

**Original Article****Nutritional Status in Preeclamptic Women: a Case-Control Study in South East of Iran**Mahdieh Sheikhi^{1*}, Elham Rezaei², Seyede hosniye Hosseini³, Mahnaz Shahrakipoor⁴, Monire Sheikhi³, Sepideh Soltani⁵

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Background and Objectives: Beyond the influence of anthropometric, demographic and race, nutrition is considered as one of the most important risk factors for development of preeclampsia (PE). The issue has grown controversial in light of recent reports. This paper, purposes to compare the nutritional and demographic status between PE women and normal pregnancy in south east of Iran.

Materials and Methods: Sixty three normal pregnant and 62 PE women were recruited to be referred to obstetrics and gynecology department of Imam-Ali Hospital, Zahedan, Iran. PE was diagnosed by using international guidelines by the expert gynecologist. Dietary intake, assessed by food frequency questionnaire (FFQ), and anthropometric measurement and medical history were collected by trained gynecologist and dietitians during the second trimester. The logistic regression model was used to assess the correlation between dietary intake and PE risk.

Results: Pregnant PE women compared with normal pregnant women had higher pre-pregnancy body mass index (BMI), cesarean delivery and low birth weight babies. There was an association between grain intake and PE risk (OR= 2.00; 95% CI=1.11-3.61). No association was found between other dietary intakes and PE risk.

Conclusions: Our findings support the association between grain intake and the risk of PE. Further prospective studies are needed to illustrate the link between dietary intake and PE status.

Keywords: Preeclampsia, Nutrition, Diet, Pregnant women

Introduction

Preeclampsia (PE) is one of the most multisystem disorders in pregnancy, which can lead to maternal and fetal morbidity and mortality (1, 2). PE prevalence was reported 2-8% in the world, mostly in nulliparous women (1, 3). The population attributable risk (PAR) for PE found 19.8-35.7% in all maternal BMI ranges in developing countries and 20.9 % In Iran (2). It is also related to an increased risk of perinatal mortality and is the cause of approximately 10% of stillbirths and 15% of preterm births (4). Social-environmental factors, such as maternal age, pre-pregnancy weight and history of previous pregnancy are reported to affect the PE incidence and

gestational outcomes (2,5-7). Despite extensive studies and recent evidence to identify the pathophysiology of PE, the etiology of this disorder is questionable and requires further investigation (8). Disturbed placentation, endothelial dysfunction, oxidative stress and a low-grade systemic inflammatory condition are related to the diagnostic criteria for PE, leading to the clinical signs including hypertension, proteinuria and edema after the twentieth week of pregnancy (9,10).

According to recent literature, higher than normal BMI, multiple pregnancies and pregnancy pause >10 y, PE family history, autoimmune diseases, young age

and history of PE in a prior pregnancy as well as insulin resistance, diabetes, dyslipidemia and chronic hypertension are some of the risk factors associated with PE (4,8,9,11). Meta-analysis studies found that obesity and high BMI can predict the risk of PE and small for gestational age newborns (2, 5). Lifestyle and dietary modification may reduce the PE risk (2,12-15). Several studies showed that additional energy intake, processed foods, refined grains and sugar-sweetened beverage consumption increases the PE risk (16,17), vice versa more fruits and vegetable consumption, milk and nuts can reduce the risk of PE (18,19). Recommended foods may protect against PE due to high content of fiber, vitamin E, C, D, selenium and zinc, while processed foods and high-fat diet increases free radicals, which can lead to increased inflammation and oxidative stress risk factors (4,5,20,21). There are different evidence regarding micronutrient effects on PE. Several studies reported the positive effects of antioxidant vitamins, while others did not observe a significant difference (13,3). A study was conducted in Iran, demonstrating that higher intakes of energy, as well as lower intakes of vitamin C, magnesium and potassium are positively associated with the risk of gestational hypertension (22).

The relationship between PE and diet have been conducted in different regions, but in the South East of Iran, less attention has been paid to this issue. PE and eclampsia are the second leading cause of maternal and perinatal morbidity and mortality in Iran and is the highest maternal mortality rate in Zahedan (23). The aim of this study was to evaluate nutritional status among pregnant women with and without PE, and possible adverse pregnancy outcomes between pregnant women living in Zahedan.

Materials and Methods

Subject's selection: We carried out a population based case-control study at the Obstetrics and Gynecology department of the Imam-Ali hospital, from June 2015 to September 2015 in Zahedan. The hospital is a referral focalize for high risk pregnancies and women from diverse social classes were admitted.

A sample size of 68 pregnant women aged 18-35 (20 weeks pregnant) were included for each group based on a power of 80% at the 5% significance level. For each PE woman, a normal pregnant woman was randomly selected and were matched together for gestational age, without having multiple gestation and

medical problems including chronic hypertension, cardiovascular or renal diseases, diabetes and use of medications. PE was diagnosed by a systolic/diastolic blood pressure of $\geq 140/\geq 90$ mmHg on two occasions more than 4 hours apart after 20 weeks and proteinuria ≥ 300 mg protein in 24-h urine collection (24).

Pregnant women were excluded if they did not give approval, have a history of pre-existing health conditions including type 1 or type 2 diabetes, younger than 18 years, gestational diabetes, hypertension disorders, heart disease, renal disease or other conditions that require special diets and medications.

Based on the exclusion criteria, 62 participants in PE and 63 participants in normal pregnancy reached the inclusion criteria. Those with >70 blank items on the food frequency questionnaire (FFQ) ($n=6$ PE, $n=5$ normal pregnancy) were excluded. A trained gynecologist and dietitians carried out the survey under standard protocols. The participants were interviewed about demographic information. The participants were followed until delivery time for collecting information on the type of delivery and infant birth weight and other measurements.

Dietary assessment: Dietary intake was assessed using a validated 168-items semi-quantitative FFQ (25). The FFQ was in a Willet format adjusted for Iranian food items (26,27). This questionnaire was used to ascertain the frequency of food intakes during pregnancy. The FFQ asked about the usual dietary intake in the last six months. Information regarding the intake frequency and portion size was changed into the amount of each food item in grams consumed on average per day. Dietary information was extracted by Nutritionist-4 software (First Databank Inc., Hearst Corp, San Bruno, CA) analyzed by a trained nutritionist. Daily consumption was changed from their unit listed in the FFQ to grams per day.

Statistical analysis: Data analysis was implemented using Statistical Package for the Social Sciences (SPSS) (version 18:0, SPSS Inc., Chicago, IL) software. Non-parametric correlation statistics were used because data failed to meet the assumptions of normality and equal variances. A p -value of <0.05 was considered as significant. The data were expressed as mean \pm SD or percentages. Statistical significances between percentages were assessed by using the chi-square test. The logistic regression

model has assessed the correlation between dietary intakes and PE risk.

Results

Demographic and lifestyle variables are determined in Table 1. The mean age ($P=0.002$) and pre-pregnancy BMI ($P=0.003$) was higher in PE women than in the normal pregnancy group but both were in normal ranges. The women with history of abortion were most likely in the PE compared with normal pregnancy (23.5% vs. 17.6%, $p=0.36$). For other variables, no significant differences were observed between PE and normal pregnancy.

According to the outcomes accessed from the FFQ, the mean energy, protein, Carbohydrates and fat intake in normal pregnancy and PE groups were not significant (Table 2) and the average intake of food groups were in the recommended range.

PE women had significantly lower intakes of meat or beans and vegetables ($P<0.001$), and higher intakes of grains compared to the normal pregnancy group. None of the women used any supplements other than

folic acid and iron that is routinely consumed during pregnancy.

The associations between dietary intakes and odds of PE are presented in table3. After adding energy intake in model 1, the odds of PE became significant in the grain intake. The odds of PE significantly was higher in the grain intake. The other food groups (meat, beans, nuts and egg, milk, vegetables and fruit) were not related to the risk of PE. No significant association was found between the risk of PE and micro or macronutrient intake.

The percentage of cesarean section was significantly higher in women with PE compared to normal pregnant women. (54.4 vs 20.6, p -value <0.0001). Newborn birth weight was significantly lower in the PE group compared to normal pregnancy group (2572.9 ± 791.4 vs 3001.6 ± 480.1 , p -value <0.003), however the mean of newborn weight was more than 2500gr in both groups. None of the women in the normal pregnancy group developed PE after delivery.

Table 1. Characteristics of women with preeclampsia and normal pregnancy

Characteristics	Preeclampsia (N = 62)	Normal gestation (N=63)	p-value
Age (yrs)	29.3±6.7	25.8±6.2	0.002
Education (yrs)	5.8± 4.9	6.8±5.2	0.32
Gestational age (wk)	33.1± 2.7	34.6± 2.1	0.63
Pre-pregnancy BMI (kg/m ²)	22.9±2.7	21.3±3.2	0.003
Primiparous (%)	23.5	33.8	0.25
History of abortion (%)	23.5	17.6	0.36
History of stillbirth (%)	10.3	16.2	0.46
History of twin birth (%)	7.4	8.8	0.77
History of preeclampsia (%)	8.8	2.9	0.14
Ethnic			0.20
Baloch(%)	79.4	69.1	
Sistani(%)	16.2	26.5	
Other(%)	4.4	4.4	
Residence			0.84
Urban(%)	76.5	75	
Rural(%)	23.5	25	

Table2. Comparison of energy, macronutrient and food intakes in preeclampsia and normal pregnancy

Daily intake	Preeclampsia (N = 62)	Normal pregnancy (N=63)	P-value
Energy(Kcal)	2707.8±1219.9	2777.4±635.1	0.16
Protein(gr)	95.1±46.8	95.4±28.1	0.35
Carbohydrates(gr)	409.9±244.6	403.7±103.7	0.35
Fat(gr)	85.6±31.7	95 ±40.1	0.24
Meat, beans, nuts and egg(ounce)	3.4±2.4	4.5±3.2	0.02
Milk (cup)	2.3±1.4	2.2±1.2	0.86
Grains (ounce)	18.4±6.5	15.8±14.3	0.008
vegetables (cup)	2.5±1.5	3.5±1.9	0.001
Fruit (cup)	2.7±2.3	3.4±2.5	0.09

Table 3. Associations between risk of preeclampsia and dietary intakes

Daily intake	Preeclampsia vs. normal		
	Crude OR(95%CI)	Model 1* OR(95%CI)	Model2** OR(95%CI)
Protein(gr)	0.98(0.83-1.16)	1.00(0.80-1.26)	1.05(0.82-1.35)
Carbohydrates(gr)	0.95(0.91-0.99)†	0.96(0.83-1.11)	0.97(0.84-1.13)
Fat(gr)	0.98(0.94-1.01)	1.01(0.75-1.36)	1.03(0.76-1.41)
Meat, beans, nuts and egg(ounce)	0.92(0.39-2.15)	0.91(0.38-2.14)	0.77(0.31-1.93)
Milk (cup)	1.31(0.23-7.40)	1.41(0.22-9.06)	1.33(0.20-8.59)
Grains (ounce)	2.02(1.13-3.62)†	2.02(1.12-3.63)†	2.00(1.11-3.61)†
vegetables (cup)	1.08(0.68-1.71)	1.07(0.67-1.71)	1.03(0.64-1.65)
Fruit (cup)	1.83(0.95-3.52)	1.79(0.90-3.55)	1.76(0.88-3.53)
Vitamin A (µg)	1.00(0.99-1.00)	1.00(0.99-1.00)	1.00(0.99-1.00)
Vitamin C (mg)	0.99(0.98-1.00)	0.99(0.98-1.00)	0.99(0.98-1.00)
Vitamin D (µg)	0.99(0.95-1.03)	0.99(0.95-1.03)	0.99(0.95-1.02)
Vitamin E (mg)	1.05(0.94-1.17)	1.05(0.94-1.17)	1.06(0.94-1.19)
Thiamin (mg)	2.40(0.34-16.48)	2.11(0.22-20.33)	1.32(0.12-14.60)
Riboflavin (mg)	1.58(0.06-36.10)	1.47(0.05-36.86)	0.97(0.03-27.85)
Niacin (mg)	1.08(0.88-1.34)	1.09(0.88-1.35)	1.06(0.86-1.32)
Vitamin B6 (mg)	1.02(0.12-8.49)	1.04(0.12-8.73)	1.35(0.15-11.96)
Folate(µg)	0.99(0.99-1.00)	0.99(0.99-1.00)	0.99(0.99-1.00)
Zinc (mg)	0.84(0.54-1.30)	0.85(0.53-1.36)	0.88(0.54-1.42)
Iron (mg)	0.94(0.80-1.09)	0.94(0.80-1.09)	0.94(0.80-1.10)
Copper (mg)	5.93(0.76-45.90)	5.81(0.74-45.50)	5.24(0.63-42.97)
Calcium (mg)	0.99(0.99-1.00)	0.99(0.99-1.01)	0.99(0.99-1.00)
Magnesium (mg)	1.00(0.98-1.01)	1.00(0.98-1.01)	1.00(0.98-1.01)
Potassium(mg)	1.00(0.99-1.00)	1.00(0.99-1.00)	1.00(0.99-1.00)

*Adjusted for energy. **Adjusted for energy, pre-pregnancy BMI and age. †P-value <0.05 was considered as significant.

Discussion

The association between nutritional status in PE women and normal pregnancy women was investigated in the present study. To our knowledge, this is the first study reporting the relationship between nutritional status and PE in pregnant women living in Zahedan. PE women had significantly lower intakes of meat or beans and vegetables and higher intake of grains compared to the normal pregnancy group but after adjusting for confounder variables, the women in the grain intake were significantly associated with the PE risk. Some studies showed that additional energy intake, processed foods, refined grains and sugar-sweetened beverage consumption increases the PE risk (16,17). A study (28) showed PE women had significantly lower intakes of milk, meat or beans and higher consumption of grains and fruit, vegetables compared to the recommended minimum

number for pregnant women. However, in the case control study in Isfahan, PE women had significantly lower intakes of grains and vegetables compared to the normal pregnancy (29). Another study reported that women who had high intakes of vegetables had lower PE risk (30).

A dietary pattern analysis study advised that adherence to a dietary pattern including high intake of fruits, vegetables, vegetable oils, rice and poultry was associated with reduced PE risk, while adherence to a dietary pattern including a high intake of processed foods (such as white bread, sausages, hamburgers, sugar-sweetened drinks, salty snacks and sweets) increased the PE risk (15).

The other food groups (meat, beans, nuts and egg, milk, vegetables and fruit) were not related to PE risk. None of micro/macro nutrients were linked to risk of PE. In this study none of micro/macro nutrients were

linked to PE risk. Whereas some studies showed nutrients may be involved in several important steps in the current proposed concepts of the pathogenesis of PE (31). The underlying mechanisms are complex and remain unclear (8-10). To date there has been controversial results in this issue. Several investigations indicated that vitamin and antioxidants decrease with PE incidence and low birth weight (19, 32). Rumbold et al (33) showed a very low intake of vitamin E in mid to late pregnancy was associated with an increased PE risk and gestational hypertension, the results were adjusted for confounding factors such as maternal age, parity, body mass index (BMI), PE in a previous pregnancy, preterm delivery in a previous pregnancy, family history of PE, smoking status. Limberaki et al found that high consumption of antioxidant rich foods, increases the total antioxidant status and developed better health (34). A possible explanation for this might be concluded as dietary intake of vitamin C was higher than recommended allowance and fruit-vegetable consumption was more than recommended minimum number during pregnancy. Conflicting evidence was shown in the literature as to approve the relationship of intake of vitamins C and E with PE. Zhang et al demonstrated that women who consumed <85mg of vitamin C daily (lower than the recommended dietary allowance), as compared with others, experienced doubled the risk of PE (35). However, Klemmensen et al concluded that incidence of PE did not correlate with dietary vitamin C and E intake (36). There was a decreasing trend in the incidence of severe PE and eclampsia with increasing dietary vitamin C intake. However several studies showed any significant relationship (1,37,38). The recent systematic review and meta-analysis by Schoenaker and colleagues reports an association between gestational hypertensive conditions, including PE, and dietary factors, based on observational studies (18). However, randomized trials and subsequent meta-analyses have demonstrated no beneficial effect of antioxidant vitamin supplementation in reducing the risk of developing PE (37, 39). WHO recommendation for PE identified important knowledge gaps in this topic (1).

In this regard, pregnancy outcome indicated the relationship of higher maternal age and pre-pregnancy BMI with increasing PE incidence, cesarean section and infants low birth weight. It must be kept in mind

that all of the associations were independent of potential confounders' impact.

Recall bias and selection bias existed as the limitations of case-control studies. So we used random selection and detailed statistical formulas for sample size determination to minimize any bias. Another limitation of this study is that the FFQ is developed for dietary assessment of previous year, but frequency of items for the last 6 months and intake of some seasonal food items may be not considered. This study has some strengths, including accounting for potential confounders, such as energy, BMI, maternal age and history of PE. Our subjects were carefully interviewed by an expert dietician. Demographic and dietary information were analyzed by questionnaires which have been filled by them. However, more prospective surveys with larger sample size are required to confirm the existing findings.

In conclusion, there are several risk factors for PE. It seems that maternal age and pre-pregnancy BMI are some independent predicting factors for the risk of PE. Throughout findings indicate that healthy dietary pattern in this population is associated with positive birth outcomes and decrease PE incidence. Prospective studies are warranted to confirm the reported findings and further analyze associations.

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