OBSTETRICS

Plasma cotinine indicates an increased risk of preeclampsia in previous and passive smokers

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OBJECTIVE: Self-reported tobacco smoking in pregnancy has been consistently associated with a decreased risk of developing preeclampsia, but the evidence has been limited and inconsistent for previous and passive smokers. Misclassifications and inaccuracies of self-reported tobacco exposure may disguise the true relationship. This study aimed to assess the association of gestational hypertension and preeclampsia with maternal smoking status as ascertained by plasma cotinine.

STUDY DESIGN: This was a prospective study of 605 pregnant women without chronic hypertension. Maternal smoking status at 24-26 weeks' gestation was defined by plasma cotinine: >3.0 ng/mL "current smokers," 0.20-3.00 ng/mL "previous and passive smokers," and <0.20 ng/mL "nonsmokers."

RESULTS: Compared to nonsmokers, the risk of developing preeclampsia did not change significantly for current smokers, but increased significantly (adjusted odds ratio, 6.06; 95% confidence interval, 2.32—15.85; $P < .001$) for previous and passive smokers. There were no significant differences in the risk of developing gestational hypertension only.

CONCLUSION: Previous and passive smoking may increase the risk of preeclampsia. Avoidance of exposure to environmental tobacco smoke in pregnancy may decrease the risk of preeclampsia.

Key words: cotinine, gestational hypertension, passive smoker, preeclampsia, previous smoker

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Tobacco smoking, or in short "smoking," is a well-known risk factor for a number of adverse pregnancy outcomes including fetal growth restriction, preterm delivery, and placental abruption.[1,2] Paradoxically, self-reported smoking during pregnancy has been consistently associated with a reduced risk of preeclampsia[3-6]—a serious pregnancy complication characterized by the de novo onset of hypertension and proteinuria occurring >20 weeks' gestation in women without known chronic hypertension or protenuria.[7] The potential protective effect of active smoking against preeclampsia could be due to the gaseous tobacco combustion molecule carbon monoxide, which has cytoprotective effects on endothelial cells and antiapoptotic properties in the human placenta.[8,9] It remains controversial whether there is a protective effect for previous smokers,[10-12] and the evidence has been scanty for passive smokers or exposure to environmental tobacco smoke. The current body of evidence largely comes from studies based on self-reported smoking status. Misclassifications and inaccuracies of exposure according to self-reports may distort the true relationship, especially for passive smokers notoriously vulnerable to reporting errors.[13] Whether there is any biologically meaningful current exposure burden in previous smokers is uncertain without a biomarker measurement. These limitations can be resolved if we use a biomarker-based smoking exposure measure. However, there have been very few and limited studies on biomarker-based smoking exposure and the risk of gestational hypertension and preeclampsia. We could identify only 2 such original studies; both addressed the risk of preeclampsia in current smokers only.[14,15] The present study sought to assess the risk of gestational hypertension and preeclampsia in current, previous, and passive smokers according to plasma cotinine levels. We hypothesized that previous and passive smoking may be associated with an increased risk of gestational hypertension and preeclampsia due to the deleterious placental effects of previous or current exposure to numerous tobacco chemicals in the absence of significant current exposure to carbon monoxide that may explain the reduced risk of preeclampsia in current smokers.

Materials and Methods

Study design

This was a prospective pregnancy cohort study using the plasma specimen bank constituted in the International Trial of Antioxidant Supplementation

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(vitamins C and E) for the Prevention of Preeclampsia (INTAPP). The trial was conducted in Canada and Mexico from 2004 through 2006, and found no association between antioxidant supplementation (from 12-18 weeks' gestation onwards) and the risk of developing preeclampsia.[16] Canadian INTAPP subjects were reconsented to participate in a biobank (n = 733) for further research on pregnancy complications. Excluding 46 subjects with chronic hypertension and 82 subjects without maternal plasma specimen available at 24-26 weeks' gestation for the measurement of plasma cotinine, the final study cohort included 605 subjects. During INTAPP, participants were requested to donate a 14-mL blood specimen at 24-26 weeks' gestation into 2 7-mL EDTA-containing tubes. Patients were aware in advance that they would be giving a blood sample. The study was approved by the University of Montreal Sainte-Justine Hospital Research Ethics Board. Maternal characteristics and clinical outcomes were similar and not significantly different between Canadian subjects who consented to contribute to the biobank versus those who did not. Mexican subjects did not participate as it was not feasible to reconsent INTAPP Mexican participants. In INTAPP, women were stratified according to the presence or absence of risk factors for preeclampsia. Women were in the high-risk stratum for preeclampsia if they met at least 1 of the 4 criteria: prepregnancy chronic hypertension, prepregnancy diabetes, a multiple pregnancy, or a history of preeclampsia; the remaining subjects were in the low-risk stratum. Women with chronic hypertension were excluded in the present study because the diagnosis of gestational hypertension is not applicable to such patients. The study definitions of gestational hypertension and preeclampsia were according to the criteria of the Society of Obstetricians and Gynecologists of Canada: gestational hypertension was defined as de novo hypertension (≥2 readings of diastolic blood pressure ≥90 mm Hg taken 4 hours apart) occurring at ≥20 weeks' gestation; preeclampsia was defined as gestational hypertension with de novo proteinuria (urine protein dipstick test ≥2+ or urinary excretion of ≥0.3 g in 24-hour urine collection).[7] Sensitivity analyses were conducted to assess whether the main findings remained valid if alternatively, gestational hypertension was defined as diastolic blood pressure ≥90 mm Hg and/or systolic blood pressure ≥140 mm Hg (the Canadian definition considered diastolic blood pressure only).

Plasma cotinine assays

Plasma specimens were stored at −80°C until assays. Maternal plasma cotinine (ng/mL) at 24-26 weeks' gestation was measured using an enzyme-linked immunosorbent assay kit (Calbiotech, Spring Valley, CA). Based on measurements using standard cotinine concentrations and blank controls provided by the kit, the detection limit was 0.20 ng/mL; intraassay and interassay coefficients of variation were 6.0% and 10.1% (at 5.0 ng/mL), respectively.

Smoking status according to plasma cotinine

Because only limited information on smoking status was obtained in INTAPP—the question for capturing smoking status was only a limited part of the INTAPP baseline questionnaire (did you ever smoke in this pregnancy?)—without information on smoking cessation during pregnancy in subsequent visits, the number of cigarettes smoked, or exposure to environmental tobacco smoke, the present study defined smoking status according to plasma cotinine. Maternal smoking status at 24-26 weeks' gestation was defined according to plasma cotinine: >3.00 ng/mL "current smokers," 0.20-3.00 ng/mL "previous or passive smokers" (impossible to distinguish between the two), and <0.20 ng/mL "nonsmokers" (reference group). The use of the relatively lower circulating cotinine concentration cutoff of 3.0 ng/mL to define current smokers has been recommended recently in contrast to the previously commonly used 14-ng/mL cutoff in studies of early years, considering the decreasing numbers of smokers and the ban of smoking in most public facilities and consequently lower background exposure to environmental tobacco smoke in recent decades in North America.[17] The 0.20-ng/mL cutoff in plasma cotinine to detect even light passive exposure to tobacco smoke is similar to the 0.21-ng/mL cutoff reported in a recent study.[18]

Sensitivity analyses were conducted to examine whether the main findings remained valid if alternatively, plasma cotinine >4.85 ng/mL was used to define current smokers—a recently recommended cutoff for Caucasians,[17] the majority ethnic group in the study population—or the previously commonly used 14.0-ng/mL cutoff was applied to define current smokers.

Statistic analysis

Logistic regression was used to estimate the crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) of developing gestational hypertension only, preeclampsia, or either condition in association with current, previous, and passive smoking. The adjusted ORs were controlled for prespecified potential confounding factors including risk stratum (low risk, high risk), maternal ethnicity (Caucasian, others), age (≥35 years, yes/no), primiparity (yes/no), prepregnancy obesity (body mass index ≥30 kg/m^2, yes/no), education (university, yes/no), employment (yes/no), and treatment group (antioxidant supplementation, yes/no). The risk stratum was used rather than individual risk conditions in multivariate logistic regression to reduce the number of covariables and improve the stability of the regression models. Two-sided P values < .05 were considered statistically significant. All analyses were performed using SAS software (version 9.2; SAS Institute Inc, Cary, NC). Ad hoc power calculations indicated a power of 80.5% to detect an OR of ≥4.0 association of previous and secondhand smoking with gestational hypertension and preeclampsia.

RESULTS

According to plasma cotinine at 24-26 weeks' gestation, 47 pregnant women were smokers, 42 were previous or passive smokers, and 516 were nonsmokers