, Oral contraceptive;* ***FRAP****: Ferric reducing ability of plasma;* ***ORAC****: Oxygen radical absorbance capacity.*

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Table 5 provides multivariable-adjusted odds ratios for the association between some dietary components and preeclampsia. The risk of preeclampsia was 70% lower among subjects in the highest tertile of vitamin C compared to the first tertile ($OR_{T3–T1}$=0.30, 95% CI:0.11–0.79). Furthermore, participants with moderate intake of vitamin A and beta carotene (second tertile) had respectively 61% (OR=0.39, 95% CI:0.17–0.88) and 62% (OR=0.38, 95% CI:0.17–0.86) lower risk of preeclampsia (these relationships existed only in the first adjusted models) than those in the lowest tertile.

Table 5. Odds ratios and 95% confidence intervals for the association between some dietary components and preeclampsia.

Variable	Tertials of components of dietary			P_{trend}
	I	II	III	
Vitamin A				
Model 1	Reference	0.39 (0.17-0.88)	0.46 (0.20-1.04)	0.05
Model 2	Reference	0.45 (0.18-1.13)	0.60 (0.24-1.48)	0.24
Vitamin E				
Model 1	Reference	1.11 (0.51-2.45)	1.39 (0.63-3.11)	0.40
Model 2	Reference	1.38 (0.55-3.42)	1.54 (0.60-3.90)	0.36
Vitamin C				
Model 1	Reference	0.36 (0.16-0.79)	0.33 (0.14-0.76)	0.01
Model 2	Reference	0.44 (0.17-1.08)	0.30 (0.11-0.79)	0.01
Folate				
Model 1	Reference	0.54 (0.23-1.25)	0.51 (0.18-1.40)	0.19
Model 2	Reference	0.50 (0.19-1.31)	0.42 (0.13-1.37)	0.14
Beta carotene				
Model 1	Reference	0.38 (0.17-0.86)	0.51 (0.23-1.10)	0.07
Model 2	Reference	0.42 (0.17-1.05)	0.54 (0.22-1.30)	0.14
Selenium				
Model 1	Reference	0.96 (0.40-2.27)	1.27 (0.49-3.29)	0.58
Model 2	Reference	0.85 (0.32-2.28)	1.40 (0.44-4.42)	0.52

Model 1*: Adjusted for age and energy;* ***Model 2****: Further adjusted for gestational age, pre-pregnancy body mass index, primiparous, gravidity, abortion history, pregnancy interval, education, previous preeclampsia history, family history of preeclampsia, caffeine, gestational weight gain, status of physical activity, Oral contraceptive.*

Discussion

The authors discovered a significant inverse association between ORAC and preeclampsia. Although this relationship was not significant regarding FRAP models, in analysis of dietary intake of single antioxidants, dietary intake of vitamin C was significantly associated with lower risk of preeclampsia. To the best of the authors' knowledge, this study was among the first investigations in the world (Sheikhi *et al.*, 2017).

Previous studies highlighted an inverse association between DTAC and metabolic syndrome, abdominal obesity, hypertension (Fateh *et al.*, 2022, Villaverde *et al.*, 2019), and type 2 diabetes in adults (Mancini *et al.*, 2018). Furthermore, dietary intake of individual antioxidants such as vitamin C, E, folate, and carotenoids were assessed in association to preeclampsia (Kang *et al.*, 2022, Saputra *et al.*, 2017, Wang *et al.*, 2015). As DTAC evaluates total dietary antioxidants from a wide range of food items, focusing on DTAC seems to be better than examining dietary antioxidants individually.

Some previous studies reported a beneficial effect of DTAC in association with non-alcoholic fatty liver disease (Sohouli *et al.*, 2020), polycystic ovary syndrome (Shoaibinobarian *et al.*, 2022), gestational diabetes mellitus (Daneshzad *et al.*, 2020), and hypertension (Fateh *et al.*, 2022, Villaverde *et al.*,

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2019); however, another study did not find any relationship between DTAC and pre-eclampsia (Sheikhi *et al.*, 2017). These discrepant results might be explained by different methods for measurement of DTAC, failure to control the effect of potential confounders, different study designs, subjects' health status, different dietary habits and cooking types, and different tools for assessment of dietary intake (FFQ and 24-hour dietary intake record).

In this study, the authors estimated ORAC mainly attributed to fruits (49%), vegetables (22%), and tea (8%), while FRAP was mainly attributed to tea (41%), fruits (26%), and vegetables (10%). Thus, the reverse association of DTAC and preeclampsia could be due to its healthy food components. A meta-analysis reported that high adherence to healthy dietary patterns reduced the risk of preeclampsia; this dietary pattern consisted of the consumption of vegetables, fruits, fish, and whole grains and a low intake of meat, processed foods, and sugar-sweetened foods (Traore *et al.*, 2021). On the other hand, following western dietary patterns was related to the odds of preeclampsia; and simple sugars, refined grains, and saturated fatty acids were the main components of this dietary pattern related to oxidative stress, insulin resistance, and metabolic syndrome (Abbasi *et al.*, 2021). Moreover, a case-control study of pregnant women found that participants in the highest quartile of dietary approach to stop hypertension (DASH) had 47% less risk of preeclampsia compared with the lowest quartile ($OR_{Q4–Q1}$=0.53, 95% CI: 0.36–0.78, P_{trend}=0.001); whole grains, fruits, vegetables, legumes, nuts, and dairy products were the main components of DASH diet (Cao *et al.*, 2020). A prospective cohort study conducted in Norway on 32933 nulliparous women demonstrated that added sugar and sugar-sweetened beverages contributed significantly to the risk of preeclampsia; on the contrary, intake of food items containing natural sugars like fresh and dried fruit decreased risk of preeclampsia (Borgen *et al.*, 2012). In another study conducted in the USA on 1538 pregnant women, findings showed that dietary fiber intake reduced the probability of preeclampsia. Besides, their results indicated that dietary fiber reduced triglyceride concentration and increased high-density lipoprotein cholesterol concentration, which might lead to attenuation of dyslipidemia, an important clinical feature of preeclampsia (Qiu *et al.*, 2008). Thus, it seems that healthy diets with similar compositions can prevent preeclampsia.

Oxidative stress and inflammatory situation are attributed to impaired placenta implantation that result in an imbalance between pro-inflammatory and regulatory cytokines. Consumption of fruits, vegetables, and food items with a low dietary inflammatory index (DII) were associated with lower levels of inflammatory biomarkers such as interleukin (IL)-2, IL-4, and transforming growth factor beta (TGF-β). Moreover, increased antioxidants concentration in serum and placenta can prevent hypoperfusion, and might have a protective effect against preeclampsia development (Liu *et al.*, 2022). In this study, the dietary intake of fruits and nuts, as anti-inflammatory and anti-oxidant food items, were higher in controls compared to cases (P value < 0.05). Besides, subjects in the highest tertile of ORAC consumed more whole grains, vegetables, fruits, dairy products, legumes, and nuts compared to the lowest tertile.

Vitamin C, beta-carotene, and polyphenols are the most important items in calculation of DTAC. Their presence in foods as exogenous antioxidants can reduce free radical production (Liu *et al.*, 2022). The results showed that participants in the highest tertile of vitamin C intake had 70% fewer odds of preeclampsia ($OR_{T3–T1}$ = 0.30, 95% CI: 0.11–0.79, P_{trend}= 0.01) in comparison to the lowest tertile of it. This finding was in line with previous studies, which reported the beneficial effects of healthy dietary patterns, containing main sources of vitamin C in reducing preeclampsia risk (Cao *et al.*, 2020).

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Like other studies, this study had its strengths and limitations. Some strengths of the present study were using a validated and reliable questionnaire that specified for the Iranian population the total antioxidant capacity of the whole diet instead of single antioxidants beside some single components, controlling for a wide range of confounders, and matching controls to cases for two potential confounders, age, and gestational age.

This study also has some limitations that must be considered. Case-control design is susceptible to selection bias. Hence, the results cannot be extrapolated to society. Additionally, the FFQ questionnaire was based on memory; consequently, recall bias and measurement error were inevitable. All methods that measure DTAC mainly present in vitro potential antioxidant activity of food items; the bioavailability of these antioxidants might be variable in vivo (Carlsen *et al.*, 2010). Furthermore, the majority of these values are reported for raw items that might have various values compared with cooked items or in combination with other foods (Carlsen *et al.*, 2010, Haytowitz and Bhagwat, 2010). The database for measurement of ORAC and FRAP was based on the previously published database, not on Iranian food items. For some food items with no specific score, the authors considered the mean of similar food items for computing total scores, which might affect the findings.

In FRAP method, DTAC might be underestimated compared to the actual value because this assay cannot measure some antioxidants such as glutathione and small molecular weight antioxidant (Carlsen *et al.*, 2010). Although the authors assessed supplement intake, they did not find significant difference between the two groups. Finally, they could not evaluate any antioxidant or inflammatory biomarkers to strengthen our findings.

Conclusion

Data showed that pregnant women with the highest tertile of ORAC and vitamin C intake are at lower risk of preeclampsia. Prospective studies are needed to confirm the protective effects of dietary anti-oxidants on preeclampsia incidence.

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Authors' contributions

Drafting of the manuscript was done by M Taherkhani and F Montazerifar, study concept and design by M Taherkhani, F Montazerifar and A Hekmatdoost, statistical analysis by B Rashidkhani and A Payandeh, data collection by M Taherkhani, Interpretation of data by M Taherkhani, F Montazerifar and A Hekmatdoost, and critical revision of the manuscript by M Taherkhani, F Montazerifar, A Hekmatdoost and M Karajibani. All authors have read and approved this article.

Conflict of Interest

The authors declared no conflict of interests.

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