Published in final edited form as:

Ann Epidemiol. 2010 August ; 20(8): 584–591. doi:10.1016/j.annepidem.2010.05.010.

Does Chocolate Intake During Pregnancy Reduce the Risks of Preeclampsia and Gestational Hypertension?

Audrey F. Saftlas, Ph.D., MPH¹, Elizabeth W. Triche, Ph.D.², Hind Beydoun, Ph.D., MPH¹, and Michael B. Bracken, Ph.D.²

¹Department of Epidemiology, University of Iowa College of Public Health

²Center for Perinatal, Pediatric, and Environmental Epidemiology, Department of Epidemiology and Public Health, Yale University School of Medicine

Abstract

Purpose—Chocolate consumption is associated with favorable levels of blood pressure and other cardiovascular disease risk markers. We analyzed a prospective cohort study to determine if regular chocolate intake during pregnancy is associated with reduced risks of preeclampsia and gestational hypertension (GH).

Methods—Subjects were recruited from 13 prenatal care practices in Connecticut (1988–1991). In-person interviews were administered at <16 weeks gestation to ascertain risk factors for adverse pregnancy outcomes. Hospital delivery and prenatal records were abstracted to classify preeclampsia (n=58), GH (n=158), and normotensive pregnancies (n=2351). Chocolate consumption (servings/week) during the 1st and 3rd trimesters was ascertained at initial interview and immediately postpartum, respectively. Consumers of <1 serving/week comprised the referent group. Adjusted odds ratios (aOR) were estimated using logistic regression.

Results—Chocolate intake was more frequent among normotensives (80.7%) than preeclamptics (62.5%) or GH women (75.8%), and associated with reduced odds of preeclampsia (1st trimester: aOR=0.55, 95% CI: 0.32–0.95; 3rd trimester: aOR=0.56, 95% CI: 0.32–0.97). Only 1st trimester intake was associated with reduced odds of GH (aOR=0.65, 95% CI: 0.45–0.87).

Conclusions—These findings provide additional evidence of the benefits of chocolate. Prospective studies are needed to confirm and delineate protective effects of chocolate intake on risk of preeclampsia.

Keywords

Chocolate; Gestational Hypertension; Preeclampsia; Pregnancy

It is increasingly recognized that the pathophysiology of preeclampsia, a leading cause of infant and maternal morbidity and mortality worldwide, involves many of the same vascular and metabolic characteristics and risk factors for cardiovascular disease. Furthermore,

© 2010 Elsevier Inc. All rights reserved.

COMPLETE ADDRESS FOR CORRESPONDANCE AND REPRINTS: Michael B. Bracken, Ph.D. Center for Perinatal Pediatric and Environmental Epidemiology, Yale University Schools of Public Health and Medicine, 1 Church Street, 6th Floor, New Haven, CT 06510, USA michael.bracken@yale.edu Tel: 203 764-9375 Fax: 203 764-9378.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

accumulating evidence from long-term follow-up studies indicates that women with a history of preeclampsia face an increased risk of developing chronic hypertension, insulin resistance, and lipid abnormalities later in life (1-3). Large-scale clinical trials aimed at preventing preeclampsia in high risk women have variously focused on antenatal administration of low dose aspirin, calcium supplementation, and Vitamins C and E, though none have proven effective (4-7).

Recent studies indicate that regular intake of chocolate, particularly dark chocolate, has beneficial effects on cardiovascular disease risk by lowering blood pressure, insulin resistance, serum triglycerides, vascular reactivity, endothelial dysfunction, oxidative stress, indicators of inflammation, and anti-platelet activity (8). Each of these physiologic features has been observed in preeclampsia, providing strong rationale to test for a protective effect of chocolate intake on risk of preeclampsia. To date, two published studies using theobromine as a biomarker of chocolate intake have tested this hypothesis but reported conflicting findings (9,10). Triche et al. (2008) reported that regular chocolate consumption and higher levels of theobromine in cord blood are have a protective effect against preeclampsia (10). In contrast, Klebanoff and colleagues (2009) found no protective effect of increased theobromine in maternal serum collected after 26 weeks, but did not assess dietary chocolate consumption (9).

Using data from the Yale Health in Pregnancy Study, we addressed the following questions: 1) Is regular chocolate consumption during pregnancy is associated with a reduced risk of preeclampsia and gestational hypertension? 2) Do the risks of preeclampsia and gestational hypertension vary by amount of chocolate consumed? 3) Is the timing or pattern of chocolate consumption during the 1st and 3rd trimesters of pregnancy is associated with the risks of preeclampsia and gestational hypertension.

The present study adds to the current literature by examining trimester-specific chocolate intake and considering gestational hypertension (GH) as an additional outcome in a large cohort study of expectant women.

MATERIALS AND METHODS

We conducted an ancillary study within the Yale Health in Pregnancy Study cohort to identify risk factors for preeclampsia, which required detailed reviews of all prenatal and medical records belonging to subjects who were noted to have evidence of high blood pressure in the parent study (Eras 2000). These studies were approved by the Yale University Human Investigation Committee.

Study design and population

The Yale Health in Pregnancy Study is a prospective cohort study of expectant women who had their first prenatal visit between April 5, 1988 and December 31, 1991, and planned to deliver at the Yale-New Haven Hospital. The study was originally designed to assess the influence of environmental tobacco smoke exposure on fetal growth and preterm delivery. Details of study methods have been described previously (11,12). Subjects were recruited from 11 private obstetric practices and two health maintenance organizations. Exclusion criteria included: diabetes mellitus, non-English speaking, ≥ 16 weeks' gestation, or previous study participation. A total of 3,591 women screened eligible for the initial interview, which had to be completed before 16 weeks' gestation. A total of 2,967 (83%) women completed the interview; the remaining subjects either refused to participate (16%) or could not be reached for an initial contact (1.4%). The current analysis is restricted further to subjects who had singleton deliveries and hospital delivery records available for abstraction by research staff

(96%) to facilitate accurate classification of three outcome groups: preeclampsia, GH, and normal blood pressure.

The initial study interview was conducted in-person before 16 weeks' gestation by trained interviewers. The interview was usually conducted at the subject's home and took approximately 1 hour to administer. The interviewers obtained information on maternal demographics, medical and reproductive history, height, pre-pregnancy weight, antenatal smoking, alcohol, caffeine, and chocolate consumption, occupational factors, and exercise habits. Subjects also completed a postpartum interview, usually conducted in person at the hospital within the first few days of delivery, to obtain information on exposures during the 7th, 8th, and 9th gestational months. Study abstractors were trained to carefully document chart notations of elevated blood pressure for all subjects because of the link between preeclampsia and the parent study's primary outcomes.

Classification of hypertension in pregnancy

To achieve accurate and consistent case definitions of preeclampsia and GH, we conducted a supplementary review of all prenatal and hospital delivery records for the 415 (15%) participants who had some indication of elevated blood pressure during pregnancy based on hospital chart reviews or in-person interviews. The abstractors recorded blood pressure readings, urine protein values, laboratory test results, and other signs and symptoms of preeclampsia. On the basis of this review, women were assigned to one of the following categories in accordance with current criteria from the American College of Obstetricians and Gynecologists: 1) no hypertension (n=98); 2) chronic hypertension (n=73); 3) GH (n=158); 4) preeclampsia (n=58); 5) superimposed preeclampsia (n=14); and, 6) uncategorized hypertension or unknown hypertension status (n=14). Women with HELLP syndrome (n=13) were coded as superimposed preeclampsia or preeclampsia, according to the presence or absence of chronic hypertension.

The present analysis includes subjects with a final diagnosis of GH, preeclampsia, or normotensive during pregnancy. GH was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg after 20 weeks' gestation on two or more occasions at least 6 hours apart with no evidence of proteinuria. Preeclampsia was defined as GH with proteinuria (i.e., two or more dipstick readings of $\geq 1+$ or a 24-hour urine collection of ≥ 300 -mg protein). The comparison group had no indication of high blood pressure during pregnancy (n=2,324). All subjects who underwent chart review because they had a notation of elevated blood pressure were excluded from the comparison group, including the 98 with a final classification of "no hypertension".

Assessment and classification of chocolate intake

Average weekly consumption of chocolate drinks and foods was assessed by two questions included on both the initial interview (covering months 1-3) and the postpartum interview (covering months 7-9). At the initial interview, women were asked: 1. "Since you became pregnant, have you been drinking one or more cups of hot chocolate, cocoa, or chocolate milk per week?"; and, 2. "Since you became pregnant, have you been eating one or more servings of chocolate candy, chocolate cake, chocolate cookies or chocolate ice cream per week?" Women who responded "yes" were then asked to recall their average weekly intake of chocolate drinks and/or chocolate foods since becoming pregnant, using the following close-ended responses: 1) "1-3 cups (or servings) a week" 2) "4-6 cups (or servings) a week", 3) "1 cup (or serving) daily", 4) "2 cups (or servings) daily", 5) "3-4 cups (or servings) daily", 6) "5-10 cups (or servings) daily", 7) "More than 10 cups (or servings) daily". These questions were repeated at the postpartum interview, referring to months 7-9. Based upon data from the two questions, the combined number of servings of chocolate drinks and foods consumed per week was

computed separately for the 1st and 3rd trimesters, and categorized as follows: 1) No regular chocolate consumption, defined as <1 serving per week (referent category); 2) 1-3 servings per week; and 3) 4 or more servings per week. To examine for an effect of the timing of chocolate intake, a cross-classified variable was created with the following categories: 1) no regular chocolate intake during trimesters 1 and 3 (referent group); 2) regular chocolate intake during trimester 1 only; 3) intake during trimester 3 only; and, 4) intake during both trimesters 1 and 3. Self reports of chocolate consumption in the third trimester of pregnancy, using almost identical self-report questions as used here, is correlated with cord blood theobromine levels (9).

Assessment of Confounding

Established maternal risk and protective factors for preeclampsia were examined as potential confounders of the association between chocolate intake and the risks of preeclampsia and GH. Body mass index (BMI) was examined as a continuous variable and classified into four categories: underweight (<18.5), normal weight (18.5-24.9), overweight (25.0-29.9), and obese (≥30.0), per the Institute of Medicine definitions for reproductive-aged women (13). Maternal age at delivery was analyzed as a continuous and a categorical variable (<25, 25-29, 30-34 and 35+). To adjust for parity and abortion history in nulliparous women, we constructed a cross-classification variable coded as: 1) nulliparous/no history of spontaneous or induced abortion, 2) nulliparous/history of spontaneous or induced abortion, and 3) multiparous. Also examined were maternal education (high school; some college; college graduate; graduate education); cigarette smoking during pregnancy (no, yes); race (white, non-white); caffeine intake in the 1st or 7th month of pregnancy (no caffeine; month 1 only; month 7 only; months 1 and 7); fetal gender, and gestational diabetes during the index pregnancy. Caffeine consumption, a potentially important confounder, has been studied previously in this data set (14), and detailed methods for their measurement previously reported (15).

Statistical Analysis

Univariate, bivariate, and multivariate analyses were performed using the Statistical Analysis Software (SAS) version 9.1. All tests were two-sided and with an alpha level of 0.05. Chi-square tests were used to compare the associations of preeclampsia, GH, and chocolate exposure with potentially confounding variables. Logistic regression was performed to compute crude and adjusted odds ratios and 95% confidence intervals. Confounding was assessed by examining changes in exposure odds ratios when a co-variable was added or removed from the model; variables that changed the exposure estimates by at least 10% were retained in the final models.

RESULTS

We analyzed the two sources of chocolate (i.e., chocolate foods and chocolate drinks) and found no difference in the magnitude of their association with PE risk. Therefore, chocolate consumption from these combined sources was analyzed.

Table 1 shows the frequency distributions of demographic, reproductive, and lifestyle characteristics of the final analysis population (n=2,508) categorized by trimester of chocolate consumption during pregnancy, and the proportion with preeclampsia (2.4%) and GH (6.4%). 48% of subjects reported regular weekly intake of chocolate drinks or foods during both the 1st and 3rd trimesters, 10% reported intake during the 1st trimester only, 22% reported in the 3rd trimester only, and 20% reported no regular chocolate consumption. Chocolate consumption was more frequently reported by women who were <35 years old, white, had a BMI <25, drank caffeinated beverages, or who did not develop gestational diabetes during the index pregnancy.

Among the putative risk factors for preeclampsia and GH, nulliparity and obesity were significantly associated with both hypertensive disorders (table 1). Male fetal gender was significantly associated with increased risk of preeclampsia, but not GH. Although maternal age <30 years old, was significantly associated with increased risk of GH, maternal age was not associated with preeclampsia risk. Although maternal race, education, smoking during pregnancy, caffeine intake, and gestational diabetes were not significantly associated with preeclampsia or GH, rates of preeclampsia were substantially higher among non-whites and gestational diabetics.

Analysis of regular chocolate consumption in the 1st and 3rd trimesters (Figure 1) indicates that preeclamptic women were less likely to regularly consume chocolate (37.5%) than normotensive women (19.3%) or those with GH (24.2%). Nearly half (48%) of normotensive women reported regular chocolate consumption in both trimesters 1 and 3, versus 35.7% and 40.8% of women with preeclampsia and GH, respectively. Overall, few subjects reported regular chocolate consumption in the 1st trimester only (7.1% -10.5%), whereas intake in the 3rd trimester only was substantially more prevalent (19.6% - 27.4%).

Analyses of the influence of regular chocolate intake by number of weekly servings (dose) and trimester of consumption (timing of exposure) on risk of preeclampsia and GH are summarized in Table 2. Regular consumption of 1-3 servings per week during the first trimester was associated with reduced risk of preeclampsia (aOR=0.57; 95% CI: 0.30-1.09); intake of 4 or more servings per week conferred a similar level of protection (aOR=0.52; 95% CI: 0.24-1.10). Women who reported *any* regular chocolate consumption (≥ 1 -3 servings/week) during the first trimester had a significantly reduced risk of 0.55 (0.32-0.95), the same as that observed among those with *any* regular consumption during trimester 3 (aOR=0.56; 95% CI: 0.32-0.97).

Analysis of the cross-classification variable of regular chocolate intake (no, yes) by trimester of exposure further substantiated that *any* regular chocolate intake is associated with significantly reduced risk of preeclampsia relative to women who reported no regular chocolate consumption in both trimesters 1 and 3: adjusted odds ratio estimates were 0.31 (0.10-0.93) for trimester 1 consumption only, 0.44 (0.20-0.94) for trimester 3 consumption only, and 0.41 (0.21-0.77) for consumption during both trimesters.

Regular chocolate intake was also associated with a reduced risk of GH, but only among subjects who reported 1st trimester consumption (aOR=0.64; 0.46-0.90); consumption in the 3rd trimester only was not associated with reduced risk (aOR=0.98). While regular 1st trimester consumption of 1-3 servings per week was protective against GH (aOR= 0.54; 95% CI: 0.36-0.92), a higher intake of 4 or more servings per week did not confer further protection (aOR= 0.80; 95% CI: 0.53-1.21). Analysis of regular chocolate consumption by trimester of intake also suggests that 1st trimester consumption alone (aOR=0.52; 95% CI: 0.26-1.04) but not 3rd trimester consumption alone (aOR=1.04; 95% CI: 0.65-1.66) is protective against GH.

DISCUSSION

Women who reported regular chocolate consumption of ≥ 1 -3 servings/week had a 50% or greater reduced risk of preeclampsia, which did not appear to be dose-dependent. Analysis by timing of exposure suggested that regular chocolate intake during the 1st or 3rd trimester was equally protective against preeclampsia. The highest rate of preeclampsia (4.5%) occurred among women who did not regularly consume chocolate in the 1st and 3rd trimesters of pregnancy. In contrast, only women who regularly consumed chocolate during the first trimester had a reduced risk of GH.

Given our current understanding of the pathophysiology of preeclampsia as a “2-stage disease process”, it is biologically plausible that trimesters 1 and 3 would be “critical windows” for

exposure and possible intervention. Defective placentation of preeclampsia is initiated in the first trimester of pregnancy (16,17). The resulting placental oxidative stress and inflammation is hypothesized to trigger the release of pro-inflammatory syncytiotrophoblast-derived factors (eg. sFlt-1), which lead to maternal systemic vascular endothelial disruption and the eventual clinical manifestation of preeclampsia in the 3rd trimester of pregnancy (16).

Triche et al. (2008) also found that self-reported, regular consumption in the 3rd trimester was protective against preeclampsia; however, they did not find a protective effect of 1st trimester consumption (10). Our findings are also consistent with their report of a 60% reduction in preeclampsia associated with levels of cord blood theobromine at or above the 2nd quartile of exposure (9). In contrast, our findings are not consistent with those of Klebanoff et al. (2009) who found no protective effect of theobromine measured in maternal serum after the 26th week of gestation for preeclampsia (9). They found also reported that preeclampsia risk increased in a dose-response fashion with increasing levels of theobromine measured in maternal serum collected before 20 weeks gestation. Possible explanations for the disparate findings include the very different study populations; differences in the length of storage of the serum specimens;; different definitions of preeclampsia; and differences in the possible sources of theobromine over the 40-year period separating these studies.

Although Triche et al found evidence of an inverse dose-response relationship of theobromine levels in cord serum with preeclampsia risk (Triche et al, 2008), our questionnaire assessment of dietary chocolate intake was not adequately robust to detect a dose-response effect. Different chocolate products and sources contain varying amounts of cocoa; such heterogeneity in cocoa content makes it very difficult to assess for dose-response relationships using food frequency questionnaires. This is not an unusual problem in epidemiology; even in a recent study of the association of vitamin D intake with risk of preeclampsia, no association was observed based on food frequency dietary measurements of Vitamin D intake; however, a 27% reduced risk of preeclampsia was detected when analyses were restricted to assessments of vitamin D intake from supplements alone (10-15 microg/d vs no supplementation)(18).

There is considerable pathophysiologic and epidemiologic support for our findings from literature examining the cardiovascular effects of chocolate intake in adult populations. A recent review reported findings from eleven human studies of direct, beneficial effects of cocoa exposure on endothelial function, including improvements in vasodilation, coronary circulation, nitric oxide levels, blood pressure, and platelet function (8). Endothelial dysfunction is implicated as a central feature in the pathogenesis of preeclampsia. A recent 16-year epidemiologic follow-up study of post-menopausal participants in the Iowa Women's Health Study revealed chocolate intake was associated with reduced rates of cardiovascular disease mortality (19).

A recent systematic review of 10 RCTs assessed the antihypertensive effects of flavanol-rich cocoa reported significant declines in systolic (-4.5 mmHg) and diastolic (-2.5 mmHg) blood pressure (20). Most of the reviewed trials used relatively high doses of cocoa for periods of 2-18 weeks. One trial examined very low doses of dark chocolate (6.3g/d) over 18 weeks but still found highly significant reductions in blood pressure (-2.9 mmHg systolic and -1.9 mmHg diastolic (21). Two new trials of low dose chocolate intake report similar drops in systolic and diastolic blood pressure (22)(23). Desch et al compared low-dose (6g/d) versus high dose (25g/d) intakes over 3 months but found no difference in blood pressure changes between the two groups (20). In an adult German population, significant reductions in blood pressure were also observed with low-dose consumption (6g/d), with a larger reduced risk for MI and stroke (22). The difference between a small effect on blood pressure and a larger clinical effect may result from the influence of cocoa on other cardiovascular risk factors, particularly those

influencing inflammation. A diet of 6.7 g/d of dark chocolate has been associated with decreased serum C-reactive proteins, a marker of inflammation (24).

Several recent studies conducted in various patient populations suggest there are sustained benefits in vascular function following a single dose intake of flavanol-rich cocoa (25,26). A recent study of oral intake of cocoa found that the highest plasma levels of flavanols peak 2-3 hours after ingestion -- but are still measurable 8 hours following ingestion (27,28).

There are several strengths of the current study analysis. Data are derived from a large cohort of women interviewed early in pregnancy for risk factors relating to adverse pregnancy outcomes. First trimester exposure data were obtained prospectively with respect to the outcomes. Furthermore, recall bias is unlikely to influence third trimester exposure self-reports because chocolate was not recognized as having anti-hypertensive properties during the study period (1988-1991). Classification of preeclampsia and GH was based on abstraction of blood pressure and urinary protein readings from both prenatal and hospital delivery chart data, and strict research definitions were uniformly applied to reduce misclassification and increase specificity of case diagnoses. We were also able to consider timing of regular chocolate intake during pregnancy, and had extensive data on a number of potentially confounding variables. The study utilized both self-report and medical chart data in the assessment of exposure, outcome, and confounding variables. In addition, this is the first study to examine the association between chocolate consumption and risk of GH.

There are some limitations of the current research. The self-reported exposure data may have led to misclassification as it is very difficult to accurately quantify serving sizes and cocoa content of different products. In addition, our questionnaire did not differentiate between dark and other types of chocolate. Because the data were collected prospectively with respect to the outcome, we would expect that the misclassification would be non-differential and lead to attenuation of risk estimates. Our study would have been enhanced by having biomarker data (e.g., theobromine) to validate associations between self-reported chocolate consumption and risk of preeclampsia and GH.

As we did not assess other dietary constituents other than caffeinated beverages, it is possible that our results are subject to unmeasured confounding. While there are very few well established risk factors for preeclampsia, we have controlled for many of these. To date, there are no dietary factors that have been consistently associated with preeclampsia, providing support that our study findings would be unlikely to change with additional information about diet during pregnancy (29).

Another potential bias is that overweight women may underreport their chocolate intake. We re-ran the analyses, restricted to women with normal pre-pregnancy BMI, to address this potential bias and found nearly identical risk estimates as those for all women. Similarly, to address the possibility of residual confounding by smoking during pregnancy, which has been associated with a reduced risk of preeclampsia, we re-ran the final models among only non-smokers and found no change in the risk estimates.

We also considered the possibility of reverse causality whereby women who developed high blood pressure might be less likely to consume chocolate after diagnosis. However, we excluded from analysis women who had elevated blood pressure prior to 20 weeks gestation. Furthermore, the protective influence of regular chocolate consumption was apparent with first trimester exposure, which, by definition, preceded all diagnoses of preeclampsia, GH or high blood pressure readings in this study population. We also noted that women with gestational diabetes reported reduced chocolate consumption, particularly later in pregnancy. There was no evidence, however, that gestational diabetes was a confounder of the association of

chocolate consumption and risk of either hypertensive outcome. Further, when models were restricted to non-diabetic women, no changes in risk estimates were noted.

In conclusion, these findings provide additional evidence of the potential benefits of chocolate consumption. Prospective studies are needed to confirm and delineate protective effects of chocolate intake on risk of preeclampsia. Such studies require detailed assessments of dietary chocolate intake and its metabolites over the course of pregnancy.

Acknowledgments

Dr. Saftlas was supported by National Institute of Child Health and Human Development Grant R01-HD32579.

List of Abbreviations

aOR	Adjusted odds ratio
GH	Gestational hypertension
SAS	Statistical Analysis Software
BMI	Body mass index

Bibliography

1. Irgens HU, Reiser L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after preeclampsia: population based cohort study. *BMJ* 2001;323:1213–1217. [PubMed: 11719411]
2. Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension* 2009;53:944–51. [PubMed: 19433776]
3. Wilson BJ, Watson MS, Prescott GJ, Sunderland S, Campbell DM, Hannaford P, et al. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. *BMJ* 2003;326:845–849. [PubMed: 12702615]
4. Coomarasamy A, Honest H, Papaioannou S, Gee H, Khan KS. Aspirin for prevention of preeclampsia in women with historical risk factors: a systematic review. *Obstetrics and Gynecology* 2003;101:1319–1332. [PubMed: 12798543]
5. Levine RJ, Hauth JC, Curet LB, Sibai BM, Catalano PM, Morris CD, et al. Trial of calcium to prevent preeclampsia. *N Engl J Med* 1997;337:69–76. [PubMed: 9211675]
6. Polyzos NP, Mauri D, Tsappi M, Tzioras S, Kamposioras K, Cortinovis I, et al. Combined vitamin C and E supplementation during pregnancy for preeclampsia prevention: a systematic review. *Obstetrical and Gynecological Survey* 2007;62:202–206. [PubMed: 17306042]
7. Roberts JM, Myatt L, Spong CY, Thom EA, Hauth JC, Leveno KJ, et al. Vitamins C and E to prevent complications of pregnancy-associated hypertension. *N Engl J Med* 362:1282–91. [PubMed: 20375405]
8. Corti R, Flammer AJ, Hollenberg NK, Luscher TF. Cocoa and cardiovascular health. *Circulation* 2009;119:1433–1441. [PubMed: 19289648]
9. Klebanoff MA, Zhang J, Zhang C, Levine RJ. Maternal serum theobromine and the development of preeclampsia. *Epidemiology* 2009;20 epub ahead of print.
10. Triche EW, Grosso LM, Belanger K, Darefsky AS, Benowitz NL, Bracken MB. Chocolate consumption in pregnancy and reduced likelihood of preeclampsia. *Epidemiology* 2008;19:459–464. [PubMed: 18379424]
11. Eras JL, Saftlas AF, Triche E, Hsu CD, Risch HA, Bracken MB. Abortion and its effect on risk of preeclampsia and transient hypertension. *Epidemiology* 2000;11:36–43. [PubMed: 10615841]
12. Lundsberg LS, Bracken MB, Saftlas AF. Low-to-moderate gestational alcohol use and intrauterine growth retardation, low birthweight, and preterm delivery. *Ann Epidemiol* 1997;7:498–508. [PubMed: 9349918]

13. Engler MB, Engler MM. The emerging role of flavonoid-rich cocoa and chocolate in cardiovascular health and disease. *Nutr Rev* 2006;64:109–18. [PubMed: 16572598]
14. Grosso LM, Rosenberg KD, Belanger K, Saftlas AF, Leaderer B, Bracken MB. Maternal caffeine intake and intrauterine growth retardation. *Epidemiology* 2001;12:447–55. [PubMed: 11428387]
15. Bracken MB, Triche E, Grosso L, Hellenbrand K, Belanger K, Leaderer BP. Heterogeneity in assessing self-reports of caffeine exposure: implications for studies of health effects. *Epidemiology* 2002;13:165–71. [PubMed: 11880757]
16. Redman CW, Sargent IL. Placental stress and pre-eclampsia: a revised view. *Placenta* 2009;30(Suppl A):S38–42. [PubMed: 19138798]
17. Roberts JM, Hubel CA. The two stage model of preeclampsia: variations on the theme. *Placenta* 2009;30(Suppl A):S32–7. [PubMed: 19070896]
18. Haugen M, Brantsaeter AL, Trogstad L, Alexander J, Roth C, Magnus P, et al. Vitamin D supplementation and reduced risk of preeclampsia in nulliparous women. *Epidemiology* 2009;20:720–6. [PubMed: 19451820]
19. Mink PJ, Scrafford CG, Barraj LM, Harnack L, Hong CP, Nettleton JA, et al. Flavanoid intake and cardiovascular disease mortality: a prospective study in postmenopausal women. *Am J Clin Nutr* 2007;85:895–909. [PubMed: 17344514]
20. Desch S, Schmidt J, Kobler D, Sonnabend M, Eitel I, Sareban M, et al. Effect of cocoa products on blood pressure: systematic review and meta-analysis. *Am J Hypertens* 23:97–103. [PubMed: 19910929]
21. Taubert D, Roesen R, Lehmann C, Jung N, Schomig E. Effects of low habitual cocoa intake on blood pressure and bioactive nitric oxide: a randomized controlled trial. *Jama* 2007;298:49–60. [PubMed: 17609490]
22. Buijsse B, Weikert C, Drogan D, Bergmann M, Boeing H. Chocolate consumption in relation to blood pressure and risk of cardiovascular disease in German adults. *Eur Heart J*.
23. Desch S, Kobler D, Schmidt J, Sonnabend M, Adams V, Sareban M, et al. Low vs. Higher-Dose Dark Chocolate and Blood Pressure in Cardiovascular High-Risk Patients. *Am J Hypertens*.
24. di Giuseppe R, Di Castelnuovo A, Centritto F, Zito F, De Curtis A, Costanzo S, et al. Regular consumption of dark chocolate is associated with low serum concentrations of C-reactive protein in a healthy Italian population. *J Nutr* 2008;138:1939–45. [PubMed: 18806104]
25. Balzer J, Rassaf T, Heiss C, Kleinbongard P, Lauer T, Merx M, et al. Sustained benefits in vascular function through flavanol-containing cocoa in medicated diabetic patients a double-masked, randomized, controlled trial. *J Am Coll Cardiol* 2008;51:2141–9. [PubMed: 18510961]
26. Faridi Z, Njike VY, Dutta S, Ali A, Katz DL. Acute dark chocolate and cocoa ingestion and endothelial function: a randomized controlled crossover trial. *Am J Clin Nutr* 2008;88:58–63. [PubMed: 18614724]
27. Serafini M, Bugianesi R, Maiani G, Valtuena S, De Santis S, Crozier A. Plasma antioxidants from chocolate. *Nature* 2003;424:1013. [PubMed: 12944955]
28. Rein D, Lotito S, Holt RR, Keen CL, Schmitz HH, Fraga CG. Epicatechin in human plasma: in vivo determination and effect of chocolate consumption on plasma oxidation status. *J Nutr* 2000;130:2109S–14S. [PubMed: 10917931]
29. Xu H, Shatenstein B, Luo ZC, Wei S, Fraser W. Role of nutrition in the risk of preeclampsia. *Nutr Rev* 2009;67:639–57. [PubMed: 19906251]

Figure 1.
Distribution of chocolate consumption by hypertension status in pregnancy, Yale Health in Pregnancy Study, 1988 – 1991

TABLE 1

Distribution of Population Characteristics by Timing of Chocolate Consumption During Pregnancy, and by Preeclampsia and Gestational Hypertension Status, Yale Health in Pregnancy Study, 1988-1991

	Chocolate intake during pregnancy					Preeclampsia		Gestational hypertension			
	No.1	No regular intake (%)	Trimester 1 only (%)	Trimester 3 only (%)	Trimesters 1 and 3 (%)	No.	(%)	χ^2 p-value	No.	(%)	χ^2 p-value
Overall	2508	20.0	10.2	22.2	47.6	2382	2.4		2482	6.4	
Maternal age								0.002			0.03
18-24	140	18.6	10.0	25.7	45.7	132	3.8		138	8.0	
25-29	693	17.0	10.3	18.3	54.4	646	2.3		691	8.7	
30-34	1069	19.6	10.7	23.0	46.7	1027	2.7		1051	5.0	
35-39	521	23.8	10.2	24.0	42.0	495	1.6		517	5.8	
40+	85	28.2	4.7	25.9	41.2	82	2.4		85	5.9	
Race								<0.0001			0.94
White	2287	19.2	9.8	22.0	49.2	2170	2.3		2264	6.4	
Non-white	219	28.8	15.1	24.2	32.0	210	3.8		216	6.5	
Maternal education								0.07			0.09
High school	450	17.1	13.3	23.6	46.0	420	3.3		442	8.1	
Some college	638	19.6	10.3	19.8	50.3	598	2.7		629	7.5	
College graduate	747	19.4	8.8	23.0	48.7	715	2.4		739	5.6	
Graduate school	673	23.0	9.5	22.6	44.9	649	1.7		672	5.1	
Body mass index (kg/m ²)								0.0005			<0.0001
<18.5	76	25.0	9.2	13.2	52.6	76	2.6		76	2.6	
18.5-24.9	1753	18.3	9.5	22.5	49.7	1686	2.0		1739	5.0	
25.0-29.9	465	22.4	10.3	22.8	44.5	428	3.0		457	9.2	
>30.0	187	26.2	17.1	21.4	35.3	162	5.6		180	15.0	
Parity								0.97			<0.0001
Nulliparous, no prior pregnancy	670	20.8	10.0	22.4	46.9	614	4.9		648	9.9	
Nulliparous, with prior pregnancy	439	20.1	10.7	23.2	46.0	414	3.1		435	7.8	
Parous	1399	19.7	10.2	21.7	48.5	1354	1.1		1399	4.3	

	Chocolate intake during pregnancy					Preeclampsia		Gestational hypertension			
	No.1	No regular intake (%)	Trimester 1 only (%)	Trimester 3 only (%)	Trimesters 1 and 3 (%)	No.	(%)	No.	(%)	χ^2 p-value	χ^2 p-value
Smoked during pregnancy											
No	2139	20.4	9.8	22.4	47.5	2018	2.4	2100	6.2		0.25
Yes	367	17.4	12.8	21.0	48.8	340	2.7	359	7.8		
Caffeine - month 1 or 7											
Neither	692	23.0	8.2	25.3	43.5	659	2.1	679	5.0		0.23
Month 1 only	330	22.4	13.0	23.9	40.6	312	3.5	319	5.6		
Month 7 only	292	19.2	12.3	21.9	46.6	270	3.0	285	8.1		
Months 1 and 7	1114	17.3	10.3	19.9	52.4	1044	2.1	1098	6.9		
Fetal gender											
Female	1249	18.8	9.3	23.1	48.8	1186	1.6	1246	6.3		0.83
Male	1232	21.4	10.8	21.3	46.5	1165	3.3	1206	6.6		
Gestational diabetes											
No	2359	18.9	8.6	23.0	49.5	2237	2.3	2334	6.4		0.59
Yes	122	44.3	37.7	5.7	12.3	114	4.4	118	7.6		

TABLE 2

Crude and Adjusted Odds Ratios and 95% Confidence Intervals for Associations Between Chocolate Consumption Variables and Risk of Preeclampsia and Gestational Hypertension, Yale Health in Pregnancy Study, 1988-1991

Chocolate Consumption Variable ²	Preeclampsia					Gestational Hypertension				
	No.	%	Crude OR	95% CI	Adjusted OR ³	95% CI	No.	%	Crude OR	95% CI
Chocolate - 1st trimester										
No regular consumption ¹	986	3.4	1.00		1.00		1034	7.8	1.00	
1-3 servings/wk	799	1.9	0.54	(0.29-1.02)	0.57	(0.30-1.09)	822	4.6	0.53	(0.35-0.80)
4+ servings/wk	591	1.5	0.47	(0.22-1.00)	0.52	(0.24-1.10)	621	6.3	0.74	(0.50-1.10)
Chocolate - 1st trimester										
No regular consumption ¹	986	3.4	1.00		1.00		1034	7.8	1.00	
1+ servings/wk	1390	1.7	0.51	(0.30-0.87)	0.55	(0.32-0.95)	1443	5.3	0.62	(0.45-0.87)
Chocolate - 3rd trimester										
No regular consumption ¹	711	3.7	1.00		1.00		735	6.8	1.00	
1-3 servings/wk	843	1.8	0.46	(0.24-0.89)	0.54	(0.28-1.07)	877	5.6	0.82	(0.55-1.24)
4+ servings/wk	803	2.0	0.51	(0.27-0.97)	0.57	(0.29-1.10)	845	6.9	0.90	(0.60-1.35)
Chocolate - 3rd trimester										
No regular consumption ¹	711	3.7	1.00		1.00		735	6.8	1.00	
≥1-3 servings/wk	1646	1.9	0.48	(0.28-0.83)	0.56	(0.32-0.97)	1722	6.2	0.86	(0.60-1.22)
Chocolate - 1st or 3rd trimester										
Neither trimester ¹	464	4.5	1.00		1.00		481	7.9	1.00	
Trimester 1 only	244	1.6	0.35	(0.12-1.02)	0.31	(0.10-0.93)	252	4.8	0.59	(0.30-1.16)
Trimester 3 only	513	2.1	0.41	(0.19-0.89)	0.44	(0.20-0.94)	545	7.9	0.99	(0.62-1.56)
Trimesters 1 and 3	1130	1.8	0.35	(0.19-0.66)	0.41	(0.21-0.77)	1174	5.5	0.62	(0.41-0.95)

¹ No regular consumption = consuming <1 serving of chocolate food or drink per week during the 1st or 3rd trimester

² Separate logistic models were run for each of the five chocolate consumption variables

³ Adjusted for body mass index and parity/abortion