High intake of energy, sucrose, and polyunsaturated fatty acids is associated with increased risk of preeclampsia

Torun Clausen, MD,[a] Malene Slott, MS,[b*] Kari Solvoll, PhD,[b] Christian A. Drevon, MD, PhD,[b] Stein E. Vollset, MD, PhD,[c] and Tore Henriksen, MD, PhD[d]

Oslo, Norway

OBJECTIVE: Preeclampsia is associated with high body mass index, insulin resistance, and hypertriglyceridemia. Our objective was to investigate prospectively whether diet in the first half of pregnancy is associated with the risk for preeclampsia.

STUDY DESIGN: This prospective, population-based, cohort study of pregnant women investigated dietary intake early in the second trimester with a quantitative food frequency questionnaire.

RESULTS: The questionnaire was completed by 3133 women (83%). Preeclampsia developed in 85 women. Adjusted odds ratio (95% CI) for preeclampsia was 3.7 (1.5-8.9) for energy intake of >3350 kcal/d compared with ≤2000 kcal/d. Adjusted odds ratio (95% CI) for preeclampsia was 3.6 (1.3-9.8) for sucrose intake (percent of total energy) of >25% compared with ≤8.5% and 2.6 (1.3-5.4) for polyunsaturated fatty acids intake (percent of total energy) of >7.5% compared with ≤5.2%. Other energy-providing nutrients were not associated with the risk for preeclampsia.

CONCLUSION: The current study suggests that high intakes of energy, sucrose, and polyunsaturated fatty acids independently increase the risk for preeclampsia. (Am J Obstet Gynecol 2001;185:451-8.)

Key words: Preeclampsia, diet, polyunsaturated fatty acids, sucrose, energy

The objective of the current study was to determine whether the increasing prevalence of overweight metabolic syndrome and, by implication, changes in dietary and physical behaviors[1] have adverse obstetric and perinatal consequences.

Preeclampsia is characterized by the development of hypertension and proteinuria after 20 weeks' gestation.[2] Preeclampsia is found in 3% to 10% of pregnancies and remains a major cause of maternal and fetal morbidity and mortality worldwide.[2]

Although hypertension is the main clinical characteristic of preeclampsia, preeclampsia is much more than a hypertensive disease.[3] Preeclampsia develops as a consequence of a complex interaction among a multiplicity of factors originating in two genetically different individuals, the mother and the fetus.

From the Departments of Obstetrics and Gynecology, Aker and Ullevaal University Hospitals[a] and National Hospital,[d] the Institute for Nutrition Research,[b] University of Oslo, and the Section for Medical Informatics and Statistics, University of Bergen.[c]

Supported by the Throne-Holst Foundation, the Freia Foundation, and Eckbos Legate.

Received for publication October 27, 2000; revised February 30, 2001; accepted April 24, 2001.

Reprint requests: Torun Clausen, MD, Department of Obstetrics and Gynecology, Ullevaal University Hospital, 0407 Oslo, Norway. E-mail: torun.clausen@ioks.uio.no.

**Currently at the Norwegian Radium Hospital.*

0002-9378/2001 $35.00 + 0 ***6/1/116687***

doi:10.1067/mob.2001.116687

In pregnancies affected by preeclampsia, there is insufficient development of the uteroplacental unit called "shallow placentation."[3] The uterine spiral arteries, which carry the maternal blood to the placenta, are not remodeled to the extent found in healthy pregnancies. This inadequate remodeling of the spiral arteries causes insufficient blood supply to the intervillous space of the placenta, which promotes local ischemia.[3] It is then assumed that ischemic damage of uteroplacental tissues leads to the release of oxidized products, other cell components, cytokines, and activated leukocytes, which may induce endothelial dysfunction in the systemic maternal circulation.[3]

In addition to components from the uteroplacental unit, several nontrophoblastic maternal factors also play a critical role in the development of the disease. These factors include chronic hypertension, dyslipidemia, insulin resistance, diabetes, adiposity, and hemostatic disturbances.[4-6] All of these conditions are characteristics of the so-called metabolic syndrome or insulin resistance syndrome.[4] Endothelial cell dysfunction is present in persons with the metabolic syndrome.[4] Patients with features of the metabolic syndrome may therefore have vascular endothelium that is particularly sensitive to the components released from the uteroplacental unit.

Thus all factors that promote metabolic syndrome may also increase the risk for the development of preeclampsia.[7] Furthermore, excessive postprandial glucose levels and excessive postprandial lipidemia are associated with

the dysfunction of vascular endothelium.[8] Therefore dietary factors might play a role in the development of preeclampsia. In this prospective study of 3133 women, we have investigated the relationship between diet in the first half of pregnancy and the risk of the development for preeclampsia.

Material and methods

Study population. The study was performed at Aker University Hospital in Oslo, Norway. The study population covered defined geographic areas of Oslo, representing all socioeconomic classes. Nearly 95% of the pregnant women in these areas gave birth at this hospital. The transfer of women to other hospitals because of medical reasons was exceptional (<0.5%). All pregnant women who were to have their baby delivered at Aker Hospital were offered an ultrasonographic scan at 17 to 19 weeks' gestation. From December 1994 to August 1996, the 4748 Caucasian women who received the offer of an ultrasonographic scan in the first or early second trimester were simultaneously asked to fill in a food frequency questionnaire and return it at the time of the scan. Women with pregestational diabetes were not included because they were followed up at a separate outpatient clinic for persons with diabetes. Nine hundred fifty-four of the women initially asked were excluded for the following reasons: abortion (<22 weeks' gestation) (n = 143), Caucasians who only spoke foreign languages (n = 29), blind (n = 2), twin or triple pregnancies (n = 58), patients who gave birth in other hospitals primarily as a result of moving out of the area (n = 393), medical records missing (n = 8), and patients who were lost to follow-up (n = 344). Women in the "lost to follow-up" group did not show up for the routine ultrasonographic scan at the hospital and/or did not deliver at Aker Hospital. A completed questionnaire was obtained from 3133 (83%) of the remaining 3771 women. The study was approved by the Regional Medical Ethics Committee and written informed consent was obtained from each woman who participated.

Definition of preeclampsia. Diagnosis of preeclampsia required the presence of proteinuria and pregnancy-induced hypertension. Proteinuria was defined by readings of ≥+1 on a dipstick (300 mg/24 h); readings were taken at least twice, with an interval of ≥6 hours between measurements. Pregnancy-induced hypertension was defined either as blood pressure ≥140/90 mm Hg or as an increase in diastolic pressure of ≥15 mm Hg compared with average measurements before 20 weeks' gestation. In both cases two measurements taken ≥6 hours apart were required. The diagnosis of preeclampsia was made by 3 of the authors (T. Clausen, M. Slott, and T. Henriksen) after reviewing the medical records of each woman after delivery. The women diagnosed with preeclampsia were divided into groups of early- and late-onset preeclampsia. We defined early-onset preeclampsia to be present if the diagnosis was made before 37 completed weeks' gestation. The rationale behind this categorization was that early-onset preeclampsia is clinically more complicated because of the severity of the disease, the problem of premature delivery, and the increased prevalence of intrauterine growth retardation.[2]

Quantitative food frequency questionnaire. The dietary intake was assessed by a self-administered quantitative food frequency questionnaire listing approximately 180 food items. The method has been described in detail elsewhere[9-13] and was designed to cover as much of the total diet as possible. The questionnaire included foods normally used in bread-based meals, foods for main meals, cakes, cookies, fruits, typical snack products, and beverages. Dietary supplements, such as cod liver oil, fish oil capsules, and 4 items of vitamin and mineral supplements were included. In the current study the women were asked to indicate their food intake during the current pregnancy.

The food frequency questionnaire has been evaluated in 4 different studies.[10-12] The completed forms, with frequencies and portion sizes filled in, were processed by optical mark reading. The reading program and the program calculating the average consumption per person per day for each food item were developed especially for this purpose. The mean individual daily intake of energy and nutrients was calculated after the questionnaire data were transferred into a nutrition calculation system developed at the Institute for Nutrition Research at the University of Oslo.

The questionnaire also included questions about physical activity. Frequency of exercise was evaluated by the question: How often do you have physical exercise for at least 20 minutes (walking, jogging, bicycling, and swimming)? The following options could be marked: never, <1 time/wk, 1 time/wk, 2-3 times/wk, 4-6 times/wk, and daily. Intensity of exercise was determined by the categories "easy exercise, not out of breath or sweating" or "hard exercise, out of breath or sweating."

Satisfactory completion of the questionnaire was checked on return of the questionnaire. In 7 cases satisfactory completion of the questionnaire was not achieved, and these women were categorized as nonresponders.

Data about educational level and smoking habits were collected from the medical records.

Statistical analysis. Proportions were compared using the χ^2 test. The 2-sample t test was used to compare means of continuous variables. When more than two groups were being compared, linear regression was used to test for a linear trend in means between categories. Correlation was estimated by the Pearson correlation coefficient.

Relative risk for preeclampsia was evaluated by multiple logistic regression analyses. We used the odds ratio

Table I. Characteristiscs of the cohort and daily intake of energy and energy-providing nutrients

	Cohort (n = 3133)*	*Without preeclampsia* (n = 3048)*	*Preeclampsia (all)* (n = 85)*	*Statistical significance†*	*Preeclampsia at ≥37 weeks' gestation* (n = 58)*	*Preeclampsia at <37 weeks' gestation* (n = 27)*	*P trend‡*
Age (y)	29.8 (4.5)	29.9 (4.5)	29.2 (4.9)	.16	29.6 (4.8)	28.2 (5.0)	.07
BMI in first trimester (kg/m^2)	22.9 (3.7)	22.9 (3.7)	23.7 (4.3)	.04	23.2 (3.3)	24.9 (5.7)	.009
Blood pressure before 20 weeks' gestation (mm Hg)	113/68 (11/8)	113/68 (10/8)	117/70 (11/9)	<.001/.01	117/71 (11/8)	117/69 (13/11)	.001/.04
Blood pressure at delivery (mm Hg)	118/74 (12/10)	117/73 (11/9)	146/96 (15/10)	<.001/<.001	143/95 (12/8)	154/99 (19/11)	<.001/<.001
Gestational age (wk)	39.6 (1.8)	39.5 (1.7)	37.8 (3.4)	<.001	39.4 (1.4)	34.0 (3.8)	<.001
Birth weight (g)	3584 (555)	3598 (535)	3072 (932)	<.001	3495 (603)	2168 (887)	<.001
Maternal weight gain (kg)	15.3 (5.4)	15.3 (5.4)	16.8 (6.4)	.05	19.1 (5.4)	11.4 (5.0)	.73
Smoking, No. (%)	693 (22.0)	682 (22.4)	11 (12.9)	.04§	7 (12.1)	4 (14.8)	
Nullipara, No. (%)	1623 (51.8)	1560 (51.2)	63 (74.1)	<.001§	41 (70.7)	22 (81.5)	
Diet							
Energy, kcal/d	2020 (576)	2015 (571)	2192 (708)	.03	2091 (671)	2409 (749)	.001
Total fat (E%)	30.3 (5.2)	30.4 (5.2)	30.1 (5.0)	.63	30.2 (4.9)	29.7 (5.3)	.55
Saturated (E%)	12.0 (2.4)	12.0 (2.4)	11.5 (2.3)	.07	11.6 (2.3)	11.5 (2.3)	.07
Monounsaturated (E%)	10.6 (2.0)	10.6 (2.0)	10.6 (2.0)	.90	10.6 (1.9)	10.5 (2.3)	.82
Polyunsaturated (E%)	5.4 (1.7)	5.4 (1.7)	5.7 (1.6)	.20	5.7 (1.6)	5.6 (1.4)	.26
ω-3 Fatty acids (E%)	0.96 (0.45)	0.96 (0.45)	1.05 (0.51)	.06	1.06 (0.48)	1.02 (0.57)	.10
ω-6 Fatty acids (E%)	4.05 (1.43)	4.05 (1.43)	4.20 (1.28)	.34	4.21 (1.37)	4.18 (1.07)	.38
Protein (E %)	15.9 (2.4)	16.0 (2.3)	15.5 (2.7)	.05	15.9 (2.2)	14.5 (3.3)	.008
Nonsucrose carbohydrate (E%)	43.8 (6.2)	43.8 (6.2)	42.9 (6.6)	.17	44.2 (5.5)	40.1 (7.8)	.03
Sucrose (E%)	9.6 (5.9)	9.6 (5.9)	11.4 (7.6)	.03	9.5 (5.3)	15.4 (10.0)	<.001

*Values are mean (SD).
†Student *t* test ("without preeclampsia" and "preeclampsia").
‡Linear regression in means between categories ("without preeclampsia," "late-onset preeclampsia," and "early-onset preeclampsia").
§χ^2 test ("without preeclampsia" and "preeclampsia").

(OR) to approximate relative risk. In all regression analyses, the covariates were represented by indicator variables to allow for nonlinear dose-response relationships. Systolic blood pressure measured before 20 weeks' gestation was included in the model as a continuous variable. The independent nutrient variables were categorized according to the following percentiles of distribution: ≤50, 50-90, 90-97.5, and >97.5. This categorization allowed for examination of the dose-response relationship for extreme upper categories. For some of the nutrients, the number of cases in the >97.5 percentile group was too small for statistical analysis; therefore the two upper categories were combined. Tests for linear trends were used to assess graded associations.

P values <.05 were considered to indicate statistical significance.

Results

The main characteristics of the 3133 pregnant women in the cohort are presented in Table I.

Preeclampsia developed in 85 (2.7%) of the 3133 women in the cohort. Twenty-seven women had early-onset preeclampsia (<37 weeks' gestation). Two women with preeclampsia had gestational diabetes and 2 had chronic hypertension. Ten of the women with preeclampsia developed hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome; 7 of these women were in the group with early-onset preeclampsia. Preeclampsia developed in 5 women (9.6%) of the 52 subjects who were 20 years old or younger. We found no statistical difference in risk for preeclampsia among women with different educational levels and different levels of leisure-time physical activity (data not shown).

Intake of energy and energy-providing nutrients. Table I shows the mean intake of energy and energy-yielding nutrients among women in the cohort. The mean intakes among women with and without subsequent preeclampsia and in the subgroups of late- and early-onset preeclampsia are also presented. Intake of energy and sucrose in percent of total energy (E%) was higher in women with preeclampsia compared with women without preeclampsia. When categorizing the women according to disease status, we found a significant trend toward increasing intake of energy (kcal/d) and sucrose (E%) across the categories

Table II. Adjusted risk (OR)* for preeclampsia related to daily intake of energy and energy-providing nutrients in percent of energy

	No. in cohort	*No. of subjects with preeclampsia (%)*	*OR* (95% CI) not adjusted for energy*	*OR* (95% CI) adjusted for energy*
Energy (kcal/d)				
≤2000	1652	36 (2.2)		1.0
2000-2750	1167	29 (2.5)		1.2 (0.7-2.0)
2750-3350	233	12 (5.2)		2.7 (1.3-5.4)
>3350	81	8 (9.9)		5.4 (2.3-12.4)
P for trend				.0001
Total fat (E%)				
≤30.0	1535	40 (2.6)	1.0	1.0
30.0-37.0	1265	41 (3.2)	1.4 (0.9-2.2)	1.3 (0.8-2.1)
>37.0	333	4 (1.2)	0.6 (0.2-1.8)	0.5 (0.2-1.4)
P for trend			.83	.74
Saturated fatty acids (E%)				
≤12.0	1601	49 (3.1)	1.0	1.0
12.0-15.0	1220	32 (2.6)	0.9 (0.6-1.4)	0.9 (0.5-1.4)
>15.0	312	4 (1.3)	0.5 (0.2-1.4)	0.4 (0.1-1.1)
P for trend			.24	.10
Monounsaturated fatty acids (E%)				
≤10.5	1512	40 (2.6)	1.0	1.0
10.5-13.0	1274	36 (2.8)	1.2 (0.7-1.9)	1.2 (0.7-1.8)
>13.0	347	9 (2.6)	1.3 (0.6-2.8)	1.1 (0.5-2.4)
P for trend			.38	.59
Polyunsaturated fatty acids (E%)				
≤5.2	1426	29 (2.0)	1.0	1.0
5.2-7.5	1395	44 (3.2)	1.7 (1.1-2.8)	1.6 (1.0-2.7)
>7.5	312	12 (3.8)	2.5 (1.3-5.1)	2.3 (1.1-4.6)
P for trend			.004	.01
ω-3 Fatty acids (E%)				
≤0.9	1683	39 (2.3)	1.0	1.0
0.9-1.6	1154	35 (3.0)	1.4 (0.9-2.3)	1.4 (0.9-2.2)
>1.6	296	11 (3.7)	1.9 (0.9-3.8)	1.8 (0.9-3.7)
P for trend			.04	.06
ω-6 Fatty acids (E%)				
≤3.8	1537	34 (2.2)	1.0	1.0
3.8-5.8	1264	38 (3.0)	1.5 (0.9-2.4)	1.4 (0.8-2.2)
>5.8	332	13 (3.9)	2.2 (1.1-4.4)	1.9 (1.0-3.8)
P for trend			.01	.05
Protein (E%)				
≤16.0	1583	52 (3.3)	1.0	1.0
16.0-19.0	1264	27 (2.1)	0.6 (0.4-0.9)	0.7 (0.4-1.1)
>19.0	286	6 (2.1)	0.5 (0.2-1.2)	0.6 (0.3-1.5)
P for trend			.02	.11
Nonsucrose carbohydrate (E%)				
≤43.0	1423	46 (3.2)	1.0	1.0
43.0-52.0	1433	33 (2.3)	0.6 (0.4-1.0)	0.7 (0.5-1.2)
52.0-56.0	194	5 (2.6)	0.7 (0.3-1.9)	0.9 (0.3-2.4)
>56.0	83	1 (1.2)	0.4 (0.1-2.9)	0.5 (0.1-3.4)
P for trend			.07	.25
Sucrose (E%)				
≤8.5	1581	37 (2.3)	1.0	1.0
8.5-17.0	1246	33 (2.6)	1.1 (0.7-1.8)	1.0 (0.6-1.6)
17.0-25.0	226	9 (4.0)	1.8 (0.9-3.9)	1.5 (0.7-3.2)
>25.0	80	6 (7.5)	3.8 (1.5-9.8)	2.8 (1.0-7.2)
P for trend			.01	.10

*OR adjusted for age, smoking (yes or no), BMI (≤20, 20-25, 25-30, >30), systolic blood pressure before 20 weeks' gestation, and nullipara (yes or no). The following data were missing: BMI (n = 45; without preeclampsia), smoking (n = 8; without preeclampsia), BMI and smoking (n = 2; without preeclampsia), systolic baseline blood pressure (n = 32; 31 without preeclampsia and 1 with preeclampsia).

"without preeclampsia," "late-onset preeclampsia," and "early-onset preeclampsia." In particular the mean (SD) intake of sucrose was 15.4 (10.0)% among women with early-onset preeclampsia compared with 9.5 (5.3)% among women without preeclampsia ($P < .001$). Intake of protein and nonsucrose carbohydrates in E% was lowest among the women with early-onset preeclampsia.

When the intake was calculated as grams per day, there was a significant trend toward increasing intake of monounsaturated and polyunsaturated fatty acids, total fat, and sucrose across the categories "without preeclampsia," "late-onset preeclampsia," and "early-onset preeclampsia" (data not shown). Mean (SD) intake of sucrose was 2-fold higher in women with early-onset preeclampsia com-

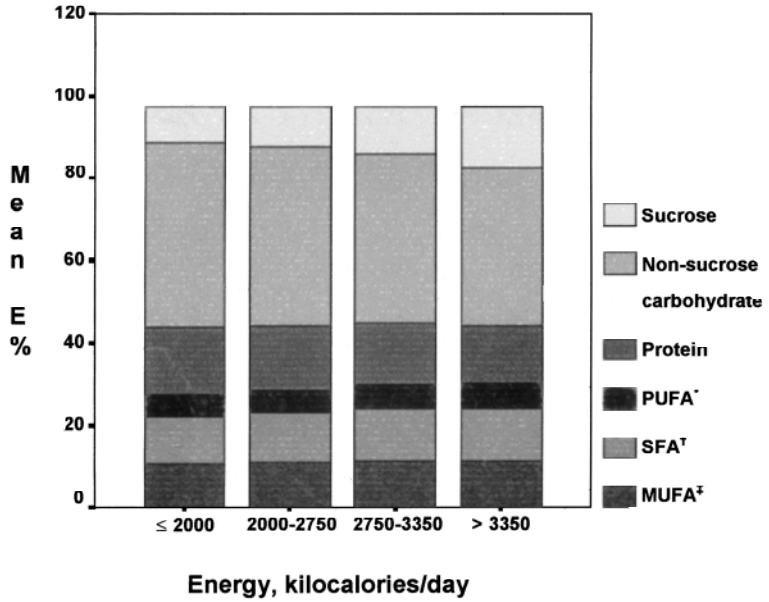

Fig 1. Mean intake of energy-providing nutrients in percent of total energy intake (E%) according to increasing levels of energy intake (kcal/d) among 3133 pregnant women. *PUFA,* Polyunsaturated fatty acids; *SFA,* saturated fatty acids; *MUFA,* monounsaturated fatty acids.

pared with the women without preeclampsia (100 [86] g/d vs 49 [38] g/d; $P = .004$).

Odds ratios of preeclampsia according to intake of energy and energy-giving nutrients. Table II shows OR for preeclampsia related to energy intake and energy-providing nutrients with adjustment for age, parity, smoking, body mass index (BMI), and systolic blood pressure before 20 weeks' gestation. The OR of preeclampsia related to energy-providing nutrients (E%) was estimated both with and without adjustment for total energy intake. Energy and energy-providing nutrients were intercorrelated (Fig 1). We therefore included those nutrients associated with preeclampsia into a combined final model shown in Table III.

ORs (95% CI) for preeclampsia increased with increasing levels of energy intake. With ≤2000 kcal/d as the reference level, the OR for preeclampsia was 2.7 for energy intake of 2750-3350 kcal/d and 5.4 for intake of >3350 kcal/d ($P = .0001$; Table II). In the final combined model (Table III), the corresponding values for OR were 2.3 and 3.7 ($P = .003$).

With ≤8.5% as the reference level for sucrose intake, the energy-adjusted ORs for preeclampsia for sucrose intake (E%) between 17% to 25% and >25% were 1.5 and 2.8, respectively (Table II). The corresponding values were 1.7 and 3.6 in the combined model ($P = .04$; Table III).

We also found a positive association between intake of polyunsaturated fat (E%) and energy-adjusted risk for preeclampsia. With ≤5.2% as the reference level, the OR for preeclampsia was 1.6 for intake between 5.2% and 7.5% and 2.3 for intake of >7.5% (Table II). In the combined model (Table III), the corresponding values were 1.8 and 2.6 ($P = .004$). Further adjustments for intake of vitamins C and E did not change the results (data not shown). When the intake of polyunsaturated fat was categorized into ω-3 and ω-6 fatty acids, a positive and independent association with the risk for preeclampsia was found for each category.

The associations between risk for preeclampsia and intake of sucrose (E%) and polyunsaturated fatty acids (E%) were stronger without adjustment for energy (Tables II and III).

The data suggested a tendency toward decreasing OR for preeclampsia with increasing intake of protein (E%) (Table II). We did a multiple logistic regression analysis that included protein (E%), polyunsaturated fatty acids (E%), sucrose (E%), and total energy intake. In this model the associations between risk for preeclampsia and intake of energy, polyunsaturated fatty acids, and sucrose remained, but the association between protein intake and risk for preeclampsia disappeared. Protein intake was therefore not included in the final model.

BMI was positively associated with risk for preeclampsia after adjustment for energy, sucrose, and polyunsaturated fatty acids ($P = .046$; data not shown).

The associations between nutrient intake and risk for preeclampsia were also analyzed using crude intakes (g/d) with adjustment for energy. Essentially, similar results were found as in the models using relative values (E%; data not shown).

We analyzed the associations between intake of energy, sugar (E%), and polyunsaturated fatty acids (E%) and OR for early-onset preeclampsia. As shown in Table III, intakes of energy and sucrose had a stronger association

Table III. AOR* for preeclampsia and early-onset preeclampsia (<37 weeks' gestation) related to different intakes before 20 weeks' gestation

		Preeclampsia			*Preeclampsia <37 wk gestation*		
	No. of subjects in cohort	*No. (%)*	*OR* (95% CI) model not inluding energy*	*OR* (95% CI) model inluding energy*	*No. (%)*	*OR* (95% CI) model not including energy*	*OR* (95% CI) model including energy*
Energy (kcal/d)							
≤2000	1652	36 (2.2)		1	9 (0.5)		1
2000-2750	1167	29 (2.5)		1.1 (0.7-1.9)	9 (0.8)		1.4 (0.6-3.7)
2750-3350	233	11 (4.7)		2.3 (1.1-4.6)	4 (1.8)		3.1 (0.9-10.9)
>3350	81	8 (9.9)		3.7 (1.5-8.9)	5 (6.2)		8.6 (2.4-30.6)
P for trend				.003			.001
Sucrose (E%)†							
≤8.5	1581	37 (2.3)	1	1	8 (0.5)	1	1
8.5-17	1246	33 (2.6)	1.2 (0.7-1.99)	1.1 (0.6-1.7)	11 (0.9)	1.8 (0.7-4.6)	1.6 (0.6-4.1)
17-25	226	9 (4.0)	2.1 (1.0-4.5)	1.7 (0.8-3.8)	3 (1.3)	2.9 (0.7-11.4)	1.9 (0.4-8.0)
>25	80	6 (7.5)	5.0 (2.0-13.1)	3.6 (1.3-9.8)	5 (6.3)	17.8 (5.2-61.4)	10.3 (2.8-38.5)
P for trend			.003	.04		.0001	.003
Polyunsaturated fatty acids (E%)							
≤5.2	1426	29 (2.0)	1	1	10 (0.7)	1	1
5.2-7.5	1395	44 (3.2)	1.9 (1.2-3.1)	1.8 (1.1-3.0)	15 (1.1)	2.2 (0.9-5.1)	2.0 (0.8-4.7)
>7.5	312	12 (3.8)	3.0 (1.4-6.1)	2.6 (1.3-5.4)	2 (0.7)	1.7 (0.3-8.1)	1.3 (0.3-6.6)
P for trend			.0009	.004		.18	.29

*Multiple regression analysis including the following covariates: age, smoking (yes/no), BMI (≤20, 20-25, 25-30, >30), systolic blood pressure before 20 weeks' gestation, nullipara (yes/no), sucrose in percent of total energy (E%; 4 categories), and polyunsaturated fatty acids in percent of total energy (E%; 3 categories). The following data were missing: BMI (n = 45; without preeclampsia), smoking (n = 8; without preeclampsia), BMI and smoking (n = 2; without preeclampsia), BMI and systolic baseline blood pressure (n = 2; without preeclampsia), systolic baseline blood pressure (n = 29; 28 without preeclampsia and 1 with preeclampsia), systolic baseline blood pressure and smoking (n = 1; without preeclampsia).

†Percent of total energy.

with the risk for early-onset preeclampsia than for the entire group of women with preeclampsia.

Individual food items and preeclampsia. We also assessed the risk for preeclampsia with respect to individual food items. The most striking finding was the intake of sugar-containing soft drinks. Women in whom preeclampsia did not develop had an intake of 189 mL/d, whereas the intake was 203 mL/d among women with late-onset preeclampsia and 653 mL/d among women with early-onset preeclampsia. We found no differences in intake of meat, fish, vegetables, and fruits.

Among the women with high sucrose intake (ie, >25% of total energy intake), sugar-containing soft drinks accounted for 68% of the sucrose intake (g/d) compared with 20% for women with sucrose intake ≤8.5% of total energy intake.

Comment

In this prospective cohort study of 3133 pregnancies, we found increased risk for preeclampsia among women reporting high dietary intake of energy, sucrose, and polyunsaturated fatty acids early in the second trimester.

The validity of the reported dietary intake depends on the method of data collection. The method used in the current study has been extensively validated against 14-day weighed records, 48-hour recalls, and the concentration of very-long-chain ω-3 fatty acids in plasma phospholipids.[10-12] These studies have shown that the questionnaire used in the current study is useful to rank energy intake among subjects and groups and to assess intakes in a wide range of nutrients, although the method has not been validated for pregnant women. However, the primary purpose of the current study was not to record the absolute values of the nutritional intakes but rather to compare the dietary intakes in groups of pregnant women from the same cohort and assess the associations between categories of dietary intake and risk for preeclampsia.

We have categorized the subjects into groups with different intakes of energy and energy-providing nutrients according to 50, 90, and 97.5 percentiles. Our results might reflect systematic overreporting or underreporting among groups of subjects, although we consider this unlikely. In a Norwegian nationwide survey using the same questionnaire as in our study, underreporters were older, had lower physical activity scores, higher BMIs, and were more likely to be obese.[13] Overreporters were younger, had lower BMIs, were more likely to smoke, and were more likely to be lean.[13] We found similar tendencies in our cohort (data not shown). The fact that women with preeclampsia had higher BMIs and smoked less frequently than the healthy pregnant women makes overreporting in this group unlikely. Furthermore, in the

multiple logistic regression analyses performed in the current study, we adjusted for the factors that characterize overreporters (ie, BMI, age, and smoking).

Adjustment for energy in studies of association between nutrient intake and disease has been extensively discussed.[14] Because energy intake may reflect differences in physical activity as well as metabolic efficiency, we have chosen to include adjustment for total energy in our analyses.

Intake of energy. The main determinants of variation in individual energy intake are body size, metabolic efficiency, and physical activity.[14] Changes in body energy stores because of intakes greater than or less than energy expenditure may also account for a part of the observed variation among subjects.[14] Pregnancy is an anabolic state in the first and second trimesters.[15] The total energy expenditure during pregnancy seems to vary substantially among subjects because of profound intersubject differences in metabolic response to pregnancy, deposition of lipid reserves, and variation in physical activity among pregnant women.[15] The association between energy intake and risk for preeclampsia in the current study was independent of BMI and estimates of physical activity. However, evaluation of the latter was formed solely on the basis of information from the questionnaire, which made us somewhat cautious about the impact of physical activity. The higher BMIs in the women with preeclampsia argue against higher physical activity among these women.

There are plausible physiologic explanations for the association between high energy intake and increased risk for preeclampsia that make our findings biologically plausible. Given similar physical activity and metabolic efficiency, a higher intake of energy will promote increased deposition of fat. We found a positive association between reported energy intake and weight gain through pregnancy in the cohort (data not shown). However, weight gain is difficult to evaluate in women with preeclampsia because of an increased frequency of edema. Assuming increased fat stores in the group with preeclampsia, the physiologic insulin-resistance evoked by pregnancy per se may be amplified. The metabolic dysfunction, including dyslipidemia, that characterizes insulin resistance syndromes is also a feature of women with preeclampsia.[4] Dyslipidemia is already present early in pregnancy in women in whom preeclampsia develops later, implying that these women may be particularly susceptible to the adverse effects of high energy intake or weight gain during pregnancy.[5]

Intake of sugar (sucrose). The insulin response during pregnancy is altered toward insulin resistance.[16] During glucose challenge the pregnant woman is stimulated to produce additional insulin, but her blood glucose level still remains elevated for a longer period.[16] Within normal range, the level of plasma glucose 1 hour after an oral glucose challenge at 17 weeks' gestation has been shown to be positively correlated with the risk for preeclampsia.[17] Furthermore, carbohydrate intolerance in pregnant women without overt gestational diabetes seems to be associated in a graded manner with an increased risk for preeclampsia.[18] It is likely that high intake of sugar in pregnant women, particularly in those with glucose intolerance, promotes prolonged periods of increased circulating glucose levels. Hyperglycemia after glucose loading suppresses endothelium-dependent vasodilatation.[19] Endothelial dysfunction is a central part of the pathogenesis of preeclampsia.[3] Thus the association between high intake of sucrose and the increased risk for preeclampsia may be explained by an adverse effect of hyperglycemia on the maternal vascular endothelial cells. Hyperglycemia could also induce vascular dysfunction by glycosylation of protein.[20] The observation that subjects with diabetes, who have high levels of glycosylated hemoglobin, also have the highest risk for preeclampsia is compatible with the role of protein glycosylation in the pathogenesis of preeclampsia.[21] Finally, high intake of sucrose may worsen the dyslipidemia already present in women in whom preeclampsia develops.[7] Dyslipidemia is also associated with endothelial dysfunction.[5]

Intake of polyunsaturated fatty acids. Chung et al[22] observed a significantly higher intake of polyunsaturated fatty acids among women with preeclampsia. In recent years controlled studies have failed to show any protective effect of marine fatty acids on the risk for preeclampsia.[23] Although there seems to be a general agreement that moderate intake of long-chain polyunsaturated fatty acids reduces the risk of cardiovascular diseases, there are indications that too high intake of polyunsaturated fat may be harmful.[24] The latter has been attributed to the pro-oxidative effect of polyunsaturated fatty acids.[5] Our data may indicate that persons with high intake of polyunsaturated fat (both ω-3 and ω-6) have increased risk for the development of preeclampsia. We cannot exclude that dietary intake of polyunsaturated fatty acids is a confounder related to other dietary habits. However, our findings are biologically reasonable because the easily oxidizable polyunsaturated fatty acids may enhance the oxidative stress known to be present in preeclampsia.[25]

Non–energy-providing nutrients. High intake of sucrose among women with preeclampsia could be associated with lower intake of "protective" nutrients. However, we found similar intakes of calcium, vitamin C, and vitamin E in the two groups (data not shown).

Early- and late-onset preeclampsia. Early-onset preeclampsia differs in several ways from late-onset preeclampsia. First, early-onset preeclampsia is generally more complicated because placental insufficiency (intrauterine growth retardation) is more often present, preterm delivery is often indicated, maternal complications are generally more severe, and the risk of recurrence in later pregnancy is higher.[2] Factors that may increase the risk of the development of early-onset pre-

eclampsia are therefore of particular interest. The most striking finding in the current study was the marked effect of a high intake of energy and sucrose on the risk for the development of early-onset preeclampsia.

This prospective cohort study of the relationship between diet and preeclampsia suggests that high intake of energy, sucrose, and polyunsaturated fatty acids may increase the risk for preeclampsia. Thus dietary patterns that are increasingly prevalent in many parts of the world may adversely affect the many efforts to reduce hypertensive complications during pregnancy.

The continual support by Professor Halvard Gjoennaess is greatly appreciated. We thank Kristin Hoimyr for excellent technical assistance.

REFERENCES

1. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. JAMA 1999;282:1523-9.
2. Ness RB, Roberts JM. Epidemiology of hypertension. In: Lindheimer MD, Roberts JM, Cunningham FG, editors. Chesley's hypertensive disorders in pregnancy. Stamford (CT): Appleton & Lange; 1999. p. 43-65.
3. Roberts JM, Redman CW. Pre-eclampsia: more than pregnancy-induced hypertension. Lancet 1993;341:1447-51.
4. Innes KE, Wimsatt JH. Pregnancy-induced hypertension and insulin resistance: evidence for a connection. Acta Obstet Gynecol Scand 1999;78:263-84.
5. Lorentzen B, Henriksen T. Plasma lipids and vascular dysfunction in preeclampsia. Semin Reprod Endocrinol 1998;16:33-9.
6. Dekker GA, de Vries JI, Doelitzsch PM, Huijgens PC, von Blomberg BM, Jacobs C, et al. Underlying disorders associated with severe early-onset preeclampsia. Am J Obstet Gynecol 1995;173:1042-8.
7. Daly ME, Vale C, Walker M, Alberti KG, Mathers JC. Dietary carbohydrates and insulin sensitivity: a review of the evidence and clinical implications. Am J Clin Nutr 1997;66:1072-85.
8. Lefebvre PJ, Scheen AJ. The postprandial state and risk of cardiovascular disease. Diabet Med 1998;15(Suppl 4):S63-8.
9. Johansson L, Solvoll K, Opdahl S, Bjorneboe GE, Drevon CA. Response rates with different distribution methods and reward, and reproducibility of a quantitative food frequency questionnaire. Eur J Clin Nutr 1997;51:346-53.
10. Andersen LF, Solvoll K, Johansson LR, Salminen I, Aro A, Drevon CA. Evaluation of a food frequency questionnaire with weighed records, fatty acids, and alpha-tocopherol in adipose tissue and serum. Am J Epidemiol 1999;150:75-87.
11. Andersen LF, Solvoll K, Drevon CA. Very-long-chain n-3 fatty acids as biomarkers for intake of fish and n-3 fatty acid concentrates. Am J Clin Nutr 1996;64:305-11.
12. Solvoll K, Lund-Larsen K, Scyland E, Sandstad B, Drevon CA. A quantitative food frequency questionnaire evaluated in a group of dermatologic outpatients. Scand J Nutr 1993;37:150-5.
13. Johansson L, Solvoll K, Bjorneboe GE, Drevon CA. Under- and overreporting of energy intake related to weight status and lifestyle in a nationwide sample. Am J Clin Nutr 1998;68:266-74.
14. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr 1997;65:S1220-8.
15. Prentice AM, Spaaij CJ, Goldberg GR, Poppitt SD, van Raaij JM, Totton M, et al. Energy requirements of pregnant and lactating women. Eur J Clin Nutr 1996;50(Suppl 1):S82-110.
16. Stanley K, Fraser R, Bruce C. Physiological changes in insulin resistance in human pregnancy: longitudinal study with the hyperinsulinaemic euglycaemic clamp technique. Br J Obstet Gynaecol 1998;105:756-9.
17. Joffe GM, Esterlitz JR, Levine RJ, Clemens JD, Ewell MG, Sibai BM, et al. The relationship between abnormal glucose tolerance and hypertensive disorders of pregnancy in healthy nulliparous women. Calcium for Preeclampsia Prevention (CPEP) Study Group. Am J Obstet Gynecol 1998;179:1032-7.
18. Sermer M, Naylor CD, Gare DJ, Kenshole AB, Ritchie JW, Farine D, et al. Impact of increasing carbohydrate intolerance on maternal-fetal outcomes in 3637 women without gestational diabetes. The Toronto Tri-Hospital Gestational Diabetes Project. Am J Obstet Gynecol 1995;173:146-56.
19. Williams SB, Goldfine AB, Timimi FK, Ting HH, Roddy MA, Simonson DC, et al. Acute hyperglycemia attenuates endothelium-dependent vasodilation in humans in vivo. Circulation 1998;97:1695-701.
20. Bierhaus A, Hofmann MA, Ziegler R, Nawroth PP. AGEs and their interaction with AGE-receptors in vascular disease and diabetes mellitus. I. The AGE concept. Cardiovasc Res 1998;37:586-600.
21. Hanson U, Persson B. Epidemiology of pregnancy-induced hypertension and preeclampsia in type 1 (insulin-dependent) diabetic pregnancies in Sweden. Acta Obstet Gynecol Scand 1998;77:620-4.
22. Chung R, Davis H, Ma Y, Naivikul O, Williams C, Wilson K. Diet-related toxemia in pregnancy. I. Fat, fatty acids, and cholesterol. Am J Clin Nutr 1979;32:1902-11.
23. Sibai BM. Prevention of preeclampsia: a big disappointment. Am J Obstet Gynecol 1998;179:1275-8.
24. Ravnskov U. The questionable role of saturated and polyunsaturated fatty acids in cardiovascular disease. J Clin Epidemiol 1998;51:443-60.
25. Hubel CA. Oxidative stress in the pathogenesis of preeclampsia. Proc Soc Exp Biol Med 1999;222:222-35.