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Effects of Smoking and Preeclampsia on Birth Weight for Gestational Age

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Abstract

Objective—A counterintuitive interaction between smoking during pregnancy and preeclampsia on birth weight for gestational age (BWGA) outcomes was recently reported. In this report, we examine the relationship between these factors in a well-documented study population with exposure data on trimester of maternal smoking.

Methods—Preeclamptic (n=238), gestational hypertensive (n=219), and normotensive women (n=342) were selected from live-births to nulliparous Iowa women. Disease status was verified by medical chart review, and smoking exposure was assessed by self-report. Fetal growth was assessed as z-score of birth weight for gestational age (BWGA). Multiple linear regression was used to test for the association of maternal smoking and preeclampsia with BWGA z-score.

Results—There was no interaction between smoking with preeclampsia or gestational hypertension on fetal growth. BWGA z-scores were significantly lower among women with preeclampsia and those who smoked any time during pregnancy ($\beta=-0.33$, $p=<0.0001$ and $\beta=-0.25$, $p=0.05$) compared to normotensive and non-smoking women, respectively. Infants of women with gestational hypertension were comparable in size to infants born to normotensive women.

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Declaration of Interest

None of the authors have any conflicts of interest to disclose

Conclusions—Women who developed preeclampsia and those who smoked during pregnancy delivered infants that were significantly smaller than infants of women who did not develop preeclampsia and non-smoking women, respectively.

Keywords

Pregnancy; z-score; epidemiology; fetal growth; low birth weight

INTRODUCTION

Preeclampsia is a potentially devastating hypertensive disorder of pregnancy that complicates approximately 3% of all deliveries in the United States, and is a leading cause of maternal and infant morbidity and mortality worldwide [1]. Many risk factors for preeclampsia have been identified including a family history of the disease [2], nulliparity [3], primipaternity [4], obesity [5], and chronic hypertension [6], yet few protective factors have been discovered [7].

Paradoxically, smoking is associated with increased risk for a number of pregnancy complications including low birth weight and preterm delivery, but is associated with an estimated 30% decreased risk of preeclampsia [7, 8]. Moreover, additional studies have reported that among smokers who develop preeclampsia, maternal and fetal outcomes are significantly worse than those among nonsmoking women who develop preeclampsia [9, 10]. Because the etiology of preeclampsia is not fully understood, elucidating the relationship between smoking and preeclampsia could increase understanding of the pathophysiology of preeclampsia and inform therapeutic interventions.

A recent nested case-control study within the Montreal Prematurity Study was conducted to assess whether maternal cigarette smoking modified the effects of preeclampsia on fetal growth [11]. As expected, the authors found that smoking during pregnancy and the development of preeclampsia were independently associated with lower birth weight for gestational age (BWGA) z-scores. They also observed an interactive effect of smoking and preeclampsia on BWGA that was unexpected: smoking during pregnancy modified the effect of preeclampsia on fetal growth such that the adverse effect of preeclampsia on birth weight for gestational age was significantly attenuated. As this observation is contradictory to previous literature on the relationship between smoking and preeclampsia, the objective of our study was to confirm their results in our population of nulliparous Iowa women.

METHODS

Subject Selection

Data for this research were obtained from two large population-based case-control studies conducted in Iowa. Preeclamptic and gestational hypertensive women were participants in the Study of Pregnancy-induced Hypertension in Iowa (SOHPIA); normotensive women were participants in SOPHIA and the Iowa Health in Pregnancy Study (IHIPS), an Iowa based case-control study of preterm and small-for-gestational-age (SGA) outcomes during

the same time period. All protocols and informed consent procedures were approved by the University of Iowa Institutional Review Board.

SOPHIA—SOPHIA is a case-control study of preeclampsia that was designed to examine the roles of maternal-fetal human leukocyte antigen and sexual history with the baby's father. A detailed description of this study has been described elsewhere [12, 13]. Briefly, primaparous mothers who resided in one of 42 Iowa counties and delivered a live birth from August 2002 to May 2005 were identified from electronic birth certificates, which indicated hypertension occurred during the pregnancy, and a random sample of births to women with no indication of hypertension on the birth record. Willing subjects were screened for initial eligibility and excluded based on any of the following criteria: age < 18 years at delivery; non-English speaking; a prior pregnancy lasting more than 20 weeks; recurrent spontaneous abortion; received donor eggs, sperm or embryos to conceive the index pregnancy; or a diagnosis of chronic hypertension, chronic renal disease, type 1 or type 2 diabetes mellitus, systemic lupus, rheumatoid arthritis, or HIV. The final case status for all eligible and consenting subjects was determined using clinical information collected through computer-assisted telephone interviews (CATI) and confirmed by medical chart reviews. A total of 258 preeclampsia cases, 221 gestational hypertension cases, and 174 normotensive controls were ascertained. Due to the small number of normotensive women who smoked in the first trimester only (n=7) or continued to smoke into the second and third trimesters (n=23), we supplemented the normotensive group with normotensive subjects from IHIPS, a case-control study conducted simultaneously in four Iowa counties.

IHIPS—IHIPS is a population-based case–control study of preterm delivery and SGA birth outcomes among residents of four of Iowa's largest counties (also included in SOPHIA) who delivered a live birth over the period from May 2002 through June 2005. Potential control subjects were selected from electronic birth records if there was no indication that the delivery was preterm or SGA. IHIPS applied the same exclusion criteria as SOPHIA with the following exceptions: IHIPS included women who were parous or had chronic hypertension. Subjects from the IHIPS with completed medical record abstractions were eligible for this analysis (n=1,052). To replicate exclusion criteria of SOPHIA, we excluded IHIPS subjects who were parous (n=607) and those that had some indication of possible preeclampsia, gestational hypertension, or chronic hypertension either by self-report or from their medical charts (n=42). Because the outcome variable for this analysis is the BWGA z-score, we also excluded infants initially selected as possible SGA cases who were later classified as controls (n=299). With this exclusion, we avoid over representing small infants in the normotensive group. Also, during the conduct of the two studies, all control subjects were part of either IHIPS or SOPHIA—none of the subjects participated in both studies. After the above-mentioned exclusions, 168 normotensive women from IHIPS were combined with the 174 normotensive women from SOPHIA for this analysis. Of note, the normotensive groups from both studies were similar with regards to smoking status, BWGA z-score, age, race, and prepregnancy BMI.

Disease Definitions and Ascertainment

Medical records from the antenatal, intrapartum, and postpartum periods were abstracted to identify elevated blood pressure and urinary protein levels during pregnancy. Preeclampsia was defined according to the National Heart, Lung, and Blood Institute (NHLBI) guidelines: 1) sustained *de novo* hypertension (≥ 140 mmHg systolic or ≥ 90 mmHg diastolic on two or more occasions at least 6 hours apart) with onset after the 20th week of gestation, and 2) proteinuria, defined as urinary protein concentrations ≥ 30 mg/dL (equivalent to a dipstick value of 1+ from two 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 hospitalization, or a 24-hour urine collection with ≥300 mg of protein) [14]. Women who experienced sustained *de novo* hypertension after 20 weeks gestation with no evidence of proteinuria were classified as gestational hypertension.

Exposure and Outcome Ascertainment

In both SOPHIA and IHIPS, CATI interviewers collected detailed information on smoking status during each month of pregnancy and on a wide range of demographic, reproductive, medical, and lifestyle characteristics. All women were asked to report their smoking status during each month of pregnancy with the following question: “During which months of your pregnancy did you smoke cigarettes?”. We then categorized subjects as either nonsmokers, those who smoked during their first trimester (months 1–3) only, and those who smoked in the second and third trimesters (months 4–9).

All birth weight and gestational age information was abstracted from the antenatal and delivery medical charts. BWGA z-scores were calculated using birth weight and gestational age data from 391,681 US births occurring in 33 states for the years 1998–2006 as the population-based standards [15]. In our study population, subjects with a gestational age less than 37 completed weeks were excluded if their z-score for gestational age and gender was more than 3 standard deviations from the sample mean for that gestational age (n=5). Subjects with a gestational age of at least 37 completed weeks were excluded if their birth weight was more than 3 standard deviations away from the sample mean for that gestational age (n=3). After exclusions, there were 238 preeclamptic, 219 gestational hypertensive, and 342 normotensive women available for analysis.

Statistical Analysis

Univariate and multivariate analyses were performed using Statistical Analysis Software (SAS) version 9.3 (SAS Institute, Cary NC). All statistical tests were two-sided with an alpha of 0.05. We compared the characteristics of the study participants stratified by study group (preeclampsia, gestational hypertension, and normotensive women) using chi-square tests for categorical variables and t-tests for continuous variables.

Fetal growth was assessed as the z-score of BWGA using the formula: z = (observed birth weight – mean birth weight)/SD, where the mean birth weight and SD were based on published United States population-based standards, stratified by infant gender and gestational age in completed weeks.[15] A negative z-score represents an infant with a BWGA smaller than the average BWGA of an infant in the reference population whereas a

positive z-score is indicative of an infant with a larger BWGA for than the reference population.

We constructed multivariate linear regression models with z-score of BWGA as the dependent variable and maternal smoking (self-reported yes/no for anytime during the pregnancy), “preeclampsia” (preeclampsia + gestational hypertension), and an interaction term for “preeclampsia” and smoking exposure as the independent variables. As the previous study utilized the Canadian Hypertension Society classification for the diagnosis of preeclampsia [11], they classified women who developed gestational hypertension with proteinuria (traditional preeclampsia definition of the International Society for the Study of Hypertension in Pregnancy [16]) and women who developed gestational hypertension without proteinuria but with at least one adverse condition (e.g. diastolic pressure >110 mmHg, platelet count < 100,000 × 10^9/L, severe vomiting and nausea, visual disturbances) as preeclamptic [17]. Thus, we conducted a portion of our analyses with a combined group of both women with preeclampsia and women with gestational hypertension (based on the NHLBI guidelines [14]). We also constructed multivariate linear regression models of fetal growth separating preeclampsia and gestational hypertension into separate models. Additionally, we analyzed maternal smoking as a categorical variable with the following exposure groups: nonsmokers, those who smoked only during the first trimester, and those who smoked into the second and third trimesters. Covariates for all models included maternal age (continuous), prepregnancy BMI (continuous), education (high school graduate or less, some college, or college graduate or higher), and race (white or nonwhite).

RESULTS

Characteristics of the study population are shown in Table 1. Women with preeclampsia, with gestational hypertension, and those who remained normotensive throughout pregnancy were similar in age distribution. Women with preeclampsia and gestational hypertension were more likely to be white, less educated, smoke during pregnancy, and have a higher prepregnancy BMI than normotensive women. Compared to women who developed gestational hypertension and those who remained normotensive, women with preeclampsia delivered at an earlier gestational age and had infants of lower birth weight for gestational age. Women who developed gestational hypertension delivered babies at a similar gestational age and birth weight as normotensive women, though their BWGA z-scores were slightly higher.

Table 2 shows the effects of smoking by trimester on the unadjusted mean BWGA z-score for each of the three groups. In all groups, nonsmokers gave birth to infants with the highest mean BWGA z-scores. Those who smoked into the first trimester gave birth to infants who were smaller, on average, than infants of nonsmokers, but were larger than babies born to women who continued to smoke into the second or third trimester. Preeclamptic women who smoked in the first trimester only had substantially smaller infants than nonsmokers, with a mean BWGA z-score of −0.21 versus −0.12, respectively. Furthermore, women who continued to smoke into the second or third trimester had a mean BWGA z-score more than 5 times lower than that of nonsmokers: −0.63 versus −0.12, respectively. Among the women who developed gestational hypertension, nonsmokers and first trimester smokers delivered

larger babies than the normotensive women (BWGA z-score 0.30 vs. 0.21 in nonsmokers; 0.26 vs. 0.00 in those who smoked in first trimester only). However, gestational hypertensives who smoked into the second or third trimester delivered smaller babies than the normotensive women (BWGA z-score −0.18 vs. −0.05).

Results from our replication analysis of the prior study [11] are found in the first model of Table 3, along with additional models for preeclampsia and gestational hypertension analyzed separately. Findings from the linear regression analysis show that infants born to women in the combined group of preeclampsia + gestational hypertension had lower BWGA z-scores (β=−0.14, p=0.04) than infants born to normotensive women as did infants born to women who smoked anytime during pregnancy (β=−0.25, p=0.06) when compared to infants of nonsmokers. There was no evidence of an interaction between preeclampsia + gestational hypertension with smoking status (β=0.05, p=0.78), a result differing from the original study [11]. Estimates did not change after adjustment for maternal age and prepregnancy BMI. When preeclampsia and gestational hypertension were analyzed in separate models, gestational hypertension was not associated with lower BWGA z-scores (β=0.08, p=0.31), whereas preeclampsia was strongly and significantly associated with low BWGA z-scores (β=−0.33, p=<0.0001). In both of these models, smoking demonstrated a marginally significant association with BWGA z-scores (β=−0.25, p=0.05). No interactions between preeclampsia or gestational hypertension and self-reported smoking were identified. After adjustment for maternal age and prepregnancy BMI, the results remained the same (Table 3). Models analyzed without the interaction term yielded similar estimates for the independent effects of smoking and hypertension status on BWGA z-score (data not shown).

We conducted further analyses to examine the effects of timing of gestational smoking on fetal growth (Supplemental Table 1). In all three models, smoking in the first trimester only and smoking into the second or third trimester was non-significantly associated with lower BWGA z-scores (β=−0.21, p=0.27 and β=−0.27, p=0.09, respectively). There was no interaction between maternal smoking by trimester and preeclampsia + gestational hypertension, preeclampsia alone, or gestational hypertension alone. Results were similar after adjustment for maternal age and prepregnancy BMI. Models analyzed without the interaction term yielded similar estimates for the independent effects of smoking and hypertension status on BWGA z-score (data not shown).

DISCUSSION

Our study did not confirm the findings of previous work reporting an interaction between smoking and preeclampsia on BWGA z-score where preeclamptic women who smoked had larger babies than non-preeclamptic women who did not smoke [11]. Our findings indicate that infants born to preeclamptic women who smoked had significantly smaller babies than normotensive non-smokers. However, we did not observe a significant interaction between maternal smoking and preeclampsia on BWGA z-score.

Strengths and limitations

Our study has a number of strengths. The SOPHIA study applied standardized definitions of preeclampsia and gestational hypertension based upon blood pressure and urinary protein measurements recorded in the medical charts. Likewise, all normotensive subjects also underwent a stringent chart review process to verify that they had no indication of high blood pressure or urinary protein during their pregnancy that could lead to misclassification. In addition, the study collected pregnancy smoking exposure data by month of pregnancy.

There are also some limitations to the study. Our exposure data were based on self-report and may have resulted in misclassification; however the previous study to which we compared our results and many of the other studies that have examined smoking and preeclampsia also have relied on self-reported smoking status because biomarkers of smoking exposure, such as cotinine, are difficult to obtain [11]. In addition, the study population of Iowa women was fairly homogenous in regard to race (over 90% white), which limits the generalizability of our findings to other racial groups.

The difference in results between our study and the previous study could be plausibly explained by several reasons. The latter study classified preeclampsia using the diagnostic criteria from the Canadian Hypertension Society [17], which includes women with gestational hypertension without proteinuria but must have had at least one of 17 other adverse qualifying conditions (n=49); women with chronic hypertension and superimposed preeclampsia (n=3) were also included. Consequently, nearly half of the preeclampsia group also included women with gestational hypertension, most of who would not be classified as preeclampsia in our study. Most other classifications for the diagnosis of preeclampsia(e.g., International Society for the Study of Hypertension in Pregnancy[16]), consider gestational hypertension and superimposed preeclampsia to be separate hypertensive disorders of pregnancy that are distinct from de novo preeclampsia as they tend to be characterized by divergent risk factors and pathophysiologies. As demonstrated by our analyses, women who developed gestational hypertension delivered substantially larger babies than women who develop preeclampsia, independent of smoking exposure, as indicated by their mean z-scores (gestational hypertension $\beta=0.08$, preeclampsia $\beta=-0.33$). Thus, combining the two groups may have biased their results. While we attempted to replicate their classification by combining our preeclampsia and gestational hypertension women, our group of women with gestational hypertension included those with mild and severe gestational hypertension, which may explain the difference in results.

Second, the prior study did not provide information on the trimesters of pregnancy during which women smoked. It is possible that a high percentage of the Canadian subjects quit smoking during the first trimester, which has a smaller impact on fetal growth than smoking into the second or third trimester (as shown in Table 2). Sixty percent of the study population in the previous study was comprised of parous women who are more likely to give birth to larger infants in subsequent pregnancies, resulting in larger BWGA z-scores [18]. Furthermore, while the Canadian study adjusted for diabetes, chronic hypertension, and parity, unmeasured confounding may still play a role in the discrepant findings as our study population excluded women with the aforementioned conditions. Finally, selection bias may have been introduced when the authors failed to adjust for a previous diagnosis of

preeclampsia among parous women, as this was a strong risk factor for preeclampsia in their sample. Stratification by or control for preeclampsia without controlling for a previous diagnosis has the potential to introduce selection bias, which in turn could lead to a spurious finding of effect modification between smoking and preeclampsia on the BWGA z-score outcome [19, 20].

Our analysis did not confirm findings of a previous study that suggested an interaction effect between maternal smoking during pregnancy and preeclampsia on fetal growth. We found that women who developed preeclampsia deliver infants with a smaller mean BWGA z-score than women who developed gestational hypertension or who remained normotensive throughout pregnancy. While preeclamptic women who smoked into the second and third trimesters of pregnancy delivered infants with an even smaller mean BWGA z-score, an interaction between preeclampsia diagnosis and cigarette smoking was not observed. Further exploration of the association between smoking- and preeclampsia-associated fetal growth could increase the understanding of the pathophysiology of preeclampsia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of the study participants, by hypertensive status, in the Study of Pregnancy Hypertension in Iowa

Characteristics	PE (n= 238)	GH (n=219)	NT Controls[a] (n = 342)	P-value
Age group n (%)				
18–24	86 (36.0)	79 (36.1)	100 (29.2)	0.35
25–29	92 (38.5)	89 (40.6)	159 (46.5)	
30–34	45 (18.8)	39 (17.8)	56 (16.4)	
35–41	16 (6.7)	12 (5.5)	27 (7.9)	
Gestational age (wk) mean (std)	36.7 (2.9)	38.7 (1.5)	39.2 (1.4)	<0.0001
Birth weight (g) mean (std)	2840.4 (794.6)	3419.4 (502.9)	3476.3 (447.0)	<0.0001
BWGA z-score mean (std)[b]	−0.17 (0.90)	0.25 (0.90)	0.18 (0.8)	0.0004
Race n (%)				
White	220 (92.4)	208 (95.0)	305 (89.2)	0.05
Non-white	18 (7.6)	11 (5.0)	37 (10.8)	
Body mass index[c] n (%)				
Underweight/Normal	103 (43.1)	97 (44.3)	234 (68.4)	<0.0001
Overweight	66 (27.6)	69 (31.5)	73 (21.4)	
Obese	70 (29.3)	53 (24.2)	35 (10.2)	
Education n (%)				
High school graduate or less	38 (16.0)	34 (15.5)	44 (12.9)	0.0004
Some college	89 (37.4)	78 (35.6)	81 (23.7)	
College graduate or higher	111 (46.6)	107 (48.9)	217 (63.5)	
Smoking during pregnancy n (%)				
Never	192 (80.5)	166 (75.8)	290 (84.8)	0.01
1st trimester only	28 (11.8)	32 (14.6)	20 (5.6)	
2nd/3rd trimesters	18 (7.6)	21 (9.6)	32 (9.4)	

Abbreviations: PE, preeclampsia; GH, gestational hypertension; NT, normotensive; BWGA, birth weight for gestational age

[a] 174 NT controls from Study of Pregnancy Hypertension in Iowa and 168 NT controls from Iowa Health in Pregnancy Study

[b] Reference population used in calculation of Z-score birth weight for gestational age from Olsen et al [15]

[c] BMI was categorized based on the following clinical cut points: underweight/normal, <25; overweight, 25.0–29.9; obese, ≥ 30 kg/m^2

Table 2

Unadjusted mean birth weight for gestational age z-scores by trimester of smoking and hypertension status

	Preeclampsia			Gestational Hypertension			Normotensive Controls		
Smoking Status	**N**	**Mean**	**95% CI**	**N**	**Mean**	**95% CI**	**N**	**Mean**	**95% CI**
Never	192	−0.12	−0.24, 0.00	166	0.30	0.17, 0.43	290	0.21	0.11, 0.31
1st Tri. Only	28	−0.21	−0.52, 0.11	32	0.26	−0.04, 0.55	20	0.00	−0.37, 0.38
2nd/3rd Tri.	18	−0.63	−1.02, −0.23	21	−0.18	−0.54, 0.19	32	−0.05	−0.35, 0.24

Reference population used in calculation of Z-score birth weight for gestational age from Olsen et al [15]

Table 3

Examination of potential interaction effects between maternal smoking and preeclampsia and gestational hypertension combined, preeclampsia, or gestational hypertension, and fetal growth

Model	Unadjusted β (95% CI)	P value	Adjusted β[a] (95% CI)	P value
Model 1[b] - Preeclampsia and gestational hypertension combined **z-score = smoker (y/n) + (preeclampsia + gestational hypertension) + interaction term**				
Smoker	−0.25 (−0.50, 0.01)	0.06	−0.26 (−0.53, 0.004)	0.05
(Preeclampsia + gestational hypertension)	−0.14 (−0.28, −0.01)	0.04	−0.17 (−0.31, − 0.03)	0.02
Smoker*(Preeclampsia + gestational hypertension)	0.05 (−0.28, 0.37)	0.78	0.05 (−0.27, 0.37)	0.76
Model 2 - Preeclampsia **z-score = smoker (yes/no) + preeclampsia+ interaction term**				
Smoker	−0.25 (−0.49, 0.003)	0.05	−0.24 (−0.50, 0.02)	0.07
Preeclampsia	−0.33 (−0.49, −0.18)	<0.0001	−0.37 (−0.53, −0.21)	<0.0001
Smoker*Preeclampsia	−0.003 (−0.37, 0.36)	0.98	−0.02 (−0.38, 0.35)	0.93
Model 3 - Gestational Hypertension **z-score = smoker (yes/no) + gestational hypertension+ interaction term**				
Smoker	−0.25 (−0.49, 0.002)	0.05	−0.25 (−0.51, 0.01)	0.06
Gestational hypertension	0.08 (−0.08, 0.24)	0.31	0.03 (−0.13, 0.20)	0.70
Smoker*Gestational hypertension	0.04 (−0.32, 0.39)	0.85	0.04 (−0.32, 0.40)	0.81

[a] Analysis adjusted for age (continuous) and BMI (continuous)

[b] In model 1, preeclampsia and gestational hypertension subjects were combined into one category and compared to controls

Referent groups: smoking (y/n) - nonsmokers; (Preeclampsia + gestational hypertension) - controls;