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Nutritional Status of Pregnant Women and Urine Calcium-to-Creatinine Ratio During 24th - 28th Weeks of Pregnancy and Their Relationship with the Incidence of Hypertensive Disorders During Pregnancy

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Abstract

Background: Considering that gestational hypertension may have severe effects on the mother and fetus, this study was conducted to examine the nutritional status of pregnant women and urine calcium-to-creatinine ratio during 24th - 28th weeks of pregnancy and their relationship with the incidence of hypertensive disorders during pregnancy.

Methods: This prospective longitudinal study recruited 538 pregnant women attending prenatal clinics in Tehran, Iran in 2011. A food frequency questionnaire (FFQ) was completed for all mothers at the baseline for nutritional intake assessment, and a random urine sample was taken between 24th - 28th weeks of pregnancy to calculate the Ca/Cr-ratio. Hypertensive disorders were classified into two groups: a, gestational hypertension in case of detecting a blood pressure $\geq$ 140/90; and b, preeclampsia in case of increased proteinuria. Data were analyzed using SPSS V.16 and N4 software programs.

Results: In this study, 14 (6.2%) pregnant women had hypertensive disorders during pregnancy. The desired nutritional status and Ca/Cr-ratio had no significant relationship with hypertensive disorders during pregnancy. The regression test was used to investigate the variables affecting hypertensive disorders, which showed the significant relationship of pre-pregnancy BMI and mother's age with hypertensive disorders during pregnancy ($P \leq 0.05$).

Conclusions: In this study, the incidence of hypertensive disorders had no relationship with the Ca/Cr-ratio and the nutritional status of the pregnant women. However, since more than 80% of the participants had undesirable nutrition, mothers' nutrition in the first half of pregnancy is necessary to be under observed.

Keywords: Nutritional Status, Hypertensive Disorders During Pregnancy, Urine Calcium/Creatinine Ratio

1. Background

Pregnancy is one of the important events of the reproductive age. After conception, many physiological adaptations begin with pregnancy, and these adaptations continue throughout pregnancy. These changes may cause hypertension in people with a history of high blood pressure. The mechanism is though still unknown (1, 2). Hypertensive disorders are the most common health complications of pregnancy that occur in 5% to 10% of all pregnancies (3). Hypertensive disorders during pregnancy are classified into 4 categories: gestational hypertension, preeclampsia-eclampsia syndrome, preeclampsia superimposed on chronic hypertension syndrome, and chronic hypertension. Preeclampsia is the most serious complication during pregnancy. The incidence rate of preeclampsia is about 5% (4, 5). Hypertensive disorders during pregnancy can lead to serious complications such as placental abruption, severe hemorrhage caused by liver infarction, brain hemorrhage, acute renal failure, pulmonary edema, premature birth, blindness, impaired uterine-placenta blood supply, impaired fetal growth, intrauterine fetal death and HELLP syndrome in extreme cases (4, 6).

Pregnancy is associated with an increase in the need for nutrients, including energy, proteins and vitamins. During pregnancy, the need to receive all the minerals also increases (7, 8). Elements like calcium, iron, sodium, magnesium, iodine, zinc, and fluorine have a great influence on pregnancy and its outcomes. Various studies have shown that diet can play a role in the incidence of hypertensive

disorders during pregnancy. Some of these studies have highlighted the high levels of energy intake and low levels of calcium intake in people with hypertensive disorders during pregnancy, while others have rejected such a relationship. It has also been reported in some studies that there is a relationship between magnesium, omega-3 fatty acids, and antioxidant vitamins in preventing hypertensive disorders during pregnancy. In general, different studies have reported various results (9-11). The developing fetus needs about 30 grams of calcium to store in its skeleton. Therefore, adequate calcium intake by the mothers is necessary to prevent excessive calcium absorption from their body (12). In a normal pregnancy, the rate of urinary calcium excretion increases, and this excretion usually increases during every trimester, reaching its highest level in the third trimester. One explanation for hypercalciuria in pregnancy is the increase in glomerular filtration. One of the changes in the urinary system during this period is glomerular filtration and increased renal plasma flow rates by about 50%. Urine calcium can be used as a predictive marker for the diagnosis of preeclampsia. Severe morbidity and mortality associated with preeclampsia or eclampsia in the developed countries have been substantially reduced, but they are still a serious and dangerous problem that threatens a safe motherhood particularly in developing countries (2, 13). With that in mind, it is important to know the factors that are associated with these disorders and that careful care and treatment of the disease are necessary. Among these factors are the nutritional status and the urine Ca/Cr-ratio. Studies have determined the relationship between urinary calcium excretion and preeclampsia, and even hypercalciuria can be used as a predictive factor for preeclampsia. There is still no definitive test for the early detection of hypertensive disorders, including preeclampsia. Over the past few decades, numerous clinical, biophysical and biochemical tests have been proposed to identify women at risk of preeclampsia. An overview of previous studies showed their insignificant predictive value in the early diagnosis of preeclampsia (14). Initial diagnosis and proper treatment of hypertensive disorders during pregnancy increase the length of pregnancy and improve the maternal and fetal outcomes. The existence of methods to prevent or modify the severity of hypertensive disorders during pregnancy has necessitated the early prediction of these disorders. Due to the diverse reports on the relationship between the nutritional status of pregnant women and the incidence of hypertensive disorders, this study aimed to examine the relationship of nutritional status and urine Ca/Cr-ratio with the incidence of hypertensive disorders during pregnancy.

2. Methods

This prospective longitudinal study recruited 538 pregnant women in Tehran, Iran in 2011. Samples were selected by multistage sampling from pregnant women presenting to prenatal clinics of hospitals affiliated to Tehran University of Medical Sciences (Imam Khomeini, Arash, and other hospitals), Shahid Beheshti University of Medical Sciences (Shohada-ye Tajrish, Mahdieh, and other hospitals), Baqiyatallah University of Medical Sciences (Baqiyatallah and Najmiyeh hospitals), Shahed University of Medical Sciences (Mustafa Khomeini and Hazrat Zainab hospitals) after obtaining a written consent. The inclusion criteria were mothers aged 18 - 35 years old, singleton pregnancy, no alcohol or drug use, non-smoker, gestational age $\leq$ 20 weeks, mothers with $\leq$ two pregnancies, Iranian citizenship, no hypertension before pregnancy and from the beginning of the current pregnancy. The exclusion criteria were major embryonic anomalies or intrauterine fetal deaths, hyperemesis gravidarum, any chronic and metabolic diseases, and the use of medications that interfere with calcium metabolism in any way.

Researchers used three primary methods to collect nutritional intake data. Cross-sectional evaluation is one of the most common types of nutritional assessment. The 24-hour dietary recall (24HR) and dietary record (DR) are among these methods. Retrospective assessments are used to examine the effects of previous diets of individuals and determine their relationship with the current disease, and in this case, the food frequency questionnaire (FFQ) is used. In prospective and interventional assessments, all three methods are used to assess nutritional and physiological changes (15). FFQ is the most commonly used nutrition assessment tool for epidemiological studies that can provide common nutritional information with minimal cost to the researcher. The questionnaire reports the amount of nutrition and nutrient intake in periods of time, especially long-term periods. The questionnaire is designed to rank and evaluate all diets consumed over the past 12 months based on their average consumption. This questionnaire has some limitations, including the fact that the information in this questionnaire is based on the individuals' memory, and a lot of information about food consumption may be lost (16).

A standard FFQ and a general questionnaire were completed for all the subjects. The questionnaire was modified by nutritionists. The information in the questionnaire was obtained through interviews. The questionnaire used in this study was of an Iranian type and contained 60 items and was completed based on the food consumed by a person in the last month. The questionnaire data were converted to grams based on the standard scale tables of all

nutrients provided by nutrition experts to the researchers, and were entered into the N4 nutritional software (NUTRITIONIST IV) to calculate the micronutrient and macronutrient intakes of mothers. This software is the first database on nutrition and is related to American college of agriculture products.

Using the recommended dietary allowances (RDA) and dietary reference intake (DRI), the amount of daily intake of micronutrients and macronutrients of each subject was divided into two groups of normal and with nutrient deficiency, or normal and abnormal. Desirable nutrition was defined based on RDA values above 75% in four factors of calcium, vitamin B2, protein and energy, and sodium, based on values less than the total determined DRI. If all of the four factors listed above had values above 75% RDA and the sodium amount was below standard, the subject was placed in the desirable nutrition group.

The standard intake values for the four factors in terms of total RDA are as follows: Calcium = 1000 mg/day, Protein = 71 g/day, Energy = 2743 Kcal/day, Vitamin B2 = 4.1 mg/day, and Sodium in terms of DRI = 1500 mg/day (17, 18).

The general questionnaire with 21 items was completed on the first visit, and included items about mothers' demographic characteristics, pregnancy and labor, smoking in close relatives, history of diseases in previous pregnancies, use of medications and supplements in the current pregnancy, blood pressure, weight, height, and weight before pregnancy. A urine sample (1.5 cc) was taken from all subjects at weeks 24 and 28 of pregnancy. All urine samples were transferred to the laboratory for analysis. All urine calcium and creatinine tests were performed by a certain technician in the biochemistry laboratory of Tarbiat Modares University and the urine Ca/Cr-ratio was calculated. Ca/Cr-ratio has been used as an indicator of 24-hour urine calcium in many studies. The Shimadzu. AA-670 atomic absorption spectrophotometer was used to determine the urine calcium level. Urine calcium was assessed by the photometric method using Cresolphthalein Complexone. Urine calcium level was determined using a urine calcium kit procured from Parsazmun Co. (http://www. irancode. ir/Home/PersonalPage?MemberCode=18514&gProduct-orderBy=CombaseName-desc&gProduct-page=3). Urine creatinine level was assessed by enzymatic testing method, and colorimetry without removing proteins based on Jaff's method. The methods used to carry out the tests required for this research in the laboratory had sufficient scientific credibility according to the credible scientific resources and their performance in one laboratory with a certain machine and a certain technician. All subjects were monitored for hypertensive disorders until delivery. In each routine prenatal care that was performed for the subjects, symptoms of preeclampsia and eclampsia such as edema, epigastric pain, blurry vision, and double vision were assessed. Blood pressure was measured after a few minutes of resting using a standard sphygmomanometer in sitting position. Pregnancy-related hypertension was diagnosed if blood pressure was $\geq$ 140/90 mmHg in at least two blood pressure measurements with at least 6 hours of interval and without protein excretion. Preeclampsia was diagnosed if blood pressure was $\geq$ 140/90 mmHg and proteinuria was greater than +1 in at least two random urine samples with at least 6 hours of interval or if protein excretion was $\geq$ 300 mg in the 24-hour urine after the 20th gestational week.

SPSS-16 software was used to analyze the information and perform statistical tests, and the N4 software was used to analyze the nutritional information. All statistical analyses were performed with a 95% confidence level, and nonparametric tests were used due to the non-normality of the data.

3. Results

The demographic information of the mothers is presented in Table 1. In this study, most mothers were housewives with high school education and their BMI was within the normal range. Frequency distributions of desirable and undesirable nutrition in mothers based on 75% RDA are presented in Table 2. Frequency distributions of nutritional deficiencies of calcium, vitamin B12, protein and energy in mothers based on 75% RDA are presented in Table 3. Frequency distributions of normal and abnormal levels of sodium intake in women are presented in Table 4.

Mann-Whitney test showed no significant relationship between micronutrient and macronutrients intakes and the incidence of preeclampsia and gestational hypertension. Mann-Whitney test showed no significant relationship between the urine Ca/Cr-ratio and the incidence of preeclampsia and gestational hypertension.

The logistic regression test showed the significant relationship of the incidence of hypertensive disorders during pregnancy with pre-pregnancy BMI and mother's age (P value $\leq$ 0.05). Each unit of increase in pre-pregnancy BMI increased the incidence rate of hypertensive disorders during pregnancy by 1.12 times. Each unit of increase in age increased the incidence rate of hypertensive disorders during pregnancy by 1.18 times. The examined variables are presented in Table 5.

4. Discussion

In this study, five important factors affecting the development of hypertensive disorders were used to study

Table 1. Demographic and Fertility Data of the Pregnant Women (538 People)

Variable	No.	Percent
Number of pregnancies		
First pregnancy	319	59.3
Second pregnancy and above	219	40.7
Education (number of years of study), y		
Less than and equal to 12	376	59.9
12 - 16	152	28.3
More than 16	10	1.9
Occupation		
Housewife	456	84.8
Employed	82	15.2
Smoking in close relatives		
Yes	72	13.4
No	466	86.6
History of severe vomiting in the current pregnancy		
Yes	49	9.1
No	489	90.9
Supplement consumption		
Iron	294	54.6
Folic acid	505	93.9
Multi-vitamine	183	34.1
BMI in the first visit		
Less than or equal to 19.8	64	11.9
19.8 - 26	307	57.1
26 - 29	110	20.4
More than 29	57	10.5

Table 2. Frequency Distribution of Desirable Nutrition in the Studied Mothers (N = 538)

Variable	No.	Percent
Desirable nutrition	85	15.8
Undesirable nutrition	453	84.2

the nutritional status of pregnant women considering the consumption pattern problems and existing deficiencies of key nutrients in Iran. The factors were calcium, sodium, riboflavin (vitamin B2), protein and energy. Values greater than 75% RDA of protein, energy, calcium and riboflavin, and values less than the total DRI for sodium were defined as an indicator of the desirable nutrition state, and according to this definition, only 15.8% (N = 85) of the pregnant women had desirable nutrition.

In 2008, Ismaillzadeh et al. conducted a study in Maku, Iran, to investigate the nutritional patterns of pregnant women in urban and rural areas and found that protein and energy intake in both groups were higher than 75% RDA, calcium intake in both groups was less than 75% RDA, and riboflavin intake in the urban population was less desirable than the rural population (19). In the present study, calcium and riboflavin deficiency were observed, too. However, in terms of protein and energy intake, the results of this study were different. This can be due to the difference in the time of conducting the studies. FFQ was completed in the first half of pregnancy in the present study while Ismailzadeh's have determined no specific time for completing the questionnaires. The differences in nutritional status and socioeconomic and cultural conditions in Tehran and Maku were also possibly effective in this regard. A study in Zahedan, Iran in 2010 to assess the effect of pregnant women's nutritional status on neonatal birth weight, showed that calcium and energy intakes of pregnant women were 544 mg/day and 1802 calories/day, respectively, which were lower than calcium and energy standard values (20). In their study, the mean daily calcium and energy intake was 969.6 mg/day and 1987 kg/day, respectively, which corresponds to the daily energy consumption of the present study. Meanwhile, calcium intake was higher in the present study, which might be due to the economic and cultural poverty in the deprived areas of Iran, and the differences between different regions of Iran. In a study by the national institute of nutrition and food industry in 1995 in Iran, severe deficiency of riboflavin and calcium intake was identified as a health problem. In that study, 30% and 70% of the subjects had a calcium and riboflavin intake of 80% RDA, respectively (21). Various studies have shown that malnutrition exists in different dimensions in different parts of Iran. The most important nutritional problems of Iran are protein-energy malnutrition; anemia, iron deficiency; iodine deficiency disorders; zinc, calcium, and vitamins D and A deficiency (22). McLaren suggested that if at least 20% of the population receive less than 75% RDA of a nutrient, the deficiency of that nutrient is a major health problem in that population (23). In this study, calcium, protein and energy intake of at least 20% of the population was less than 75% RDA. Hence, according to McLaren, pregnant women have a health problem in terms of these three nutrients in the first half of their pregnancy. Nausea and vomiting are common complaints of women in the first half of pregnancy. Lacroix et al. (2000) found that about three-quarters of pregnant women reported that problem, and the problem continued up to 14 weeks or more in half of them (24). The nutrition deficiency in the first half of pregnancy could cause nausea and vomiting in the first weeks of pregnancy, and pregnant women's inadequate intake of nutrients and their reduced desire to eat.

Table 3. Frequency Distributions of Nutritional Deficiencies of Calcium, Vitamin B2, Protein and Energy in Mothers Based on 75% RDA (N = 538)[a]

Variable, Daily	Mean Intake Rate	Lower Intake Based on 75% RDA	Lower Intake Based on Total RDA
Calcium, mg	979.6 ± 553	205 (38.1)	328 (61)
Vitamin B2, mg	2.1 ± 1.4	46 (8.6)	139 (25.8)
Protein, g	82.9 ± 48.01	117 (21.7)	241 (44.8)
Energy, kcal	1987 ± 871	320 (59.5)	449 (83.5)

[a]Values are expressed as mean ± SD or No. (%).

Table 4. Frequency Distributions of Normal and Abnormal Levels of Sodium Intake in the Studied Mothers (N = 538)[a]

Variable	Mean Intake Rate	Value More Than DRI	Value Less Than DRI (Normal)
Sodium, mg	2037.1 ± 12439	149 (27.7)	389 (72.30)

[a]Values are expressed as mean ± SD or No. (%).

Table 5. The Relationship Between Effective Factors and Hypertensive Disorders in the Studied Mothers (N = 538)

Variable	OR	95% Confidence Interval		P Value Logistic Regression Statistical Test
		Lower	Higher	
Number of pregnancies	0.16	0.03	0.747	0.052
Pre-pregnancy BMI	1.149	1.03	1.21	0.005*
Gestational Diabetes	0	0	0	0.998
Desirable nutrition	4.03	0.578	28.2	0.160
Urine Ca/Cr-ratio	0.303	0.006	15.7	0.554
Smoking in close relatives	0.978	0.181	5.2	0.98
Age	1.18	1.005	1.3	0.044*
Preeclampsia history	0	0	0	1
Insufficient daily energy intake	2.21	0.316	15.4	0.424
Insufficient daily calcium intake	0.452	0.063	3.2	0.428

In this study, hypertensive disorders during pregnancy (preeclampsia and gestational hypertension) were not significantly related to desirable or undesirable nutritional status. Since there was no significant relationship between nutritional status and hypertensive disorders during pregnancy, the relationship of other micronutrients and macronutrients with these disorders was also investigated, but no significant relationship was found. Hypertensive disorders during pregnancy had no significant relationship with consuming calcium, multivitamins, and folic acid supplements. Mortazavi et al. (2009) found similar results, too (25).

The results of a study conducted in Iran on non-pregnant women by Esmaeilzadeh et al. indicated hypertension was reversely related with calcium and potassium, while such a relationship was not found between magnesium intake and hypertension (26). This lack of a relationship between hypertensive disorders and nutrition and its components can be due to the small sample size and the low incidence of hypertensive disorders (2.6%). In this study, there was no significant correlation between urine Ca/Cr-ratio and hypertensive disorders during pregnancy (preeclampsia and gestational hypertension). However, urine Ca/Cr-ratio was lower in mothers with hypertensive disorders, such that the mean urine Ca/Cr-ratio in the 24th - 28th weeks of gestation in women with hypertensive disorders and normal women was 12.12 mg/dL and 0.79 mg/dL, respectively. Baker et al. obtained similar results in 1994 and did not find any significant relationship between urine Ca/Cr-ratio and hypertensive disorders (27). In another study in 2007 in Yazd, Iran by Dehghani Firoozabadi et al., there was no significant relationship between the urine Ca/Cr-ratio and gestational hypertension in the second trimester (28). McGrowder et al. (2009) found a significant relationship between urine calcium and hypertensive disorders during pregnancy, and suggested the urine Ca/Cr ratio as a proper screening test for preeclampsia (29). Other researchers have found similar results, too (30). It is

noteworthy that the lack of a relationship between urine Ca/Cr-ratio and hypertensive disorders in the present study could be due to the small sample size and low incidence of hypertensive disorders. A similar study with a larger sample size in different regions of Iran might produce different results. The present study examined some of the factors affecting the incidence of hypertensive disorders such as pre-pregnancy BMI, inadequate daily calcium intake, desirable nutrition, urine Ca/Cr-ratio, preeclampsia history, insufficient daily intake of energy, smoking in close relatives, mother's age, and parity in the logistic regression test. There was a significant relationship between hypertensive disorders and mother's age and pre-pregnancy BMI. In a 2007 study by Samuels-Kalow in Canada on 13722 pregnant women, pre-pregnancy BMI was shown to increase the risk of hypertensive disorders during pregnancy and mortality (31).

4.1. Conclusions

According to the results of this study, no significant relationship was found between urine Ca/Cr-ratio and hypertensive disorders during pregnancy, however, the level of urine Ca/Cr-ratio was lower in people with hypertensive disorders than that in normal people. A similar study with a larger sample size and a wider scope is recommended. There was also no relationship between nutritional status and hypertensive disorders during pregnancy, which might be due to the low incidence of hypertensive disorders (2.6%) in this study. Hypertensive disorders during pregnancy had a significant relationship with BMI and mother's age. It can be recommended that mothers with a high BMI who are at a high risk for hypertensive disorders receive weight loss training before pregnancy, and be monitored for weight gain during pregnancy. Since more than 80% of pregnant women in this study had undesirable nutrition, they need advice on how to properly consume food during pregnancy and relevant training.

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