



## Associations of macro and micronutrients and antioxidants intakes with preeclampsia: A case-control study in Jordanian pregnant women

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### KEYWORDS

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**Abstract** *Background and objectives:* A study was conducted to evaluate whether preeclampsia in pregnant women is associated with dietary factors and antioxidant intake (vitamin C, vitamin E, vitamin A, and selenium).

*Methods and results:* In this case–control study, a group of 79 pregnant Jordanian women (36 preeclamptic pregnant women and 43 healthy pregnant women aged 18–45 years with a gestational age  $\geq 20$ th week of pregnancy) were recruited from the obstetrics and gynecology clinics at Royal Medical Services, King Hussein Medical Center, Amman, Jordan. Information about socio-demographics, anthropometric measurements, biochemical measurements, nutritional intake, and dietary habits was collected through a structured interview. Three 24-hour dietary records were also made. Data were analyzed using Statistical Package for the Social Sciences (SPSS), and dietary intake was analyzed using ESHA software. Prepregnancy BMI, age, multiple pregnancies, energy intake, beta-carotene, vitamin C, and sodium showed significant difference between preeclamptic pregnant women and healthy pregnant women. The odds ratio (OR) and the corresponding 95% confidence interval (CI) show that a strong association with preeclampsia exists for the intake of fat (OR = 6.40, 95% CI: 1.85–22.17) and saturated fat (OR = 3.35, 95% CI: 1.0–11.54). Inverse associations with preeclampsia were found for fruit intake (OR = 0.16, 95% CI: 0.47–0.55) and olive oil intake (OR = 0.20, 95% CI: 0.05–0.78).

*Conclusion:* In this case–control study in Jordanian pregnant women, preeclampsia was associated with a high intake of fat, saturated fat, and sodium and a low intake of fruits, fiber, vitamin C, B-carotene, and olive oil.

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### Introduction

Hypertension is not unusual during pregnancy. Usually before delivery and at some point, pregnant women may have higher than normal blood pressure values [1]. Preeclampsia, observed in 2%–8% of pregnancies, can be defined as hypertension accompanied by proteinuria, which usually occurs during the second half of pregnancy [1].

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Many years ago, high maternal morbidity and mortality in middle- and low-income countries was highlighted as an issue that needs more attention. Nevertheless, most maternal deaths can be avoided with appropriate maternity services and emergency obstetric care. Many of the root causes of maternal morbidity and mortality are related to poverty and the inequity of opportunities for women [1]. That is why the health of mothers and their fetus has changed from a marital concern to public health urgency.

The diagnosis of preeclampsia involves both proteinuria and pregnancy-induced hypertension, according to the criteria of the American College of Obstetricians and Gynecologists [2]. Usually, preeclampsia starts after 20 weeks of gestation and is characterized by high blood pressure (140/90 mmHg) and proteinuria, that is, 300 mg or more of protein in a 24-hour urine specimen collected from previously nonproteinuric, normotensive women [3].

The pathophysiology of preeclampsia during pregnancy is not yet clear, but many pathophysiological elements may exist, such as inflammation, dyslipidemia, cytokine production [4], oxidative stress [5], and elevated homocysteine. In addition, an imbalance between prostacyclin and thromboxane is involved in the etiology of preeclampsia [4]. Many years ago, the most common pathogenetic mechanism of preeclampsia was the toxemia theory, which suggests that the affected placenta produces substances leading to the maternal syndrome of preeclampsia [5]; therefore, it is important to understand that the prime reason for preeclampsia is abnormal placentation. Two theories regarding the occurrence of preeclampsia appear to be interlinked: an immunological theory and a genetic theory [6].

Preeclampsia can cause fetal growth restriction, preterm delivery, and maternal and infant morbidity and mortality [7], as well as an increased risk of having infants who are born prematurely with a high risk of complications [6]. In a preeclamptic mother, the chances of cardiovascular diseases such as ischemic heart disease, chronic hypertension, and stroke increase later in life [8], while children born from preeclamptic pregnancies have an increased risk of metabolic syndrome, coronary heart disease, and stroke in the adult life [9]. Further, they are at a higher risk for a variety of disorders such as endocrine and nutritional disorders throughout adolescence [10].

Disparate studies have investigated the association between the risk of preeclampsia and maternal oxidative stress. In preeclampsia, there is an imbalance between antioxidant defenses and pro-oxidant production [7], but it remains unknown whether an imbalance between antioxidants and prooxidants (oxidative stress) leads to preeclampsia or occurs after preeclampsia [4]. It has been reported that an imbalance between the antioxidant defense system and free radical production may play a major role in the pathogenesis of preeclampsia [4,5]. Furthermore, several experimental studies have reported an association between the high intake of dietary antioxidants (e.g., vitamin E, vitamin C, copper, and selenium) and low levels of oxidative stress [4]. Many studies have approved that the maternal diet is significantly associated with the

development of preeclampsia. Scholl et al. [4] found that diets rich in polyunsaturated fats could lead to oxidative stress associated with preeclampsia.

A meta-analysis showed that oral supplementation with antioxidants did not show effects in the prevention of preeclampsia [11]. Therefore, this study was designed to evaluate whether low intake of dietary antioxidants (vitamin C, vitamin E, vitamin A, and selenium) is a risk factor of preeclampsia in pregnant women. Moreover, we aimed to identify whether the daily intake of dietary factors such as macronutrients and micronutrients could contribute to the development of preeclampsia to design an effective educational program, in cooperation with concerned stakeholders who target women at risk of preeclampsia before conception. We hypothesized that low intake of antioxidants and high intake of saturated fats are associated with preeclampsia in pregnant women.

## Methods

### *Institutional review board*

Approval of the Institutional Review Board (IRB), Medical School of Jordan University of Science and Technology, Kind Abdullah University Hospital, Irbid, was obtained first before the study was initiated.

### *Participants*

Among 101 subjects, 88 of them accepted to participate in our study and were included and interviewed by the researcher for the study purpose (40 preeclamptic pregnant women and 48 healthy pregnant women). A group of 79 Jordanian pregnant women (36 preeclamptic pregnant women and 43 healthy pregnant women, aged 18–45 years, with a gestational age  $\geq$ 20th week of pregnancy) met the inclusion criteria, and they were recruited from the obstetrics and gynecology clinics. All women were informed about the study while they were waiting for their appointments in the reception (waiting room). Information about socio-demographics, anthropometric measurements, biochemical measurements, nutritional intake, and dietary habits was collected through a structured interview.

### *Procedure*

This was a case–control study conducted from December 2017 to April 2018 at prenatal clinics and obstetrics and gynecology clinics. All normal pregnant women who visited obstetrics and gynecology clinics and were of the reproductive age (18–45 years) after the 20th week of pregnancy, previously normotensive and nonproteinuric, were included in the study as controls. Women who had certain medical conditions including type 1 diabetes, type 2 diabetes, dyslipidemia, cardiovascular disease, thyroid disease, and celiac disease, and those who were previously diagnosed with preeclampsia were excluded from the study. In addition, women were excluded if they did not fill

out the consent form, if they were below 18 years, and if they had conditions that require special diets (9 women were excluded). Three of the excluded women were recruited in the control group, and eventually, they developed preeclampsia later on during their pregnancy and they were included again in the case group after diagnosis.

All pregnant women were asked to visit the clinic for a follow-up of their blood pressure measurements by nurses in a record sheet; after that, the expectant mother was seen by the gynecologist. Laboratory tests were ordered using the computer program HAKEEM, wherein physicians, pharmacists, medical technologists, and other clinicians were able to electronically access the patients' medical records from participating health facilities simply by entering the patient's national ID number.

Cases were selected after high blood pressure was confirmed by systolic blood pressure measurements  $>140$  mmHg or diastolic blood pressure  $>90$  mmHg on two different occasions with an interval of 4 or more hours accompanied by a protein concentration of  $+1$ . Approximately all preeclamptic women were admitted to the department of obstetrics in the hospital and remained in the hospital under good medical management. Preeclamptic pregnant women, in their last weeks of pregnancy, were referred to the delivery department. The blood pressure for all women was measured in the sitting position after a ten-minute rest period using a wall-mounted blood pressure device.

### **Ethical considerations**

All participants were informed about the study and asked to participate. The objectives, benefits, and the protocol of the study were briefly explained by the main researcher. After agreement, they were asked to sign a consent form. This protocol met the criteria set by the Institutional Review Board for the Protection of Human Research Participants Committee. The approval of Royal Medical Services was also taken to facilitate the researcher's tasks such as filling out the questionnaire and interviewing the participants.

### **Interview**

All participants answered to questions given in a questionnaire through a structured interview, which was made up of five parts. The questionnaire was circulated to three faculty members, who are experts in this field, revised, and modified the questions to guarantee that the questions are clear, appropriate, and intended to measure the suggested variables and parameters. The questionnaire was filled out by the main researcher through a face-to-face interview. It was composed of the following parts:

(1) Socio-demographic information about the pregnant woman's education level, occupation, number of current pregnancy, number of abortions, number of children she already has, and whether she suffered from any health problems during her previous pregnancies, if any. (2) Anthropometric measurements consisting of current

weight, weight before pregnancy, and height. (3) Measurements and medical data were also recorded to perform the selection criteria. (4) Information about the general nutritional intake and dietary habits such as allergies from food items, frequency of the consumption of fast food in a week, number of meals and snacks, and many other questions that may describe the dietary behavior.

**Anthropometric Measurements.** Anthropometric measurements were recorded by following the World Health Organization (WHO) procedure [12]. Current weight was measured and recorded in kilograms using an advanced Tanita scale BC-730 after it was checked for zero-balance before each measurement was taken. Weight was recorded to the nearest 0.1 kg, while the height was measured and recorded in meters from the top of the head to the sole of feet; the measurement was recorded to the nearest 0.5 cm [13].

### **Body mass index (BMI)**

Prepregnancy weight and height data were obtained from the patients' records to calculate body mass index according to Quetelet's formula:  $BMI = \text{weight (kg)}/\text{height (meter)}^2$  [12]. The range for normal weight is  $> 18.5$ – $24.9$  kg/m<sup>2</sup>, overweight  $25$ – $29.9$  kg/m<sup>2</sup>, obesity grade I  $> 30$ – $34.9$  kg/m<sup>2</sup>, obesity grade II  $35$ – $35.9$  kg/m<sup>2</sup>, and obesity grade III  $\geq 40$  kg/m<sup>2</sup> [12].

### **Dietary intake**

In the first day of recruiting the subjects and data collection ( $21.4 \pm 3$  weeks of gestation), after the researcher explained the importance of recording accuracy, patients were given a three-day dietary record form (two weekdays and one weekend day) to be filled out and returned to the researcher in the next appointment. Participants were instructed and educated about quantities, cooking methods, adding seasoning, oil amount, spices, and time of eating, which were divided into a number of meals and snacks. Food, beverage models, and pictures were used as a direct demonstration to ensure comprehension and participant compliance in writing the records and to clarify the size of the serving, such as a fruit serving, rice, bread, and meat. A call or text message was sent daily to each participant to remind them to record the intake of all food items. All of them were told that they could send their food record forms through WhatsApp to the researcher, as it was more convenient for all subjects. Those records were entered into nutrition analysis software (ESHA Food Processor SQL, version 10.1.1; ESHA, Salem, OR, USA), with additional data of foods consumed entered in for further analysis [14] of daily total caloric intake, macronutrient intake, and micronutrient intake. We used a modified version of ESHA that contained dishes most likely to be popular among the population. We modified ESHA by including an Arabic food composition table based on the most common dishes in Lebanon [14].

**Biochemical Measurements.** A urine sample was taken from each participant to measure protein concentration.

The normal ranges for protein in urine are nil or trace. Blood pressure was measured with an instrument called a sphygmomanometer. Blood pressure is measured in millimeters of mercury (mmHg). Diagnosis of high blood pressure was confirmed if systolic blood pressure was >140 mmHg or diastolic blood pressure >90 mmHg on two different occasions, with an interval of 4 or more hours.

### Statistical analysis

A sample size of 38 women in each group was required for a power of 0.8 according to the Browner et al. approach [15]. The level of significance between cases and controls with regard to saturated fat and antioxidant concentration was set at 5% ( $\alpha = 0.05$ ) with 80% power ( $\beta = 0.2$ ) 2 times, once for saturated fat and the second for beta-carotene. Accordingly, the calculated sample size showed that approximately 37 subjects were needed for each group in the first time and 32 subjects were needed in the second time to detect a difference between the 2 groups. To consider the dropout of the study participants and to increase the power of the analysis, the number of participants was increased to 101 in both groups. SPSS (IBM version 20 for Windows, 2011, IBM-SPSS Inc.) was used for data processing and data analysis. The significance level was set at  $P$  value < 0.05. For descriptive statistics, standard deviation of the mean and percentages were used. A chi-square test was used for categorical variables to detect the differences in socio-demographics, dietary intake, lifestyle, and clinical parameters between cases and controls. The standard deviation of the mean was calculated for energy and total nutrient intake from the average of the three 24-hour records.

## Results

### General characteristics of participants

Table 1 describes the demographics, clinical characteristics, and study-related variables of the study sample. The mean values of age and gestational weeks among cases and controls were  $31.2 \pm 0.98$  years and  $31.1 \pm 0.73$  weeks and  $28 \pm 0.75$  years and  $29 \pm 0.56$  weeks, respectively. Sixty-one percent of women with preeclampsia were older than 30 years, while only 25.6% of the control women were older than 30 years (Table 1). The average BMI was  $24.8 \pm 4.5$  kg/m<sup>2</sup> and  $26.7 \pm 4.2$  kg/m<sup>2</sup> for controls and cases, respectively. Fifty-three percent of cases were overweight, whereas 29% of the controls were overweight. Approximately 72% of preeclamptic women had more than three pregnancies compared with only 39.6% of the control women ( $P = 0.009$ ). Approximately 80.6% of preeclamptic pregnant women and 48.8% of healthy pregnant women had children from previous pregnancies. Fifty percent of preeclamptic pregnant women compared with 29% of healthy pregnant women had a family history of preeclampsia. A previous twin pregnancy was present in 19.4% of cases and 4.7% of the controls (Table 1).

**Table 1** Demographics, clinical characteristics, and study-related variables of the study population (%).

Characteristics	Cases (n = 36)	Controls (n = 43)	P*
Age (years)	31.2 ± 0.98	28.0 ± 0.75	0.009
Gestational age (weeks)	31.1 ± 0.73	29.0 ± 0.56	0.746
Prepregnancy Body Mass Index (kg/m <sup>2</sup> )	26.7 ± 0.70	24.8 ± 0.69	0.064
Age (years)			
>30	22 (61.1)	11 (25.6)	0.001
≤30	14 (38.9)	32 (74.4)	
Body Mass Index (kg/m <sup>2</sup> )**			
Obese	7 (19.4)	6 (14.3)	0.030
Overweight	19 (52.8)	12 (28.6)	
Normal	10 (27.8)	24 (57.1)	
The number of current pregnancy			
1st	6 (16.7)	20 (46.5)	0.009
2nd	4 (11.1)	6 (14.0)	
3rd	9 (25)	10 (23.3)	
4th or more	17 (47.2)	7 (16.3)	
Number of miscarriages			
Once	8 (22.2)	8 (18.6)	0.506
More than once	5 (13.9)	3 (7)	
No abortions	23 (63.9)	32 (74.4)	
Have children before			
Yes	29 (80.6)	21 (48.8)	0.004
No	7 (14.7)	22 (51.2)	
Number of children			
1-2	14 (48.3)	14 (66.7)	0.384
3-4	9 (31)	5 (23.8)	
More than 4	6 (20.7)	2 (9.5)	
Family history of preeclampsia			
Yes	18 (50)	9 (20.9)	0.007
No	18 (50)	34 (79.1)	
A previous twin pregnancy			
Yes	7 (19.4)	2 (4.7)	0.039
No	29 (80.6)	41 (95.3)	
Educational Level			
Basic or below	6 (16.7)	3 (7)	0.625
Preparatory or secondary	14 (38.9)	16 (37.2)	
Diploma	5 (13.9)	7 (16.3)	
Bachelor	11 (30.6)	15 (34.9)	
Postgraduate	0	2 (4.6)	
Occupation			
Housewife	26 (72.2)	30 (69.8)	0.821
Government employee	8 (22.2)	9 (20.9)	
Private work	2 (5.6)	4 (9.3)	
Smoking			
Yes	8 (22.2)	6 (14)	0.338
No	28 (77.8)	37 (86)	
Blood pressure measurement in the current visit (mmHg)			
Yes (>140/>90)	35 (97.2)	3 (7)	0.001
Normal	1 (2.8)	40 (93)	
% Protein in urine			
Nil	1 (2.8)	42 (97.7)	0.001
+1	16 (44.4)	0	
+2	14 (38.9)	1 (2.3)	
+3	5 (13.9)	0	

Note: Values presented as mean ± SD or frequencies and percentages, n (%).

\*Significant at  $P < 0.05$ .

\*\*Body mass index classification: normal weight (BMI 18.5–24.9 kg/m<sup>2</sup>), overweight (BMI 25–29.9 kg/m<sup>2</sup>), and obese (BMI >30 kg/m<sup>2</sup>).

### Diet and eating habits

As indicated in Table 2, the majority of both cases and controls did not visit a dietitian in their life. Approximately 30.6% of cases compared to 41.9% of the controls followed a specific diet regimen at least once in their lives. For the variables the number of basic meals eaten daily, the main meal, number of snacks, type of snack, and daily water consumption, there were no apparent differences between the cases and controls.

### Number of servings

Regarding daily intake from food groups and major food items, our results indicated a higher intake of processed meat (1 oz  $\pm$  0.15) and a lower intake of olive oil (2.4 tsp  $\pm$  0.32) among preeclamptic women than among healthy women (0.50 oz  $\pm$  0.12 and 4 tsp  $\pm$  0.37) (Table 3).

### Energy and macronutrient intake

The daily average dietary energy and macronutrient intake are presented in Table 4. The mean intake of energy, fat, saturated fat, and omega-6 in women with preeclampsia was 2782 kcal  $\pm$  297.1, 108 g  $\pm$  6.85, 24 g  $\pm$  1.53, and

**Table 3** Number of servings consumed by the study population.

Food groups/food items	Cases (n = 36)	Controls (n = 43)	P*
Meat (ounce/d)	2.0 $\pm$ 0.33	2.1 $\pm$ 0.28	0.94
Vegetables (1 cup/d)	2.1 $\pm$ 0.28	2.0 $\pm$ 0.19	0.64
Fruit (1 medium/d)	1.3 $\pm$ 0.17	1.5 $\pm$ 0.18	0.29
Milk (1 cup/d)	0.7 $\pm$ 0.15	0.7 $\pm$ 0.13	0.94
Cereals and legumes (1/3 cup/d)	2.0 $\pm$ 0.29	1.6 $\pm$ 0.27	0.31
Bread (serving/d)	3.2 $\pm$ 0.9	3.5 $\pm$ 0.82	0.21
Fish (servings/wk)	0.5 $\pm$ 0.15	0.7 $\pm$ 0.21	0.09
Nuts (15 g/d)	2.9 $\pm$ 0.56	2.5 $\pm$ 0.47	0.60
Processed meat (1 slice/d)	1.0 $\pm$ 0.15	0.5 $\pm$ 0.12	0.02
Ready stock (1 cup/d)	2.2 $\pm$ 0.08	2.3 $\pm$ 0.12	0.24
Olive oil (1 tsp/d)	2.4 $\pm$ 0.32	4.0 $\pm$ 0.37	0.00
Frying oil (1 tsp/d)	8.7 $\pm$ 0.76	7.0 $\pm$ 0.52	0.06

Values represented as mean  $\pm$  SD.

\*Significant at  $P < 0.05$ .

6.8 g  $\pm$  1.17, respectively, compared to that in healthy pregnant women, i.e., 2203 kcal  $\pm$  68.8, 87.7 g  $\pm$  4.21, 20 g  $\pm$  1.13, and 4 g  $\pm$  0.49, respectively, ( $P < 0.05$ ). On the other hand, fiber intake was lower (18.6 g  $\pm$  1.10) in cases than in controls (22.5  $\pm$  1.29). There were no significant differences between subjects in the intake of other macronutrients mentioned in the same table.

### Micronutrient intake

Table 5 displays the results of the micronutrient intake of cases and controls. It was observed that pregnant women with preeclampsia had lower beta-carotene and vitamin C intake (924 mcg  $\pm$  162.24 and 79.5 mg  $\pm$  7.88,  $P < 0.05$ , respectively) than healthy pregnant women (1834 mcg  $\pm$  388.95 and 136 mg  $\pm$  12.26 ( $P < 0.05$ ), respectively). In contrast, preeclamptic pregnant women had a

**Table 2** Diet and eating habits of the study population, n (%).

Eating Habits	Cases (n = 36)	Controls (n = 43)	P*
Visited a nutritionist before			
Yes	7 (19.4)	7 (16.3)	0.714
No	29 (80.6)	36 (83.7)	
Followed a specific diet regimen			
Yes	11 (30.6)	18 (41.9)	0.299
No	25 (69.4)	25 (58.1)	
Weight lost by this diet regimen			
> 2 kg/month	6 (54.5)	14 (77.8)	0.189
$\leq$ 2 kg/month	5 (45.5)	4 (22.2)	
Number of basic meals/day			
1 meal	2 (5.6)	2 (4.7)	0.847
2 meals	17 (47.2)	19 (44.2)	
3 meals	12 (33.3)	18 (41.9)	
>3 meals	5 (13.9)	4 (9.3)	
The main meal			
Breakfast	5 (13.9)	4 (9.3)	0.762
Lunch	21 (58.3)	28 (65.1)	
Dinner	10 (27.8)	11 (25.6)	
Number of snacks			
No snack	3 (8.3)	1 (2.3)	0.575
1	11 (30.6)	11 (25.6)	
2-3	12 (33.3)	18 (41.9)	
>3	10 (27.8)	13 (30.2)	
Type of snack			
Salty Snacks	2 (5.7)	4 (9.5)	0.063
Sweets	7 (20)	13 (31)	
Vegetables and Fruits	7 (20)	14 (33.3)	
Salty Snacks and Sweets	7 (20)	1 (2.4)	
Mixed snacks	12 (34.3)	10 (23.8)	
Daily water consumption			
1-3 cups	8 (22.2)	8 (18.6)	0.862
4-6 cups	10 (27.8)	15 (34.9)	
7 cups or more	18 (50.0)	18 (46.6)	

\*Significant at  $P < 0.05$ .

**Table 4** Daily energy and intake of macronutrients in the study population.

Energy and macronutrients	Cases (n = 36)	Controls (n = 43)	P*
Energy (kcal)	2782 $\pm$ 297	2203 $\pm$ 68	0.04
% of Protein	13 $\pm$ 0.57	14 $\pm$ 0.42	0.29
% of Carbohydrate	49 $\pm$ 1.89	51 $\pm$ 1.25	0.46
% of Fat	37 $\pm$ 1.75	35 $\pm$ 1.32	0.34
Protein (g)	87 $\pm$ 4.47	78 $\pm$ 3	0.12
Carbohydrate (g)	376 $\pm$ 76.06	283 $\pm$ 11.94	0.19
Fiber (g)	18 $\pm$ 1.1	22 $\pm$ 1.29	0.02
Sugar (g)	174 $\pm$ 74.76	86 $\pm$ 5.95	0.20
Fat (g)	108 $\pm$ 6.85	87 $\pm$ 4.21	0.01
Saturated Fat (g)	24 $\pm$ 1.53	20 $\pm$ 1.13	0.03
Monounsaturated Fat (g)	31 $\pm$ 3.36	24 $\pm$ 2.48	0.08
Polyunsaturated Fat (g)	13 $\pm$ 1.49	10 $\pm$ 0.9	0.06
Trans Fat (g)	3 $\pm$ 0.8	2 $\pm$ 0.55	0.45
Cholesterol (mg)	212 $\pm$ 18.05	199 $\pm$ 20.4	0.62
Omega 3 (g)	0.5 $\pm$ 0.07	0.3 $\pm$ 0.04	0.10
Omega 6 (g)	6.8 $\pm$ 1.17	4.0 $\pm$ 0.49	0.02
Omega 3:Omega 6	0.12 $\pm$ 0.01	0.11 $\pm$ 0.01	0.60

Values represented as mean  $\pm$  SD.

\*Significant at  $P < 0.05$ .

**Table 5** Comparison of the daily intake of micronutrients in the study population.

Micronutrients	Cases (n = 36)	Controls (n = 43)	P*
Vitamin A-IU (IU)	4488 ± 870.61	5817 ± 1009.4	0.332
Carotene (RE)	340 ± 83.88	467 ± 89.27	0.308
Retinol (RE)	144 ± 72.23	236 ± 111.14	0.511
Beta-Carotene (mcg)	924 ± 162.24	1834 ± 388.95	0.047
Vitamin B1 (mg)	1.3 ± 0.1	1.3 ± 0.08	0.883
Vitamin B2 (mg)	1.3 ± 0.11	1.2 ± 0.08	0.477
Vitamin B3 (mg)	17 ± 1.84	16 ± 0.88	0.487
Vitamin B3-NE (mg)	23.5 ± 2.39	22.2 ± 1.17	0.610
Vitamin B6 (mg)	0.86 ± 0.09	0.98 ± 0.08	0.327
Vitamin B12 (mcg)	2.1 ± 0.39	2.5 ± 0.53	0.602
Vitamin C (mg)	79 ± 7.88	136 ± 12.26	0.001
Vitamin D (mcg)	0.6 ± 0.16	0.8 ± 0.18	0.534
Vitamin E (mg)	3.2 ± 0.42	3.3 ± 0.36	0.835
Folate (mcg)	323 ± 24.89	360 ± 27.56	0.325
Vitamin K (mcg)	71 ± 14.46	94 ± 19.94	0.363
Iron (mg)	14 ± 0.93	14 ± 0.79	0.786
Magnesium (mg)	196 ± 21.18	174 ± 10.31	0.337
Selenium (mcg)	54 ± 5.16	57 ± 4.4	0.638
Sodium (mg)	3068 ± 235.95	2444 ± 129.64	0.018
Zinc (mg)	6.6 ± 0.55	6.2 ± 0.45	0.585
Lutein and Zeaxanthin (mcg)	638 ± 128.32	1144 ± 393.66	0.260
Lycopene (mcg)	311 ± 131.11	1029 ± 468.73	0.176

Values represented as mean ± SD.

\*Significant at  $P < 0.05$ .

higher sodium intake ( $3068 \text{ mg} \pm 235.95$ ,  $P < 0.05$ ) than healthy pregnant women ( $2444 \text{ mg} \pm 129.64$ ). There were no statistically significant differences among the participants in the other micronutrients listed in the same table.

Table 6 shows that there is a strong association between the intake of fat and saturated fat with preeclampsia (OR = 6.40, 95% CI: 1.85–22.17, above the mean,  $P = 0.00$ ; OR = 3.35, 95% CI: 1.0–11.54 above the mean,  $P = 0.03$ , respectively). On the other hand, fruit intake (OR = 0.16, 95% CI: 0.47–0.55, above the mean  $P = 0.00$ ) and olive oil intake (OR = 0.20, 95% CI: 0.05–0.78 above the mean,

$P = 0.00$ ) were found to be associated with the development of preeclampsia.

Table 7 demonstrates the number and percentage of study population meeting or not meeting their RDA for many dietary elements. The majority (70%) of the cases did not meet the RDA of the total calories, which was approximately  $2740 \pm 200 \text{ kcal}$  (either more or less), while approximately one third of the control group did not meet their RDA. However, the majority (83%) of the cases met their requirements of omega 6 when compared to the controls (16%). Vitamin C intake was close to the RDA in almost 31% of the cases when compared to 67% of the controls. Finally, only 9% of women in the case group met the recommended servings of fruits, which is 3 servings  $\pm 1$ , when compared to those in the control group (91%) ( $P \leq 0.05$ ).

## Discussion

The aims of this study were to evaluate whether dietary antioxidant intake (vitamin C, vitamin E, vitamin A, and selenium) was associated with preeclampsia in pregnant women and to identify dietary factors such as daily intake of macronutrients and micronutrients that could contribute to the development of preeclampsia; therefore, the main findings of this study can be summarized as follows. The diagnosis of preeclampsia was associated with many maternal and dietary risk factors. Obesity, being pregnant with twins, age, number of current pregnancy, and family history were all maternal factors.

The findings of this study also indicated many dietary factors that are associated with preeclampsia in the study sample. On the one hand, the consumption of processed meat, fat, saturated fat, sodium, and omega 6 was associated with preeclampsia. On the other hand, a low intake of olive oil, fiber, beta-carotene, and vitamin C was associated with preeclampsia.

**Table 6** Adjusted ORs and CIs of dietary factors and preeclampsia risk.

Variables	Number of Cases	Number of Controls	OR (95% CI)*	P**
Age (years)				
≤30	14	32	1	0.001
>30	22	11	2.9 (0.93–9.0)	
BMI (kg/m <sup>2</sup> )				
Nonobese	10	24	1	0.009
Obese	26	18	2.0 (0.67–6.3)	
Number of Current Pregnancy				
1st	6	20	1	0.001
2nd	4	6	1.92 (0.31–11.9)	
3rd	9	10	2.7 (0.57–12.7)	
More than that	17	7	5.3 (0.87–32.0)	
Previous twin pregnancy				
No	29	41	1	0.04
Yes	7	2	2.27 (0.33–15.55)	
Family history of preeclampsia				
No	18	34	1	0.006
Yes	18	9	3.87 (1.20–12.32)	
Less than 5 (Bad feeling)	29	13	8.48 (2.44–29.50)	

\* OR adjusted for energy, age, BMI, # of current pregnancy, family history, and smoking.

\*\* Significant at  $P < 0.05$ .

**Table 7** Number and percentage of subjects meeting the Recommended Dietary Allowance in the study population.

Variables	Cases (n = 36) n (%)	Controls (n = 43) n (%)	Total	P*
Calorie (kcal)				0.019
Meet RDA	24 (38.7)	38 (61.3)	62 (100)	
Do not meet RDA	12 (70.6)	5 (29.4)	17 (100)	
Fat %				0.351
Meet RDA	13 (39.4)	20 (60.6)	33 (100)	
Do not meet RDA	23 (50.0)	23 (50.0)	46 (100)	
Fiber (g)				0.414
Meet RDA	5 (35.7)	9 (64.3)	14 (100)	
Do not meet RDA	31 (47.7)	34 (52.3)	65 (100)	
Omega 6 (g)				0.053
Meet RDA	5 (83.3)	1 (16.7)	6 (100)	
Do not meet RDA	31 (42.5)	42 (57.5)	73 (100)	
Beta-Carotene (mcg)				0.111
Meet RDA	24 (53.3)	21 (46.7)	45 (100)	
Do not meet RDA	12 (35.3)	22 (64.7)	34 (100)	
Vitamin C (mg)				0.003
Meet RDA	14 (31.1)	31 (68.9)	45 (100)	
Do not meet RDA	22 (64.7)	12 (35.3)	35 (100)	
Vitamin E (mg)				–
Meet RDA	0 (0)	0 (0)	0 (0)	
Do not meet RDA	36 (45.6)	43 (54.4)	79 (100)	
Selenium (mcg)				0.351
Meet RDA	12 (38.7)	19 (61.3)	31 (100)	
Do not meet RDA	24 (50.0)	24 (50.0)	48 (100)	
Sodium (mg)				0.434
Meet RDA	3 (33.3)	6 (66.7)	9 (100)	
Do not meet RDA	33 (47.1)	37 (52.9)	70 (100)	
Fruits (servings)				0.009
Meet RDA	1 (9.1)	10 (90.9)	11 (100)	
Do not meet RDA	35 (51.5)	33 (48.5)	68 (100)	

Recommended dietary intake (RDA) for nutrients: Calorie: 2740 ± 200 kcal; fat: 25–35%; fiber 28 ± 2 g; Omega 6: 13 ± 2 g; beta-carotene: 15–180 mcg; vitamin C: 85 ± 5 mg; sodium: 1500 ± 500 mg; selenium: 60 ± 2 mcg; vitamin E: 15 ± 2 mg; fruits: 3 ± 1 servings.

\* Significant at P < 0.05.

Certain dietary factors have been advocated before by findings from Brantsæter et al. [16] that women with a high intake of processed meat, salty snacks, and sweet drinks had high prevalence of preeclampsia [OR for tertile 3 vs. tertile 1: 1.21; 95% CI: 1.03, 1.42]. These findings suggest that a dietary pattern characterized by a high intake of plant foods, vegetables, and vegetable oils decreases the likelihood of preeclampsia, whereas a dietary pattern characterized by a high consumption of processed meat, sweet drinks, and salty snacks increases the likelihood of preeclampsia. In a review paper studying the associations between dietary patterns and preeclampsia, the author observed the same results as those in our study and confirmed that women with preeclampsia had a lower intake of vegetables and a higher intake of processed food including processed meat than women who did not develop preeclampsia [17]. Many studies confirmed this finding and identified that vegetarians have a lower blood pressure than nonvegetarians and that adding meat to a vegetarian diet elevates blood pressure [18].

Similarly, results from a previous study showed that a dietary pattern characterized by a high intake of plant foods, vegetables, and vegetable oils including olive oil decreases the risk of preeclampsia [19]. Bullo et al. [19] provided an explanation for the effects of olive oil intake

on preeclampsia. Olive oil has many beneficial effects such as high levels of antioxidant molecules; monounsaturated fatty acids, which are more stable regarding oxidation than polyunsaturated fatty acids (PUFA) [20]; and oleic acid, which proved to have an inhibitory effect on the expression of VCAM-1 mRNA; the vascular monocyte cell adhesion molecule and the nuclear factor-kappaB can be stimulated by proinflammatory cytokines by reducing peroxyl radicals [21]. Further, minor components in olive oil, such as tocopherol, sitosterol, triterpenes, and phenolic compounds, have been proven to have anti-inflammatory and antiendothelial activation properties [22]. These components in olive oil may modulate endothelial activation, thereby resulting in inflammation [19].

The intake of energy in preeclamptic pregnant women was significantly higher than that in healthy pregnant women. The findings reported in a previous study conducted by Clausen et al. [23] were consistent with our findings related to energy, and they found that the risk of preeclampsia increased ORs (95% CI) with increasing levels of energy intake; the risk is twofold for an energy intake of 2750–3350 kcal/day increase, while the risk increases to fivefold for an energy intake of >3350 kcal/day. Pregnancy is considered to be an anabolic state in the first and second trimesters [24]. In addition, these women may be

particularly vulnerable to the harmful effects of high energy consumption such as excessive weight gain during pregnancy [25].

In a study on preeclamptic women experiencing tissue inflammation, fat intake was determined as a cause of elevated cytokines such as plasma C-reactive protein, which further aggravated inflammatory conditions [26]. In addition, saturated fat intake has been linked to an increased likelihood of preeclampsia three times, and this effect is thought to be mediated primarily by increased concentrations of LDL [27]. There was a presumption of LDL oxidation *in vivo* that LDL is not protected by antioxidants and may be exposed more frequently to cell-derived oxidants. The prolonged contact of endothelium with LDL is one reason why the endothelium is likely to be prone to oxidative disturbances [28].

A low intake of fiber among cases was reported in this study. This finding is consistent with that reported in a previous study by Qiu et al. [29], who found that total fiber consumption was associated with reductions in the risk of preeclampsia. Women who usually consumed diets rich in fiber ( $\geq 21.2$  g/day) experienced a 67% reduced risk of preeclampsia (RR = 0.33; 95% CI = 0.14–0.79). Dietary fiber may reduce pregnancy-associated dyslipidemia [30], an important clinical characteristic of preeclampsia, which, in turn, increases inflammation of the arteries and may lead to hypertension.

Our results were consistent with findings from a study conducted by Mehendale et al. [31] that the total omega-6 fatty acids were higher in preeclamptic pregnant women than in healthy pregnant women. It was suggested that excess omega-6 fatty acids shift the physiological state in the tissues toward the proinflammatory state [32]. Hence, a maternal diet rich in omega-6 fatty acids (proinflammatory) may increase vasoconstriction, thereby leading to preeclampsia [31].

There are deductive data that an imbalance between antioxidant activity and oxidants may have an important role in the pathogenesis of preeclampsia, as free radicals and lipid peroxides lead to endothelial cell injury. There is also evidence that elevated plasma concentrations of free radical oxidation products progress the development of preeclampsia [33]. Other studies recommended supplementation with vitamins C and E as beneficial strategies in the prevention of preeclampsia in women at increased risk of the disease [34–36]. However, all of these studies propose that preeclampsia is associated with both increased oxidative stress and reduced antioxidant defenses. Another study conducted by Wannamethee et al. [37] found that dietary vitamin C intake and plasma vitamin C were significantly and inversely associated with C-reactive protein, a marker of endothelial dysfunction concentrations. Vitamin C works to quench free radicals [38].

Beta-carotene is a fat-soluble member of the carotenoids that are considered to be provitamins [38], which is present in plant-derived foods and exhibits a great radical-trapping antioxidant behavior [39]. It is considered to be a strong antioxidant, and it is the best quencher of singlet oxygen [38]. In agreement to our study findings,  $\beta$ -

carotene was significantly lower in pregnant women who were diagnosed with type 1 diabetes and preeclampsia than in those without preeclampsia [40]. Another study revealed maternal serum levels of beta-carotene to be significantly lower in patients with preeclampsia than in normal women [41].

The association between sodium and preeclampsia was studied in many studies. Results showed that 50% of cases and approximately one-third of controls were not aware of the role of salt in the development of preeclampsia. Morris et al. [42] found no indication that the intake of sodium was related to the incidence of preeclampsia or pregnancy-associated hypertension.

Like other similar studies, this study may have many limitations. One limitation to be mentioned is the case–control design of this study, whose cause and effect relationship is not clear. The blood levels of nutrient biomarkers were also not measured in the present study. The relatively small number of subjects and the dietary data collected by the subjects depend on the level of compliance and memory, which may affect the accuracy of the whole results. The significantly high intake of calories in cases may have influenced the results and caused a high consumption of many nutrients such as fat. However, the inclusive dietary data collected and analyzed are to be noted and appreciated. It is suggested that a prospective study be designed to assess nutritional intake and biomarkers, before and during pregnancy, to detect nutritional determinants for preeclampsia during pregnancy.

## Conclusion

The purpose of this study, in particular, was to evaluate the association of dietary antioxidant intake (vitamin C, vitamin A, vitamin E, and selenium) with preeclampsia in pregnancy. Findings of this study indicate that preeclamptic women had a high intake of processed meat, sodium, energy intake, saturated fat, and omega-6. A large proportion of women with preeclampsia in this study did not meet the RDA for calories and vitamin C. Moreover, a lower intake of olive oil, fiber, and beta-carotene was reported in preeclamptic pregnant women than in healthy pregnant women.

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## References

- [1] Duley L. The global impact of preeclampsia and eclampsia. *Semin Perinatol* 2009;33:130–7.

- [2] American College of Obstetricians and Gynecologists. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. *Obstet Gynecol* 2013;122:1122.
- [3] Warrington JP, George EM, Palei AC, Spradley FT, Granger JP. Recent advances in the understanding of the pathophysiology of preeclampsia. *Hypertension* 2013;62:666–73.
- [4] Scholl TO, Leskiw M, Chen X, Sims M, Stein TP. Oxidative stress, diet, and the etiology of preeclampsia. *Am J Clin Nutr* 2005;81:1390–6.
- [5] Chappell LC, Seed PT, Briley AL, Kelly FJ, Lee R, Hunt BJ, et al. Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomised trial. *Lancet* 1999;354:810–6.
- [6] Uzan J, Carbonnel M, Piconne O, Asmar R, Ayoubi JM. Preeclampsia: pathophysiology, diagnosis, and management. *Vasc Health Risk Manag* 2011;7:467.
- [7] Ouyang YQ, Li SJ, Zhang Q, Cai HB, Chen HP. Interactions between inflammatory and oxidative stress in preeclampsia. *Hypertens Pregnancy* 2009;28:56–62.
- [8] Ferguson KK, Meeker JD, McElrath TF, Mukherjee B, Cantonwine DE. Repeated measures of inflammation and oxidative stress biomarkers in preeclamptic and normotensive pregnancies. *Am J Obstet Gynecol* 2017;216:527.e1–9.
- [9] Rajmakers MT, Dechend R, Poston L. Preeclampsia. Rationale for antioxidant clinical trials. *Hypertension* 2004;44:374–80.
- [10] Wu CS, Nohr EA, Bech BH, Vestergaard M, Catov JM, Olsen J. Health of children born to mothers who had preeclampsia: a population-based cohort study. *Am J Obstet Gynecol* 2009;201:269.e1–269.e10.
- [11] Tenório MB, Ferreira RC, Moura FA, Bueno NB, Goulart MOF, Oliveira ACM. Oral antioxidant therapy for prevention and treatment of preeclampsia: meta-analysis of randomized controlled trials. *Nutr Metabol Cardiovasc Dis* 2018;28:865–76.
- [12] World Health Organization. Obesity: preventing and managing the global epidemic. Available at: [http://www.who.int/nutrition/publications/obesity/WHO\\_TRS\\_894/en/](http://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/). [Accessed 16 April 2018].
- [13] Lee RD, Nieman DC. Nutritional assessment. 4th ed. New York: McGraw Hill; 2007. p. 169–221.
- [14] Pellet PL, Shadarevian S. Tables for use in the Middle East. Food composition. Tables for use in the Middle East. Available at: <https://www.cabdirect.org/cabdirect/abstract/19746700732>. [Accessed 9 January 2018].
- [15] Browner WS, Newman TB, Hulley SB. Estimating sample size and power: applications and examples. *Des Clin Res* 2007;3:367.
- [16] Brantsæter AL, Haugen M, Samuelsen SO, Torjusen H, Trogstad L, Alexander J, et al. A dietary pattern characterized by high intake of vegetables, fruits, and vegetable oils is associated with reduced risk of preeclampsia in nulliparous pregnant Norwegian women. *J Nutr* 2009;139:116268.
- [17] Meltzer HM, Brantsæter AL, Nilsen RM, Magnus P, Alexander J, Haugen M. Effect of dietary factors in pregnancy on risk of pregnancy complications: results from the Norwegian Mother and Child Cohort Study. *Am J Clin Nutr* 2011;94:1970–4.
- [18] Steffen LM, Kroenke CH, Yu X, Pereira MA, Slattery ML, Van Horn L, et al. Associations of plant food, dairy product, and meat intakes with 15-y incidence of elevated blood pressure in young black and white adults: the coronary artery risk development in young adults (CARDIA) Study. *Am J Clin Nutr* 2005;82:1169–77.
- [19] Bullo M, Lamuela-Raventos R, Salas-Salvado J. Mediterranean diet and oxidation: nuts and olive oil as important sources of fat and antioxidants. *Curr Top Med Chem* 2011;11:1797–810.
- [20] De La Puerta R, Martínez-Domínguez E, Ruiz-Gutiérrez V. Effect of minor components of virgin olive oil on topical anti-inflammatory assays. *Z Naturforsch C Biosci* 2000;55:814–9.
- [21] Covas MI. Olive oil and the cardiovascular system. *Pharmacol Res* 2007;55:175–86.
- [22] Perona JS, Cabello-Moruno R, Ruiz-Gutiérrez V. The role of virgin olive oil components in the modulation of endothelial function. *J Nutr Biochem* 2006;17:429–45.
- [23] Clausen T, Slott M, Solvoll K, Drevon CA, Vollset SE, Henriksen T. High intake of energy, sucrose, and polyunsaturated fatty acids is associated with increased risk of preeclampsia. *Am J Gynecol Obstet* 2001;185:451–8.
- [24] Lain KY, Catalano PM. Metabolic changes in pregnancy. *Clin Obstet Gynecol* 2007;50:938–48.
- [25] Guelinckx I, Devlieger R, Beckers K, Vansant G. Maternal obesity: pregnancy complications, gestational weight gain and nutrition. *Obes Rev* 2008;9:140–50.
- [26] Walsh SW. Preeclampsia: an imbalance in placental prostacyclin and thromboxane production. *Am J Gynecol Obstet* 1985;152:335–40.
- [27] Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Saturated fat, carbohydrate, and cardiovascular disease. *Am J Clin Nutr* 2010;91:502–9.
- [28] Francis GA. High density lipoprotein oxidation: in vitro susceptibility and potential in vivo consequences. *Biochimica et Biophysica Acta (BBA) Mol Cell Bio Lipids* 2000;1483:217–35.
- [29] Qiu C, Coughlin KB, Frederick IO, Sorensen TK, Williams MA. Dietary fiber intake in early pregnancy and risk of subsequent preeclampsia. *Am J Hypertens* 2008;21:903–9.
- [30] Schulze MB, Liu S, Rimm EB, Manson JE, Willett WC, Hu FB. Glycemic index, glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women. *Am J Clin Nutr* 2004;80:348–56.
- [31] Mehendale S, Kilari A, Dangat K, Taralekar V, Mahadik S, Joshi S. Fatty acids, antioxidants, and oxidative stress in pre-eclampsia. *Int J Gynecol Obstet* 2008;100:234–8.
- [32] Simopoulos AP. Importance of the ratio of omega-6/omega-3 essential fatty acids: evolutionary aspects. *Omega-6 Omega-3 Essent Fatty Acids Ratio Sci Evid* 2003;92:1–22.
- [33] Halliwell B, Gutteridge JM. Free radicals in biology and medicine. USA: Oxford University Press; 2015. p. 96.
- [34] Chappell LC, Seed PT, Kelly FJ, Briley A, Hunt BJ, Charnock-Jones DS, et al. Vitamin C and E supplementation in women at risk of preeclampsia is associated with changes in indices of oxidative stress and placental function. *Am J Gynecol Obstet* 2002;187:777–84.
- [35] Mohindra A, Kabi BC, Kaul N, Trivedi SS. Vitamin E and carotene status in pre-eclamptic pregnant women from India. *Panminerva Med* 2002;44:261–4.
- [36] Serdar Z, Gür E, Çolakođulları M, Develiođlu O, Sarandöl E. Lipid and protein oxidation and antioxidant function in women with mild and severe preeclampsia. *Arch Gynecol Obstet* 2003;268:19–25.
- [37] Wannamethee SG, Lowe GD, Rumley A, Bruckdorfer KR, Whincup PH. Associations of vitamin C status, fruit and vegetable intakes, and markers of inflammation and hemostasis. *Am J Clin Nutr* 2006;83:567–74.
- [38] Pham-Huy LA, He H, Pham-Huy C. Free radicals, antioxidants in disease and health. *Int J Biomed Sci: IJBS* 2008;4:89.
- [39] Lin J, Cook NR, Albert C, Zaharris E, Gaziano JM, Van Denburgh M, et al. Vitamins C and E and beta carotene supplementation and cancer risk: a randomized controlled trial. *J Natl Cancer Inst* 2009;101:14–23.
- [40] Azar M, Basu A, Jenkins AJ, Nankervis AJ, Hanssen KF, Scholz H, et al. Serum carotenoids and fat-soluble vitamins in women with type 1 diabetes and preeclampsia: a longitudinal study. *Diabetes Care* 2011;34:1258–64.
- [41] Isler CM, Barrilleaux PS, Rinehart BK, Magann EF, Martin Jr JN. Postpartum magnesium sulfate prophylaxis: a prospective trial utilizing clinical parameters to indicate duration of therapy for hypertensive diseases of pregnancy. *Obstet Gynecol* 2001;97:44.
- [42] Morris CD, Jacobson SL, Anand R, Ewell MG, Hauth JC, Curet LB, et al. Nutrient intake and hypertensive disorders of pregnancy: evidence from a large prospective cohort. *Am J Gynecol Obstet* 2001;184:643–51.