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Chocolate Consumption in Pregnancy and Reduced Likelihood of Preeclampsia

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Abstract

Background—Preeclampsia is a major pregnancy complication with cardiovascular manifestations. Recent studies suggest that chocolate consumption may benefit cardiovascular health.

Methods—We studied the association of chocolate consumption with risk of preeclampsia in a prospective cohort study of 2291 pregnant women who delivered a singleton livebirth between September 1996 and January 2000. Chocolate consumption was measured by self report in the first and third trimesters, and by umbilical cord serum concentrations of theobromine, the major methylxanthine component of chocolate. Preeclampsia was assessed by detailed medical record review for 1943 of the women. We derived adjusted odds ratios (aOR) and 95% confidence intervals (CIs) from logistic regression models controlling for potential confounders.

Results—Preeclampsia developed in 3.7% (n = 63) of 1681 women. Cord serum theobromine concentrations were negatively associated with preeclampsia (aOR = 0.31; CI = 0.11–0.87 for highest compared with lowest quartile). Self-reported chocolate consumption estimates also were inversely associated with preeclampsia. Compared with women consuming under 1 serving of chocolate weekly, women consuming 5+ servings per week had decreased risk: aOR = 0.81 with consumption in the first 3 months of pregnancy (CI = 0.37–1.79) and 0.60 in the last 3 months (0.30–1.24).

Conclusions—Our results suggest that chocolate consumption during pregnancy may lower risk of preeclampsia. However, reverse causality may also contribute to these findings.

Recent research suggests that chocolate, particularly dark chocolate, may benefit cardiovascular health. Chocolate contains over 600 chemicals including flavanoids, magnesium, and theobromine. Flavanoids (including flavanols, flavones, flavanones, and others) are potent antioxidants capable of inducing nitric oxide-dependent vasodilation, as well as having antiplatelet and anti-inflammatory effects.[1,2] Magnesium deficits have been linked to hypertension, and other cardiovascular disease.[3,4] The methylxanthine theobromine is present in very high quantities, with dark chocolate containing the most.[5] The primary pharmacologic effects of theobromine include diuresis, myocardial stimulation, vasodilation, and smooth muscle relaxation,[6] and it has been used to treat hypertension, angina, and

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atherosclerosis.[7] Theobromine is widely consumed in the form of chocolate and cocoa products, and although theobromine is one of the 3 primary metabolites of caffeine, it accounts for only about 12% of total metabolized caffeine, compared with 70% to 80% for paraxanthine.[6] Thus, theobromine is a useful, specific biomarker for chocolate consumption. In addition, theobromine, along with the other methylxanthines, freely crosses the placental barrier in pregnancy.

Preeclampsia is a serious maternal complication of pregnancy that affects 3% to 8% of pregnancies.[8] Preeclampsia shares many characteristics and risk factors of cardiovascular disease, including endothelial dysfunction, oxidative stress, hypertension, insulin resistance, and hypertriglyceridemia.[9] Cardiovascular manifestations of preeclampsia include changes in vascular reactivity, hypertriglyceridemia, endothelial dysfunction, and hypertension.[8,10,11] Women with preeclampsia may also be at increased risk of cardiovascular disease and metabolic disturbances in the years following pregnancy.[12–16]

We investigate whether chocolate consumption, measured by self-reported maternal intake and fetal cord serum concentrations of theobromine, is associated with preeclampsia.

METHODS

Pregnant women were recruited September 1996 to January 2000 from 56 obstetric practices and 15 clinics associated with 6 hospitals in Connecticut and Massachusetts.[17] Women were excluded if they were more than 24 weeks' gestational age at enrollment, had insulin-dependent diabetes mellitus, did not speak English or Spanish, or intended to terminate their pregnancy.

Of 11,267 women screened for study, 9576 met eligibility criteria. To ensure an adequate number of higher caffeine consumers for a larger study, all eligible women who reported drinking ≥150 mg of caffeine per day in the prior week were invited to participate (n = 715; 11% of final sample). The remaining population consisted of random samples of women who drank <150 mg caffeine per day (n = 839; 45% of final sample) and nonconsumers (n = 2077; 44% of final sample). A total of 3631 women were invited; 2478 (68%) enrolled, 639 (18%) declined, 424 (12%) were lost to follow-up, 72 (2%) miscarried prior to enrollment, and 20 (<1%) were not eligible at enrollment interview. Among the 2478 enrolled women, 2291 (92%) delivered a singleton infant.

Cord blood biomarker data were available for 1611 infants. A total of 1995 women provided data on both first-trimester and third-trimester chocolate consumption. Preeclampsia status was determined for 1943 women; the remaining 348 were excluded because they had preexisting hypertension, indication of gestational hypertension but no proteinuria, or incomplete information to definitively classify preeclampsia. After these exclusions, the biomarker exposure analyses included 1346 women; analyses of reported chocolate consumption included 1681 women.

Most women were interviewed at home by 14 weeks (mean = 14.9 weeks, interquartile range = 12–17 weeks, min = 6.1 and max = 24.3 weeks). The structured interview collected detailed information on dietary intake of caffeinated beverages and chocolate products since becoming pregnant. Mothers reported on potential confounders including race/ethnicity, education, smoking, age, prepregnancy weight, height, and prior pregnancy history. Respondents were reinterviewed postnatally, usually during the delivery hospitalization, to obtain third-trimester exposure information.[17]

Exposure Assessment

Reported Chocolate Consumption—Women were asked if they drank hot chocolate, cocoa, or chocolate milk since becoming pregnant, and how many cups they had on a daily or weekly basis; if they ate milk or dark chocolate candy, cake, cookies, or ice cream, and how many servings of milk chocolate and dark chocolate they had on a daily or weekly basis. From this information, we calculated variables for the reported number of chocolate servings per week (<1, 1–4, and ≥5) for first and third trimesters.

Cord Serum Theobromine Concentration—At delivery, obstetricians cut the umbilical cord and collected venous and arterial cord blood, which was immediately refrigerated. The hospital laboratory separated and froze the serum within 24 hours of collection. Frozen samples were transported to the study laboratory on ice and stored at −80°C. Chemists at the Clinical Pharmacology Laboratory at the University of California, San Francisco, who were blind to exposure and pregnancy information, analyzed samples for theobromine (the major metabolite of chocolate), caffeine, paraxanthine (the major metabolite of caffeine), and theophylline.[18] Concentrations of these methylxanthines were determined using liquid chromatography coupled with tandem mass spectrometry. Stable isotope-labeled analogs were used as internal standards. The limit of quantitation was 10 ng/mL. The precision of the assay (within-run coefficient of variation) ranged from 1.7% to 10.3%, and accuracy (percent of expected values) ranged from 88% to 118% for plasma concentrations from 10 to 5000 ng/mL, respectively. All assays below the detection limit (n = 63, 5% of all samples) were assigned a value of zero. Such assays are not considered biologically significant, and assigning an alternative value (eg, halfway between 0 and the detection limit) would not affect results since methylxanthine concentrations were evaluated in quartiles.

Outcome Assessment—Obstetric records were abstracted to identify pregnancy outcomes. Abstractors were blind to exposure status. Maternal blood pressure throughout pregnancy, International Classification of Diseases (9th Revision) diagnoses, and maternal and infant medical conditions were recorded on structured abstraction forms. Blood pressure and urinary protein values from ante-, intra-, and postpartum periods were recorded if the abstractor noted 2 or more blood pressure readings ≥140 mm Hg systolic or ≥90 mm Hg diastolic during the delivery hospitalization, or an ICD-9 diagnosis indicating pregnancy-induced hypertension, preeclampsia, or HELLP syndrome for that subject.

Preeclampsia was defined according to National Heart, Lung and Blood Institute (NHLBI) guidelines.[19] The criteria required (1) de novo hypertension (≥140 mm Hg systolic or ≥90 mm Hg diastolic) on 2 or more occasions at least 6 hours apart beginning after the 20th week of gestation; (2) accompanying proteinuria, defined as urinary protein concentrations of 30 mg/dL or greater, equivalent to dipstick value of 1+ from 2 or more specimens collected at least 4 hours apart, or one or more urinary dipstick values of 2+ near the end of pregnancy, or one or more catheterized dipstick values of 1+ during delivery hospitalization, or 24-hour urine collection with protein of ≥300 mg. We excluded women for whom pre-existing hypertension could not be ruled out (eg, no readings available prior to 20 weeks' gestation; physician notes indicating chronic hypertension in the patient) or who met partial criteria for preeclampsia (eg, pregnancy-induced hypertension; proteinuria with no hypertension).

Statistical Analysis—Because of the high correlation between concentrations of theophylline and caffeine ($r = 0.96$; theophylline is a minor metabolite of caffeine), all reported analyses included caffeine rather than theophylline. Analyses replacing caffeine with theophylline did not materially change any findings.

Separate regression models were run for reported chocolate consumption and cord blood theobromine concentrations. We calculated unadjusted and adjusted odds ratios logistic regression using PC-Statistical Analysis System v. 9.1 (SAS Institute, Inc., Cary, NC). Adjusted models controlled for race/ethnicity, age, education, parity, maternal smoking, prepregnancy body mass index (BMI), and prenatal care provider (private/clinic). Models of the association between theobromine and preeclampsia also adjusted for cord blood caffeine and paraxanthine concentrations.

RESULTS

Table 1 describes the study population's characteristics and the distribution of exposure measures. Reported chocolate consumption was high, particularly in the third trimester. Consumption was higher among younger women, less well educated women, Hispanic women, women who smoked in pregnancy, and women receiving prenatal care in clinics. Obese women were less likely to report chocolate consumption than normal or overweight women in the third trimester, but not the first trimester. Cord theobromine levels were similarly higher with younger age, less education, and clinic prenatal care provider. In addition, white and parous women had higher levels of theobromine. BMI was not associated with theobromine levels.

Reported chocolate consumption was only modestly correlated with cord blood theobromine levels (quartiles): first trimester, $r_{spearman} = 0.15$ and third trimester, $r_{spearman} = 0.29$. Median theobromine concentration in women who reported consuming less than 1 serving weekly in the third trimester was low (211–237 ng/mL), regardless of how much chocolate was consumed in the first trimester. Theobromine concentrations increased with increasing third trimester consumption, with the highest median levels among women consuming 5 or more servings in both first and third trimesters (674 ng/mL).

Table 2 shows unadjusted associations between potential confounders and preeclampsia, which developed in 3.7% of 1681 women (NHLBI criteria n = 63). Higher BMI, education, and nulliparity were most strongly associated with increased risk of preeclampsia.

In unadjusted logistic regression models, reported chocolate consumption in the third trimester and cord serum theobromine concentrations were inversely (and significantly) associated with risk of preeclampsia. Point estimates for reported chocolate consumption in the first trimester were protective although with wide confidence intervals (Table 3).

In adjusted analyses, serum theobromine remained inversely associated with risk of preeclampsia (*P* for trend = 0.008). Point estimates were strikingly similar to those in the unadjusted analyses. Women with cord serum theobromine in the highest quartile had a 69% reduction (95% confidence interval [CI] = 0.11–0.87) in risk compared with women whose concentrations were in the lowest quartile. In adjusted analyses of reported chocolate consumption in the third trimester, estimates remained protective (adjusted odds ratio 0.60 [95% CI = 0.30–1.24] for women consuming 5+ versus <1 weekly serving of chocolate). Adjusted estimates of consumption in the first trimester were less strongly associated with risk of preeclampsia (0.81 [0.37–1.79] for women consuming 5+ versus <1 weekly serving).

DISCUSSION

In this prospective cohort of pregnant women, we observed that chocolate consumption, as measured by cord serum levels of the biomarker theobromine, was associated with lower risk of preeclampsia. As measured by self-reported maternal intake, increased chocolate consumption in both first and third trimesters was suggestive of reduced preeclampsia risk. Our findings are consistent with other studies that have investigated vascular and metabolic effects of chocolate. Grassi et al[20] found that consumption of dark (vs. white) chocolate reduced

blood pressure and insulin resistance, and improved nitric oxide-dependent vasorelaxation in men and women with untreated essential hypertension. In healthy men and women dark chocolate consumption lowered blood pressure and insulin sensitivity.[21] Fisher and Hollenberg[22] reported that consumption of flavanol-rich cocoa improved measures of endothelial function. A recent meta-analysis[23] of 5 trials showed significant and clinically important drops in systolic and diastolic blood pressure after cocoa administration.

A major strength of this study is use of umbilical cord blood theobromine as a biomarker for cocoa and chocolate consumption. Flavanoids and magnesium are found in numerous other substances, but theobromine is primarily found in cocoa and tea leaves. Quantifying self-reported chocolate and cocoa consumption is extremely difficult due to considerable variation in the cocoa content of chocolate products. In addition, it is difficult to standardize self-reported chocolate consumption for serving size, or in any other way. Theobromine concentrations in chocolate also vary widely from 0.15% to 0.46%.[6] Such sources of misclassification most likely drive effect estimates toward the null. These measurement issues may account for some of the differences in the magnitude of effects between reported consumption and cord serum theobromine. Umbilical cord blood levels of theobromine provide an objective indicator of recent maternal cocoa and chocolate intake since theobromine is rapidly absorbed from the gastrointestinal tract[24] and freely crosses the placental barrier[25] and are not hampered by possible recall bias of self-reported measurements.

One limitation of our study is the possibility of reverse causality. If women diagnosed with preeclampsia reduced their calorie intake (including chocolate) subsequent to their diagnosis, and if the reported third trimester consumption or cord theobromine concentration represented exposure after the time of diagnosis, reverse causality could explain some of our findings. (Reverse causality could not explain the first trimester findings.) We conducted several analyses to help elucidate the possible role of reverse causality in our data.

Examination of correlations between reported consumption in the first and third trimesters by preeclampsia status ($r_{spearman} = 0.34$ for women who developed preeclampsia; $r_{spearman} = 0.35$ for women who did not), suggested that women did not change consumption differentially based on preeclampsia diagnosis. Similarly, women diagnosed with preeclampsia were no more likely to change consumption than unaffected women. Restricting adjusted analyses to the 785 women whose category of chocolate consumption did not change from first to third trimester of pregnancy (Table 3, last column) produced estimates of associations of cord theobromine levels strikingly similar to the adjusted estimates in all women. Considering the possibility that women with preeclampsia consumed less chocolate because they were admitted to hospitals earlier than healthier women, we also analyzed times from hospitalization to delivery. Such times were essentially identical in mothers who had and had not developed preeclampsia (96% and 97% of women with or without preeclampsia, respectively, were admitted on the same or previous day as date of delivery). These analyses failed to support a role of reverse causation, although they cannot rule out this possibility.

Another potential limitation of our study is residual confounding by smoking or BMI. To address such confounding, we repeated analyses (1) restricting the sample to non-smoking women and (2) excluding obese women (but still controlling for BMI). In both analyses, we found no change in results. Results were similar when we further restricted the sample to women with normal BMI only. Finally, the small number of women with preeclampsia and the potential mis-classification of exposure may have reduced the precision of these estimates.

Our findings of an inverse relationship between cord serum theobromine concentrations and risk of preeclampsia may be due to a direct role of theobromine. During pregnancy, theobromine (or the other methylxanthines in chocolate) may improve placental circulation

and inhibit xanthine oxidase, which, in the setting of hypoxia, increases production of reactive oxygen species and free radicals.[26] Alternatively, theobromine concentrations could play an indirect role by (1) acting as a proxy for others chemicals (such as flavanols or magnesium) found in cocoa, (2) their correlation with other unmeasured dietary factors that influence risk of preeclampsia or (3) acting as a proxy for maternal metabolism of theobromine whereby enzymatic activity associated with metabolism, rather than actual theobromine concentrations, is responsible for influencing the risk of maternal outcomes.[27]

We repeated analyses (not shown) using a physician diagnosis of preeclampsia in the medical chart instead of our own designation based strictly on NHLBI preeclampsia criteria. Such analyses (n = 1907) consistently suggested an inverse relationship between all measures of chocolate consumption and preeclampsia risk. Interestingly, all the point estimates were practically unchanged, except that adjusted estimates of reported first trimester consumption were more strongly inversely associated with risk of preeclampsia (adjusted odds ratio 0.37 [95% CI = 0.13–1.08] for women consuming 5+ versus <1 weekly serving).

Our results raise the possibility that chocolate consumption by pregnant women may reduce the occurrence of preeclampsia. Because of the importance of preeclampsia as a major complication of pregnancy, replication of these results in other large prospective studies with a detailed assessment of chocolate consumption is warranted. Measurements of chocolate exposure should be designed to permit careful examination of the temporal relationship between chocolate consumption in pregnancy and subsequent risk of preeclampsia.

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TABLE 1

Associations of Potential Study Confounders With Reported Chocolate Consumption and Cord Blood Theobromine Concentrations

	Reported Chocolate Consumption in First 3 mo of Pregnancy (Servings per Week)					Reported Chocolate Consumption in Last 3 mo of Pregnancy (Servings per Week)				Cord Blood Serum Theobromine Concentrations (ng/mL)					
	No.[a]	<1%	1–4%	5+%	P (χ^2)	<1%	1–4%	5+%	P (χ^2)	No.[a]	0–155	>155–400 %	>400–900 %	>900 %	P (χ^2)
Overall	1995	48	33	19	—	31	41	29	—	1611	25	26	25	25	—
Age					<0.001				<0.001						0.001
<20	142	47	20	33		37	26	37		140	23	31	21	25	
20–24	247	44	28	28		32	31	37		216	34	26	18	23	
25–29	478	48	35	17		29	42	29		393	26	26	29	19	
30–34	718	48	36	17		27	47	26		553	22	25	24	30	
35+	409	54	31	15		36	40	24		309	24	23	29	25	
Race					<0.001				<0.001						<0.001
White	1438	47	36	17		26	45	29		1102	20	24	28	28	
Black	160	66	18	16		58	26	16		136	44	24	17	15	
Hispanic	344	46	25	29		34	33	33		329	32	30	19	19	
Asian/other	49	57	27	16		43	31	27		41	49	17	17	17	
Education					<0.001				<0.001						0.001
<High school	234	43	24	33		32	30	38		245	25	32	20	23	
High school graduate	352	51	30	19		38	36	26		286	28	31	22	19	
Some college	457	49	32	18		36	38	26		348	27	24	25	25	
College graduate	525	50	34	16		27	45	29		398	20	23	26	30	
>College	425	45	38	17		23	49	28		333	26	20	29	25	
Prenatal care provider					<0.001				<0.001						<0.001
Private	1575	48	35	17		29	43	28		1206	22	24	27	27	
Clinic	420	49	24	27		38	31	31		405	33	30	17	20	
Parity					0.49				0.56						0.003
Nulliparous, no prior pregnancy	579	51	30	19		33	39	28		460	30	26	24	21	
Nulliparous, with prior pregnancy	301	45	35	20		28	44	29		236	30	25	24	22	
Parous	1111	48	33	19		30	41	29		912	21	25	26	28	
BMI (kg/m^2)					0.38				0.004						0.16
Underweight (<19.8)	255	51	31	17		31	43	26		208	23	28	21	29	
Normal (19.8–26.0)	1170	47	33	20		28	41	31		927	24	25	26	25	
Overweight (>26.0–29.0)	223	46	35	19		30	41	29		179	26	20	26	27	
Obese (>29.0)	295	53	31	16		40	36	24		247	28	30	23	20	
Smoking in 1st trimester (cigarettes/d)					0.08				0.003						0.08
0	1705	49	33	18		31	42	27		1366	26	25	25	25	
1–9	197	43	32	26		26	37	37		164	24	34	22	21	
>10	90	43	33	23		28	31	41		78	18	22	26	35	

[a]Numbers may not sum to total due to missing data.

TABLE 2

Associations of Potential Confounders With Preeclampsia

	No.	% With Preeclampsia
Overall	1681	3.7
Age (yrs)		
<20	126	4.0
20–24	212	4.7
25–29	383	3.7
30–34	618	2.9
35+	342	4.7
Race		
White	1212	3.5
Black	123	6.5
Hispanic	301	4.0
Asian/other	43	2.3
Education		
<High school	211	2.8
High school graduate	287	5.9
Some college	372	5.4
College graduate	449	2.9
>College	362	1.9
Prenatal care provider		
Private	1322	3.4
Clinic	359	5.0
Parity		
Nulliparous, no prior pregnancy	465	4.3
Nulliparous, with prior pregnancy	238	9.2
Parous	975	2.2
BMI (kg/m^2)		
Underweight (<19.8)	231	3.0
Normal (19.8–26.0)	1013	2.4
Overweight (>26.0–29.0)	186	4.3
Obese (>29.0)	208	10.1
Smoking in 1st trimester (cigarettes/d)		
0	1451	3.9
1–9	151	2.6
>10	76	2.6

TABLE 3

Associations Between Measures of Chocolate Exposure and Preeclampsia

Chocolate Exposure Measure	No.	% With Preeclampsia	All Women		Women Whose Chocolate Consumption Did Not Change[a]
			OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Reported chocolate consumption in first 3 mo of pregnancy (servings per week)[b]					
<1[c]	812	3.9	1.0	1.0	1.0
1–4	541	4.1	0.89 (0.50–1.58)	1.03 (0.56–1.90)	0.86 (0.33–2.29)
5+	328	2.7	0.68 (0.32–1.45)	0.81 (0.37–1.79)	0.98 (0.33–2.93)
Reported chocolate consumption in last 3 mo of pregnancy (servings per week)[b]					
<1[c]	513	5.5	1.0	1.0	1.0
1–4	681	3.1	0.54 (0.30–0.97)	0.70 (0.37–1.32)	0.86 (0.33–2.29)
5+	487	2.9	0.49 (0.25–0.96)	0.60 (0.30–1.24)	0.98 (0.33–2.93)
Cord serum theobromine (quartiles; ng/mL)[d]					
0–155[c]	336	6.8	1.0	1.0	1.0
>155–400	328	4.0	0.46 (0.22–0.97)	0.49 (0.21–1.15)	0.47 (0.11–1.93)
>400–900	335	2.4	0.32 (0.14–0.73)	0.35 (0.13–0.90)	0.26 (0.06–1.25)
>900	347	2.3	0.28 (0.12–0.65)	0.31 (0.11–0.87)	0.34 (0.06–2.03)

[a] Analyses restricted to the subset of women (n = 785) whose reported level of chocolate consumption did not change from first 3 mo to last 3 mo of pregnancy. Thus, adjusted ORs are the same for reported consumption in both first 3 mo and last 3 mo of pregnancy.

[b] Separate logistic regression models were run for each reported chocolate exposure variable. Adjusted models controlled for 1st trimester smoking (No. cigarettes per day), BMI, clinic/private prenatal care provider, parity, race, maternal age, and education.

[c] Reference category.

[d] Cord serum theobromine adjusted models controlled for cord serum paraxanthine and caffeine concentrations, first trimester smoking (No. cigarettes per day), BMI, clinic/private prenatal care provider, parity, race, maternal age, and education.

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