Original Investigation

Association of cotinine levels and preeclampsia among African-American women

Vanitha Janakiraman, Marie Gantz, Sharon Maynard, & Ayman El-Mohandes

Abstract

Introduction: Although prior studies have shown that smoking reduces preeclampsia risk, the relationship between nicotine level and preeclampsia risk is not known. Our objective was to study the effects of smoking on the incidence of preeclampsia in African-American women using cotinine, a quantitative marker of nicotine.

Methods: We performed a secondary analysis of data collected prospectively in Project District of Columbia Healthy Outcomes of Pregnancy Education. Our study included 724 African-American women. Self-reported smoking, cotinine levels, and pregnancy outcomes were examined.

Results: Some 18% of participants were smokers. Women with salivary cotinine levels greater than 200 ng/ml had infants with lower birth weights and a higher incidence of small-for-gestational-age infants than women with cotinine levels of 200 ng/ml or less. Exact logistic regression analysis revealed that women with salivary cotinine levels greater than 200 ng/ml had a significantly lower incidence of preeclampsia, compared with women with cotinine levels of 200 ng/ml or less, in unadjusted analysis (odds ratio [OR]=0.16, 95% CI=0–0.90). After controlling for age, parity, and medical comorbidities, the trend was observed, but the effect was no longer significant (adjusted odds ratio [AOR]=0.19, 95% CI=0–1.11). We found no significant differences in preeclampsia rates using lower cutoffs of cotinine exposure. We did not observe a decrease in preeclampsia incidence at low or moderate cotinine levels.

Discussion: Women with the highest cotinine levels may have a decreased risk for preeclampsia, although this effect was not significant after controlling for other risk factors.

Introduction

Preeclampsia, a disease of pregnancy marked by hypertension and proteinuria, is a leading cause of maternal and fetal morbidity and mortality worldwide (Sibai, Dekker, & Kupferminc, 2005). Studies have demonstrated that smoking during pregnancy is associated with a reduced risk of preeclampsia (Conde-Agudelo, Althabe, Belizan, & Kafury-Goeta, 1999; Hammoud et al., 2005; Mitchell et al., 2002; Newman, Lindsay, & Graves, 2001; Zhang, Klebanoff, Levine, Puri, & Moyer, 1999). Such studies have relied largely on patient report rather than biochemical markers to determine the amount of nicotine exposure (Hammoud et al., 2005; Newman et al., 2001; Zhang et al., 1999) and thus may be affected by underreporting, metabolic variations, and variations in smoking efficiency (Benowitz & Jacob, 1997; Langone, Gjika, & Van Vunakis, 1973). Cotinine level, measured in blood, saliva, or urine, is a more accurate predictor of the effects of nicotine on birth outcomes, such as small-for-gestational-age infants and preterm birth, compared with patient report of number of cigarettes smoked (Bardy et al., 1993). To our knowledge, only one prior study used a biochemical marker of nicotine to evaluate the risk of preeclampsia (Lain et al., 1999). This case-control study was inconclusive regarding the existence of a dose-response relationship. Other studies of this relationship have not focused on African-American women. This group may be of special interest, since African-American women have higher cotinine levels per cigarette smoked, compared with Whites (Ahijevych & Parsley, 1999; Caraballo et al., 1998), and they have a high incidence of preeclampsia (Eskenazi, Fenster, & Sidney, 1991).

Our objective was to use salivary cotinine, a validated quantitative biochemical marker of nicotine exposure (Hukkanen, Jacob, & Benowitz, 2005), to study the effects of smoking on the

Vanitha Janakiraman, M.D., *Department of Obstetrics and Gynecology, The George Washington University Hospital, Washington, DC*

Marie Gantz, Ph.D., *RTI International, Research Triangle Park, NC*

Sharon Maynard, M.D., *Department of Renal Diseases and Hypertension, The George Washington University Hospital, Washington, DC*

Ayman El-Mohandes, M.B.B.Ch., M.D., M.P.H., *School of Public Health and Health Services, The George Washington University, Washington, DC*

Present address:

Vanitha Janakiraman, M.D., *Vincent Department of Obstetrics and Gynecology, Massachusetts General Hospital, Boston, MA*

Corresponding Author:

Vanitha Janakiraman, M.D., *Vincent Department of Obstetrics and Gynecology, Massachusetts General Hospital, Founders 4th Floor, 55 Fruit Street, Boston, MA 02114, USA. Telephone: 617-724-9030; Fax: 617-726-4267; E-mail: vjanakiraman@partners.org*

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incidence of preeclampsia in African-American women. We chose this marker because cotinine is a better predictor of poor pregnancy outcomes than smoking history alone (Bardy et al., 1993) and salivary cotinine is an easily collected marker with a stable half-life (Hukkanen et al., 2005). We hypothesized that women exposed to the highest levels of cotinine would have the lowest risk of preeclampsia. To address this objective, we performed a secondary analysis of data collected prospectively as part of Project District of Columbia Healthy Outcomes of Pregnancy Education (DC-HOPE).

Methods

Study population

Project DC-HOPE was a randomized trial to evaluate the effectiveness of a cognitive-behavioral intervention to reduce high-risk behaviors among pregnant minority women. Details of the study have been described previously (El-Khorazaty et al., 2007). Briefly, the study enrolled 1,044 African-American English-speaking women who were at less than 29 weeks estimated gestational age at enrollment and who screened positive for the risk of smoking, environmental tobacco smoke exposure, depression, or intimate partner violence victimization. The present study was an unplanned secondary analysis of the 746 women in this study for whom complete medical records information and cotinine levels were available. Of the 746 women, 366 were randomized to a cognitive-behavioral intervention and 380 to the usual care group. Given that randomization did not affect the incidence of preeclampsia, and we found no association between self-reported smoking or cotinine level and randomization status, subsequent analyses for this study were conducted without regard to randomization status.

Salivary cotinine sampling and data collection

Data on maternal age, parity, and smoking were collected an average of 9 days after enrollment. Smokers were defined as women who reported smoking a puff of a cigarette in the past week. Women who reported smoking in the past week also were asked about the number of cigarettes smoked on a typical day.

Abstractions of the mothers' medical records were conducted at enrollment and following delivery. These abstractions included documentation of the presence or absence of a clinical diagnosis of either preeclampsia or eclampsia in the medical record. A woman was considered to have preeclampsia if this diagnosis was recorded as such in the medical record by a clinician providing care for the woman during the hospitalization that culminated in completion of the pregnancy. At our institution, the clinical diagnosis of preeclampsia typically requires the new onset of hypertension (systolic >140 mmHg or diastolic >90 mmHg on two measurements at least 4 hr apart) and proteinuria (1+ or greater on urine dipstick testing or >300 mg protein on 24-hr urine collection) after 20 weeks gestation.

Data on chronic and gestational hypertension, pregestational and gestational diabetes, and renal disease other than urinary tract infection also were collected from the mothers' medical records. A woman was considered to have chronic hypertension if this diagnosis was recorded in the prenatal record by the clinician caring for the patient. Whether the pregnancy resulted in a

singleton or multiple birth was abstracted from the infants' medical records.

Salivary cotinine samples were collected an average of 19 days after the baseline telephone interview. Salivary cotinine analysis was performed in an in-house standardized laboratory with an Immulite 1000 system (Siemens Medical Solutions Diagnostics), a solid-phase competitive chemiluminescent immunoassay, using the manufacturer's Nicotine Metabolite Assay kit. A sample of 20–100 μ l was used per assay; each sample was tested in triplicate.

Data analyses

Bivariate analyses were conducted to detect significant differences in the baseline characteristics and medical diagnoses of smokers and nonsmokers. *T* tests were used for the comparison of continuous variables and chi-square tests for categorical variables. Similar bivariate analyses compared women with and without preeclampsia. Since it is unknown whether gestational hypertension and preeclampsia share common pathophysiological mechanisms, they were treated as separate outcomes.

A logistic regression model was created to predict preeclampsia based on self-reported smoking at baseline. Additional models examined the effect of salivary cotinine level on preeclampsia, using cotinine cutoffs at each 50 ng/ml cutoff up to 200 ng/ml. Due to the low incidence of preeclampsia in the higher cotinine groups, exact logistic regression was used to obtain ORs and CIs for all models predicting preeclampsia based on cotinine cutoffs of 100 ng/ml or greater. Variables found in bivariate analysis to be significantly different between smokers and nonsmokers or between women with and without preeclampsia were explored as covariates. Previous preeclampsia was not included as a covariate because it is a variable that could have been affected by smoking during prior pregnancies, and subjects' previous smoking habits were not known.

Linear and quadratic regression models were created to explore the relationship between preeclampsia and cotinine measured as a continuous variable. All statistical analyses were conducted using SAS version 9.1.3.

Results

Study population

Only 22 women developed gestational hypertension without proteinuria; due to the small number of subjects with this outcome, the relationship between cotinine level and gestational hypertension without preeclampsia could not be determined. The remaining 724 women comprised our study population. We found no significant differences between women in the study population and women who were excluded due to lack of salivary cotinine or medical abstraction data with regard to age, parity, proportion of smokers, average number of cigarettes smoked, or (when available) incidence of preeclampsia.

Characteristics of smokers versus nonsmokers

Eighteen percent of women (130/724) reported smoking at the time of the study enrollment. A comparison between self-reported

smoking and cotinine levels is shown in Figure 1. Women included in this analysis are represented by O's and those who were excluded for missing medical data are represented by X's. For women in this analysis, the correlation between self-reported number of cigarettes smoked and cotinine was .60 ($p < .0001$). Of the 130 baseline smokers, 98 participated in a follow-up interview at 34–38 weeks, during which 71 (72%) of women admitted to continued smoking.

Table 1 shows baseline characteristics of the smokers compared with nonsmokers. Women who were smokers were more likely to be older and multiparous. As expected, women who were smokers reported a higher average number of cigarettes per day and had higher cotinine levels, compared with nonsmokers. No other significant differences were found.

Pregnancy outcome and preeclampsia incidence

Infants of self-reported smokers had significantly lower birth weights compared with infants of nonsmokers (3,029 vs. 3,166 g, $p = .015$). Women with cotinine levels greater than 200 ng/ml had infants with significantly lower birth weights (2,964 vs. 3,157 g, $p = .016$) and a higher incidence of small-for-gestational-age neonates (27% vs. 16%, $p = .029$), compared with women with cotinine levels of 200 ng/ml or less. We found no significant differences in gestational age at birth between smokers and nonsmokers (38.2 vs. 38.4 weeks) or between women with cotinine levels greater than 200 ng/ml versus those with levels of 200 ng/ml or less (38.4 vs. 38.3 weeks).

The overall incidence of preeclampsia was 6.6% (48/724). Women with preeclampsia were more likely to have a diagnosis of pregestational diabetes, chronic hypertension, renal disease other than urinary tract infection, and preeclampsia in a previous pregnancy. No other significant differences were found (see Table 2).

We found a trend toward a lower incidence of preeclampsia among self-reported smokers as compared with nonsmokers. This difference was not statistically significant in unadjusted logistic regression models (4.62% in smokers vs. 7.07% in nonsmokers, $OR = 0.64$, 95% $CI = 0.26$ –1.53), or a model that controlled for age, parity, chronic hypertension, pregestational diabetes, and renal disease other than urinary tract infection ($AOR = 0.72$, 95% $CI = 0.29$ –1.78). Table 3 shows the incidence

Figure 1. Self-reported smoking compared with salivary cotinine levels (ng/ml).

Table 1. Characteristics of smokers and nonsmokers

Characteristics	Smokers (N = 130)	Nonsmokers (N = 594)
Maternal age, years; <i>M</i> (<i>SD</i>)	26.7 (6.2)	24.1 (5.1)*
Primiparous; <i>n</i> (%)	23 (17.7)	207 (34.9)*
GA at baseline interview; <i>M</i> (<i>SD</i>)	19.3 (7.1)	19.2 (6.7)
GA at saliva collection; <i>M</i> (<i>SD</i>)	22.2 (6.9)	21.8 (6.4)
Cigarettes per day (self-report); <i>M</i> (<i>SD</i>)	6.2 (5.6)	0.0 (0.0)*
Cotinine levels >50 ng/ml; <i>n</i> (%)	100 (76.9)	40 (6.7)*
Chronic hypertension; <i>n</i> (%)	9 (6.9)	36 (6.1)
Pregestational diabetes; <i>n</i> (%)	5 (3.9)	21 (3.5)
Renal disease	6 (4.6%)	21 (3.5%)
Multiple birth	3 (2.3%)	11 (1.9%) ^a
Preeclampsia in prior pregnancy	6 (4.7%) ^b	13 (2.2%) ^c

Note. GA, gestational age.

^aSample size = 585.

^bSample size = 129.

^cSample size = 593

* $p \leq .0001$.

of preeclampsia at 50 ng/ml increments of cotinine. The incidence of preeclampsia did not appear to decline with rising cotinine levels, with the exception of the group with very high (>200 ng/ml) levels, in whom there were no cases of preeclampsia. We found no statistically significant differences between these groups. Among the 57 women with cotinine levels greater than 200 ng/ml, the range of cotinine was 206–656 ng/ml, with a median of 321 ng/ml.

Preeclampsia incidence using cutoff cotinine levels

As an exploratory analysis, we chose cotinine level cutoffs between 50 and 200 ng/ml and compared the incidence of preeclampsia in women with cotinine levels above or below these cutoffs. Results

Table 2. Characteristics of women with and without preeclampsia

Characteristics	With preeclampsia (N = 48)	Without preeclampsia (N = 676)
Maternal age, years; <i>M</i> (<i>SD</i>)	24.7 (5.6)	24.6 (5.4)
Primiparous; <i>n</i> (%)	21 (43.8)	209 (30.9)
Smoking during pregnancy (self-report); <i>n</i> (%)	6 (12.5)	124 (18.3)
Chronic hypertension; <i>n</i> (%)	9 (18.8)	36 (5.3)*
Pregestational diabetes; <i>n</i> (%)	5 (10.4)	21 (3.1)*
Renal disease; <i>n</i> (%)	5 (10.4)	22 (3.3)*
Multiple birth; <i>n</i> (%)	2 (4.3) ^a	12 (1.8) ^b
Preeclampsia in prior pregnancy; <i>n</i> (%)	6 (12.5)	13 (1.9) ^c *

Note. ^aSample size = 47.

^bSample size = 666.

^cSample size = 674.

* $p \leq .01$.

Table 3. Percentage of women with preeclampsia by cotinine level

Salivary cotinine (ng/ml)	Women with preeclampsia (%)
≤50	6.9 (40/584)
51–100	11.1 (4/36)
101–150	4.6 (1/22)
151–200	12.0 (3/25)
>200	0 (0/57)

are show in Table 4. Using an exact logistic regression model, we found a significantly lower incidence of preeclampsia at a cotinine cutoff of 200 ng/ml in unadjusted analyses ($OR=0.16$, 95% $CI=0-0.90$). After adjusting for age, parity, and medical comorbidities (chronic hypertension, pregestational diabetes, and renal disease other than urinary tract infection), the effect of a cotinine level greater than 200 ng/ml was no longer significant ($AOR=0.19$, 95% $CI=0-1.11$). Logistic regression models revealed no significant difference in preeclampsia incidence in women with cotinine levels above versus below 50, 100, or 150 ng/ml, even when the models were adjusted for covariates associated with either smoking or preeclampsia. After adjusting for the same covariates, we found no significant effect of cotinine on preeclampsia incidence when it was entered into the model as a continuous effect, either linear or quadratic.

Discussion

Although pregnant smokers with salivary cotinine levels greater than 200 ng/ml had a lower risk of preeclampsia than women with cotinine levels of 200 ng/ml or less, this effect was not significant after controlling for confounders. There did not appear to be a dose-response relationship between tobacco exposure as assessed by cotinine level and preeclampsia risk. There may be a threshold effect whereby women with the highest cotinine levels have a reduction in preeclampsia risk. Future studies with more power would be needed to confirm or refute this relationship between cotinine level and preeclampsia.

We did not find a significant effect of cotinine on preeclampsia risk when viewed as a continuous variable. However, since this was an unplanned secondary analysis of a prospective study, our study may have been underpowered to detect a dose-response relationship between cotinine level and preeclampsia risk. Thus, we cannot rule out that such a relationship exists and might be detectable given more data.

To our knowledge, this is the first prospective study to report on the effect of nicotine specifically in a African-American population, a group with high cotinine levels per cigarette smoked (Ahijevych & Parsley, 1999; Hukkanen et al., 2005) and a high incidence of preeclampsia (Eskenazi et al., 1991; Shen, Tymkow, & MacMullen, 2005). Many prior studies of the effect of smoking on preeclampsia incidence have not examined the effects of maternal race (Hammoud et al., 2005; Mitchell et al., 2002). Studying this population is particularly important since African-American women are more likely to have severe complications of preeclampsia, including maternal mortality (Tucker, Berg, Callaghan, & Hsia, 2007). An important strength of the present study is the use of cotinine, a biologically relevant marker of nicotine exposure. Our study confirms that cotinine level is a predictor of neonatal outcomes. To our knowledge, this is only the second study to use this highly predictive marker of smoking to examine the effects of cigarette smoking on the incidence of preeclampsia (Lain et al., 1999).

Other studies have sought a dose-response relationship between cigarette smoke exposure and protection against preeclampsia. The results using reported numbers of cigarettes smoked alone have been mixed. Hammoud et al. (2005) did not find a clear dose-response or threshold effect, since moderate (6–10 cigarettes/day) and heavy (>10 cigarettes/day) smokers had a similar incidence of preeclampsia. Zhang et al. (1999) found a dose-response effect with the lowest incidence of preeclampsia in women who smoked 11 cigarettes/day or more. A meta-analysis that grouped women according to whether they smoked more or less than 10 cigarettes/day found a reduced incidence of preeclampsia in the heavier smokers (Conde-Agudelo et al., 1999). This finding could support either a dose-response or a threshold effect. However, all these studies used self-reported number of cigarettes smoked, rather than a direct biological measure of exposure. Lain

Table 4. Odds ratios for preeclampsia for four cutoff cotinine levels^a

Nicotine exposure		Preeclampsia		
Salivary cotinine (ng/ml)	Cigarettes/day ($M \pm SD$)	Number (%)	Unadjusted OR (95% CI)	Adjusted odds ratio ^b (95% CI)
≤50	0.1 ± 1.0	40/584 (6.9)	1.0	1.0
>50	4.7 ± 5.7	8/140 (5.7)	0.82 (0.38–1.80)	0.92 (0.41–2.06)
≤100	0.3 ± 1.3	44/620 (7.1)	1.0	1.0
>100	5.5 ± 6.2	4/104 (3.9)	0.52 (0.13–1.48)	0.60 (0.15–1.74)
≤150	0.4 ± 1.6	45/642 (7.0)	1.0	1.0
>150	6.0 ± 6.6	3/82 (3.7)	0.50 (0.10–1.63)	0.59 (0.11–1.94)
≤200	0.5 ± 2.1	48/667 (7.2)	1.0	1.0
>200	6.5 ± 7.1	0/57 (0)	0.16 (0–0.90)	0.19 (0–1.11)

Note. ^aFor each cutoff, the entire study population is separated into two groups: those with cotinine levels above and below the cutoff value. The numbers of women in each group can be determined using Table 3.

^bAdjusted for maternal age, parity, chronic hypertension, pregestational diabetes, and renal disease other than urinary tract infection.

et al. (1999) examined the relationship between urinary cotinine levels and incidence of preeclampsia. This case-control study was inconclusive about a dose-response relationship: a test of linear trend showed a lower incidence of preeclampsia with higher cotinine levels, but the incidence of preeclampsia was similar among light and heavy smokers. Our results are consistent with these findings, but they suggest that the protective effect of smoking may be observed only at high levels of nicotine exposure in African-American women.

Our study has several limitations. Our primary outcome, preeclampsia, was measured via medical record abstraction rather than by strict blood pressure and proteinuria guidelines. This may have led to under- or overreporting of preeclampsia. Unfortunately, we did not have access to the records at the time of this unplanned secondary analysis in order to validate the diagnosis of preeclampsia. However, the subjects with preeclampsia in our study were more likely to be primiparous and to have pregestational diabetes, renal disease, and multiple gestations. These known risk factors for preeclampsia help to validate the diagnosis of preeclampsia.

In our study, some women were excluded due to missing medical records information or biochemical markers. Although our baseline comparison data indicate that these women were not significantly different from the study population, including the proportion of smokers, their outcomes may have been different. Because information was not available on body mass index, we could not account for the possible confounding effect of obesity. In this analysis, cotinine levels were studied only at study enrollment. This may not accurately reflect nicotine exposure throughout the entire pregnancy. The cutoff we used for cotinine, 50 ng/ml, includes both nonsmokers and those with passive exposure. Thus, we could not look at these groups separately. Finally, the study included only women with smoke exposure, intimate partner violence, or depression. Although none of these is a known risk factor for preeclampsia, this may limit the generalizability of our results.

In conclusion, in a African-American population, heavy smokers with cotinine levels greater than 200 ng/ml had one sixth the odds of developing preeclampsia, compared with nonsmokers and light smokers combined in an unadjusted analysis. This effect lost significance after adjusting for medical risk factors for preeclampsia.

Whatever protective effect smoking may have against the incidence of preeclampsia, we do not believe that these effects outweigh the risk to mothers and their unborn fetuses if they are unable to quit smoking during pregnancy. Every effort should be made to encourage smoking cessation during pregnancy according to the recommendations of the American College of Obstetrics and Gynecology.

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Declaration of Interests

None declared.

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