

Effect of low trans-fatty acid intakes on preeclampsia: A randomized controlled trial

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Background: Preeclampsia (PE) is a high blood pressure disorder accompanied by proteinuria during pregnancy. It remains unclear whether dietary trans-fatty acid (TFA) can influence PE risk. We examined the effect of low TFA dietary intakes during pregnancy on the risk of PE. **Materials and Methods:** We conducted a randomized open-label controlled trial on 800 pregnant women admitted to public health centers from May 2014 to August 2016. In the intervention group, participants received a diet with TFA <1% and those in the comparison group, participants had dietary intakes with no change on TFA content. Dietary intakes were assessed by 24-h recalls at the first prenatal care visit (<8 weeks) and at gestational ages of 13, 25, and 35 weeks. The hazard ratio (95% confidence interval [CI]) for PE was calculated using the Cox proportional-hazards model. **Results:** There were statistically significant differences in intakes of daily TFAs between the groups ($P < 0.05$). The hazard ratio (95% CI) for the incidence of PE in the intervention group was 0.56 (0.33–0.93). **Conclusion:** Low TFA dietary intake during pregnancy reduced the risk of PE.

Key words: Diet, preeclampsia, pregnancy, trans-fatty acid

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INTRODUCTION

Preeclampsia (PE), a hypertensive disorder in pregnancy involving multiple organs,^[1,2] complicates about 8% of all pregnancies.^[3] PE is associated with adverse pregnancy outcomes such as placenta abruption, preterm birth, low birth weight, and cesarean delivery.^[3-5] This abnormality also has long-term adverse consequences for both mother and child, such as the increased risk of cardiovascular disease and type 2 diabetes.^[6] The World Health Organization reported the prevalence of PE seven times higher in developing countries than in developed countries, possibly due to their lifestyle and nutritional status.^[7]

The most established risk factors for PE include maternal age, race/ethnicity, parity, history of previous hypertension or PE, lifestyle, and dietary pattern of pregnant women, before or during pregnancy.^[1,7-9] For many years, the diet has been suggested to play a role in PE; hypotheses have been diverse and often heterogeneous. Thus, increased dietary carbohydrate and protein and reduced fat and sodium was suggested as being among the etiological factors.^[10] Trans-fatty acids (TFAs) are types of unsaturated fatty acids influencing endothelial function, which could be associated with PE.^[11] Some cohort and case-control studies found the adverse potential of TFAs on PE.^[12-16] To the best of our knowledge, no randomized clinical

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trial has been conducted to investigate the effects of daily TFAs intake on PE. The aim of this study was to investigate the effects of low TFA dietary intakes on the development of PE.

MATERIALS AND METHODS

Study design

Between May 2014 and August 2016, eight hundred pregnant women recruited in this parallel, open-label, randomized controlled trial from eight health centers. Participants randomly divided into the intervention group with low TFAs daily intake during pregnancy and the comparison group without any change in TFAs daily intake.

The study protocol was approved by the Ethics Committee of the Research Institute for Endocrine Sciences (RIES) of ShahidBeheshti University of Medical Sciences (IR.SBMU.ries.Rec. 1394.92). This research was registered on the website of the Iranian Registry of Clinical Trials (www.irct.ir) as an IRCT2016092729902N3 identification number.

Recruitment and patient selection

We assessed the eligibility of pregnant women admitted to public health centers. Participants who had a gestational age <8 weeks, singleton pregnancy, intention to receive prenatal care, $18 \leq \text{body mass index (BMI)} \leq 25 \text{ kg/m}^2$, $18 \leq \text{age} \leq 35$ years, gravid <4, and abortion ≤ 2 were included in the study. We

excluded pregnant women who had any previous histories of chronic disease, PE, or prepregnancy hypertension and those who smoked or drank alcohol. The research coordinator explained the study for the pregnant women, who were given a suitable time to reflect on the information and their questions were answered before they gave free and voluntary consent. A total of 1016 pregnant women were screened for eligibility and were randomized. Among them, 45 pregnant women did not meet inclusion criteria, 31 declined to participate and 28 participants (for other reasons) were excluded from this trial. After exclusion, 912 pregnant women were randomized into two groups (intervention group $n = 455$, control group $n = 457$). Finally, 800 pregnant women remained for the final analysis [Figure 1]. Before enrollment in the study, written informed consent was obtained from all eligible patients who were confirmed by investigators.

Study intervention

Pregnant women were randomly assigned to one of two groups, the intervention ($n = 393$) and the controls ($n = 407$). For all pregnant women, individual dietary patterns were designed based on age, height, prepregnancy weight, and physical activity. Women in the intervention group received individualized dietary patterns with TFA content <1% of total daily energy intake, and in the control group, women received individualized dietary patterns without any focus on TFA content. In the intervention group, we replaced mono- and polyunsaturated fatty acids in the dietary pattern, such as olive oil, fish, nuts, and nonfat dairy products, and

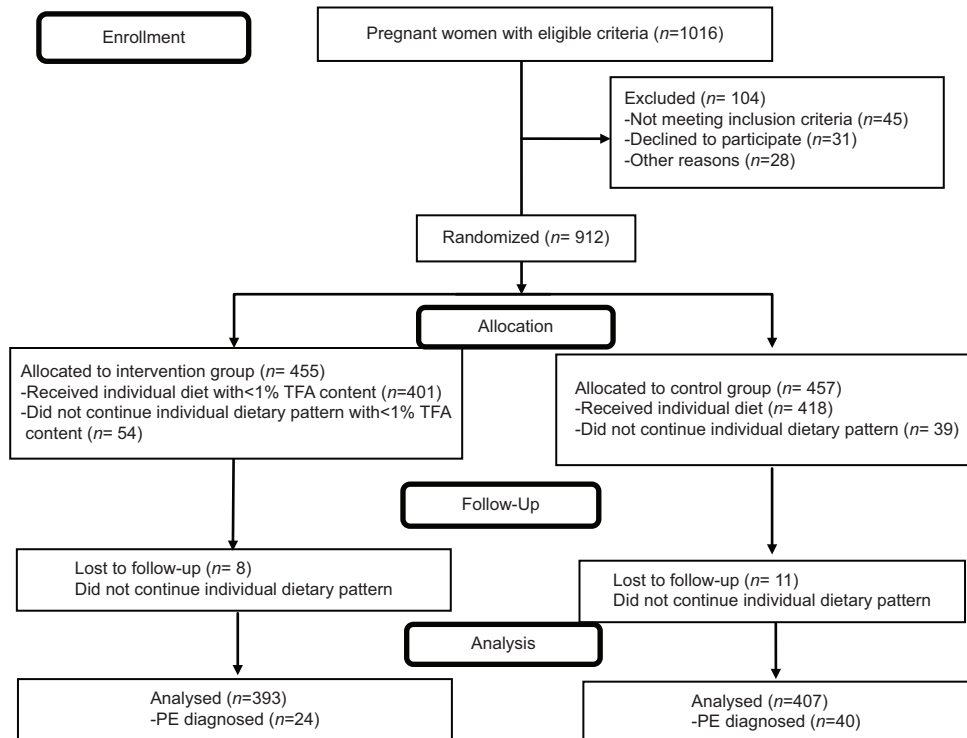


Figure 1: CONSORT flow diagram

participants were forbidden to consume any kind of fast foods, processed meat, and deep-fried foods; however, in the control group, women were allowed to consume all kinds of dairy products and oil for cooking and given routine dietary recommendations. For dietary assessment, we used 24-h dietary recalls (24 h-DRs). For this purpose, expert nutritionists during interviews (20 min) assessed dietary intake of the participants by three nonconsecutive 24-h recalls, one weekend day (Thursday or Friday) and two weekdays. Portion sizes of meals are converted to grams using household measures.^[17] Nutrient intakes, including carbohydrate, protein, and fatty acids, were calculated according to the US Department of Agriculture and the Iranian Food Composition tables.^[18,19] The first recall interviews were conducted at the health center, and the second and third recall interviews were conducted over the phone; 24 h-DRs were also collected at the first prenatal care visit and the end of every trimester (13, 25, and 35 weeks of gestational age). All recalls were checked by nutritionists, and any ambiguities were resolved with the pregnant women. Mixed dishes in 24 h-DRs were converted into their ingredients according to the participants' report on the amount of each food item consumed, thus taking into account variations in meal preparation recipes, for example, soup ingredients – usually vegetables (carrot or green beans), noodles, barley, etc., – differed according to participants' meal preparation.

Randomization

Participants were randomized to intervention or comparison groups in a one-to-one ratio using an online application with a computer-generated randomization sequence with a block size 4.

Randomization and treatment assignment were performed by the research coordinators from health centers not involved in the study.

Obstetric management

Women in both the groups received routine prenatal care. Anthropometric measurements were performed with light clothing and without shoes. Weight and height were measured at the first visit in pregnancy (<8 weeks) according to the standard protocol. BMI was calculated by dividing the weight in kilograms by the square of height in meters, on the basis of weights in prepregnancy, and <8, 13, 25, and 35 gestational weeks. Gestational age was ascertained by the 1st day of the last menstrual period or by ultrasound <12 weeks of gestational age. Pregnant women had monthly obstetric visits up to 28 weeks of gestational age, biweekly visits from week 28 to 36, and weekly visits until the end of the pregnancy. For both the groups, prenatal data were obtained from the patients' medical records.

Outcome ascertainment

Primary outcome measure

Number of patients with a diagnosis of PE was a primary endpoint. The diagnostic was performed when they presented systolic blood pressure (SBP) ≥ 140 mmHg and diastolic blood pressure (DBP) ≥ 90 mmHg on two occasions and accompanied by proteinuria ($\geq 2+$ on dipstick or >300 mg in 24-h urine), according to the definition of the Royal College of Obstetricians and Gynecologists.^[2] The pregnant women stayed seated for 15 min to measure blood pressure twice using a standard mercury sphygmomanometer calibrated by the Iranian Institute of Standard and Industrial Researches. On the basis of the circumference of the pregnant women's arm, a usual cuff is used. The cuff is placed on the right arm and inflated up to the level at which the radial pulse disappeared. There is at least a 60-s interval between those two measurements, and the mean was recorded as the pregnant woman's BP; SBP is distinguished as the appearance of the first sound (Korotkoff phase 1), and DBP is distinguished as disappearance of the sound (Korotkoff phase 5), during deflation of the cuff at 2–3 mm/s decrease rate.

The preeclampsia diagnosis did in the second half of pregnancy the in both the groups.

Sample size and statistical analysis

For evaluation of sample size, we used this formula with considering $\alpha = 0.05$, $1-\beta = 0.80$, OR = 1.2 (CI = 0.87- 1.8) as a result $P_1 = 0.08$, $P_2 = 0.15$, and the probability of miss to follow-up of 20%, left us with 400 persons per group.

$$n = \frac{\left\{ Z_{1-\frac{\alpha}{2}} \sqrt{2\bar{P}(1-\bar{P})} + Z_{1-\beta} \sqrt{P_1(1-P_1) + P_2(1-P_2)} \right\}^2}{(P_1 - P_2)^2}$$

Quantitative data were expressed as mean \pm standard deviation where applicable and qualitative data were presented as percentages. Independent sample *t*-tests and Chi-square were used to compare variables among the two groups. The normality of variables was checked by a histogram chart and one-sample Kolmogorov–Smirnov test. All conflicted variables were matched in both the groups. Since nutritional and obstetrical changes were assessed at baseline and at the end of every trimester, we used repeated measures to analyze those during follow-up. When performing the Cox proportional-hazards model, groups were considered as independent variables and PE as a dependent variable. Incident rates and hazard ratios (95% confidence interval [CI]) for PE based on groups were calculated. The potential confounders for each group were age and BMI in the first model; age, BMI, and gravid in the second model; and age, BMI, gravid, and third-trimester calories intake in the third model [Table 2]. All statistical tests

Table 1: Baseline characteristics of participants based on intervention and control groups

	All (n=800)	Control (n=407)	Intervention (n=393)
Age (years)	24.51±2.81	24.63±2.73	24.42 (2.92)
BMI (kg/m ²) at first visit	21.92±1.64	21.91±1.63	21.97 (1.71)
SBP (mmHg) <8 weeks	109.75 (7.32)	109.76 (7.31)	109.73 (7.64)
DBP (mmHg) <8 weeks	7.33 (1.3)	7.34 (1.1)	7.32 (1.3)
House wives occupation (%)	67.11	66.31	68.23
High school education (%)	67.44	68.41	67.53
Nulliparous	75.32	74.51	76.24
Without any history of abortion (%)	89.31	89.12	89.43

Data are presented as mean (SD) for continuous variables and percent for categorically distributed variables. SD=Standard deviation; BMI=Body mass index; SBP=Systolic blood pressure; DBP=Diastolic blood pressure

Table 2: Hazard ratio (95% confidence interval) for developing preeclampsia based on dietary pattern ≤1% trans-fatty acid intake

Models	Hazard ratio	95% CI	P
Model 1	0.56	0.34-0.93	0.02
Model 2	0.57	0.34-0.94	0.03
Model 3	0.56	0.33-0.93	0.02

Model 1=Adjusted for group; Model 2=Adjusted for group, age, BMI and gravid; Model 3=Adjusted for group, age, BMI, gravid, and third trimester daily calories intake. BMI=Body mass index; CI=Confidence interval

were two sided, and a significant association was confirmed at $P < 0.05$. All statistical analyses were performed using the Statistical Package for the Social Sciences (version 21; SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 800 pregnant women remained for the final analysis (intervention, $n = 393$, and comparison group, $n = 407$) [Figure 1]. Baseline demographic and clinical characteristics were similar in both the groups [Table 1].

A comparison of dietary intakes at baseline and at the end of every trimester between the control and intervention groups revealed no statistically significant differences in intake of daily energy, carbohydrate, protein, and total fat [$P > 0.05$, Table 3]. However, there were statistically significant differences in intakes of daily TFAs in between the two groups [$P < 0.05$, Table 3]. In the intervention group, all participants consumed TFAs ≤1% of their daily energy intake. Pregnant women's blood pressure for each group at weeks 13, 25, and 35 of pregnancy is presented in Table 4. Of the 800 women, 64 women (8%) were diagnosed with PE. The incidence rate of PE in the intervention group was 6%, and in the control group, it was 11%. Hazard ratios (95% CI) for PE in first model was 0.56 (0.34–0.93), for second model, it was 0.57 (0.34–0.94), and for third model, it was 0.56 (0.33–0.93) [Table 2 and Figure 2].

DISCUSSION

We found that the risk of PE in the intervention group decreased by about 50%. The incidence of PE in the

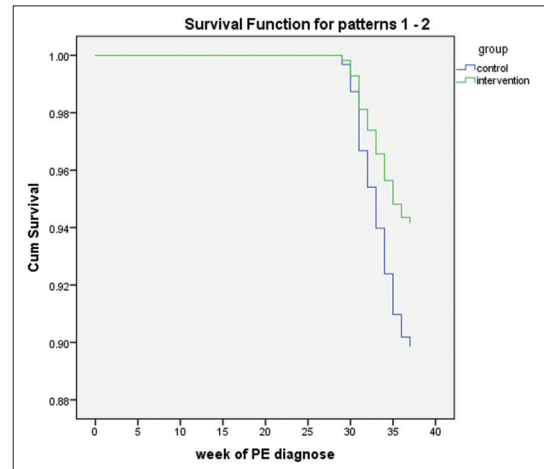


Figure 2: Probability of incident preeclampsia among pregnant women in intervention and control groups adjusted for age, body mass index, gravid, and third trimester daily energy intake ($P < 0.05$)

intervention group was 6% versus 11% in the control group.

Our findings are similar to two previous reports, which found a positive association between erythrocyte levels of TFAs and PE.^[16,20] Mahomed *et al.* reported a strong positive association between erythrocyte levels of TFAs and risk of PE.^[16] Dhaka *et al.* compared the TFA content of erythrocytes from blood samples obtained on the first postpartum day in the United States and reported that pregnant women in the highest tertile of erythrocyte TFAs had a 7.4-fold greater odds of PE compared to pregnant women in the lowest tertile.^[20] On the other hand, the Chavarro *et al.* findings are in sharp contrast with two previous reports; second-trimester intake of TFAs was unrelated to the risk of PE or severe PE.^[21] These differences may be explained by recommendation of individualized diets with TFAs content ≤1% for the intervention group and individualized diets without any focus on TFA content for the controls. In addition, there was a high compliance with the implementation of the diet in our study. Therefore, the effect of this intervention may be exclusively explained by TFA content, as any kind of confounding factor was excluded. However, Chavarro *et al.* did not have any

Table 3: Daily intakes of energy, carbohydrate, protein, total fat, and trans-fatty acids at baseline and at the end of every trimester between the control and intervention groups

	Control	Intervention	P*
Energy (weeks) (kcal)			
<7	2083±241	2024±207	0.06
13	2024±61	2015±54	0.08
25	2352±53	2346±53	0.06
35	2457±50	2447±52	0.07
Carbohydrate (weeks) (%)			
<7	50±3.81	51±3.21	0.06
13	53±3.32	55±2.55	0.07
25	52±3.13	53±2.52	0.06
35	53±2.98	54±2.62	0.07
Protein (weeks) (%)			
<7	13±1.41	12±1.36	0.06
13	18±1.24	19±1.25	0.08
25	17±1.23	18±1.26	0.07
35	17±1.11	18±1.02	0.07
Total fat (weeks) (%)			
<7	37±9.89	37±8.03	0.06
13	30±6.65	30±6.23	0.08
25	31±3.12	30±3.24	0.08
35	30±2.61	29±2.94	0.07
TFA (weeks) (%)			
<7	10±2.32	9±1.34	0.07
13	8±1.33	0.90±0.12	0.04
25	7±1.15	0.91±0.15	0.03
35	7±1.45	0.89±0.31	0.03

Data are presented as mean (SD). *P for repeated measures test. SD=Standard deviation; TFA=Trans-fatty acids

Table 4: The mean and standard deviation of blood pressure in 13,25,35 weeks of pregnancy in the control and intervention groups

	SBP		DBP		P
	Control	Intervention	Control	Intervention	
13 weeks	109 (7.2)	108 (6.3)	71 (1.5)	72 (0.9)	<0.001
25 weeks	112 (12.8)	108 (7.1)	77 (2.9)	69 (1.4)	
35 weeks	120 (17.8)	108 (6.9)	81 (3.1)	72 (1.1)	

SBP=Systolic blood pressure; DBP=Diastolic blood pressure

intervention and only prospectively investigated the diet with a food frequency questionnaire at gestation week 25.

TFA are known to have a negative effect on PE risk by influencing endothelial function, inflammatory response, and insulin resistance.^[10,11,22-25] These fats have been related with higher circulating levels of chronic inflammatory markers and endothelial dysfunction.^[11,22] Trans fats also increased insulin resistance.^[23-25] In addition, TFA levels in erythrocytes have been related to a higher risk of PE. In the current study, TFA intake was reduced to ≤1% of the

total energy intake and replaced by monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs). There are several possible mechanisms involved in expressing the effect of MUFAs and PUFA on the risk of PE. MUFAs and PUFAs in the dietary pattern play an important role in the prevention of a range of metabolic-related chronic diseases.^[9] Endothelial cell function may be influenced by MUFAs and PUFAs in dietary patterns.^[22,26] Furthermore, studies were shown that MUFAs and PUFAs in dietary patterns can reduce cardiovascular disease risk by affecting inflammatory markers and insulin resistance.^[9,27]

The strengths of the present study were individualized dietary patterns for both the groups during pregnancy (initiated <8 weeks), with differences in the TFA content (≤1% in intervention group), assessed by 24 h-DR questionnaires at the first prenatal care visit and at the end of every trimester. In addition, we had high compliance of participants, as all participants executed the dietary pattern precisely. Furthermore, we omitted other maternal risk factors that have previously been shown to be important for PE. Although we used clinically measured blood pressure and urine values, we applied research criteria to outcome definitions. Our sample size was large enough to detect the accurate effect of TFA intake on risk of PE; to the best of our knowledge, no previous clinical trials have investigated the effect of TFA intake on risk of PE.

Some limitations of the study should also be considered. First, had we taken blood samples to assess serum level TFAs, it would have given us sufficient power to truly assess circulating TFA content. Another limitation of our study is the narrow intake range for industrial TFAs in this population, which made it impossible to differentiate in our data whether TFA intake was definitely unrelated to PE or whether it was related to this condition but only at intake levels that could not be observed in our study. To resolve this question, further research is needed in populations that remain exposed to large amounts of industrial TFAs in their food supply. Answering this question has major public health concerns.

CONCLUSION

This study indicates that nutritional intervention can facilitate the control of gestational hypertension, improve prenatal outcomes, and reduce the incidence of pregnancy complications, such as PE. There were no adverse effects on the incidence of pregnancy or birth complications. Management of maternal nutrition, focusing on TFA content, should be included in routine prenatal care to facilitate interventions and guidance regarding maternal nutrition, with the goal of reducing the incidence of maternal and fetal diseases and improving the quality of

obstetric care. Further interventional studies are needed to confirm these results.

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Conflicts of interest

There are no conflicts of interest.

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