Glucose Tolerance and Risk of Gestational Diabetes Mellitus in Nulliparous Women Who Smoke during Pregnancy

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Gestational diabetes mellitus has been associated with adverse maternal and infant outcomes, including preeclampsia and fetal macrosomia. Although cigarette smoking has been associated with increased insulin resistance, its effect on gestational diabetes mellitus risk is uncertain. The authors evaluated the effects of smoking on glucose tolerance in a cohort of pregnant women who participated in the Calcium for Preeclampsia Prevention trial, a randomized study of nulliparous women conducted in five US medical centers from 1992 to 1995. Results of screening and diagnostic testing for gestational diabetes mellitus were analyzed. For 3,774 of the 4,589 women enrolled, plasma glucose concentration 1 hour after a 50-g oral glucose challenge and complete information on pregnancy outcome were available; for 3,602 of the women, gestational diabetes mellitus status was known. Adjusted mean 1-hour plasma glucose concentration (mg/dl) was elevated in women who smoked at study enrollment (112.6, 95% confidence interval: 110.0, 115.3) compared with women who had never smoked (108.3, 95% confidence interval: 106.7, 109.8; p < 0.01). Women who smoked were at increased risk of gestational diabetes mellitus when criteria proposed by the National Diabetes Data Group were used (adjusted odds ratio = 1.9, 95% confidence interval: 1.0, 3.6). These findings support an association between smoking and gestational diabetes mellitus.

diabetes, gestational; glucose tolerance test; pregnancy; smoking

Abbreviations: CI, confidence interval; CPEP, Calcium for Preeclampsia Prevention; OGTT, oral glucose tolerance test.

Gestational diabetes mellitus, or glucose intolerance first detected during pregnancy, affects 3–5 percent of pregnancies (1). It is believed to occur when pancreatic beta cells fail to produce adequate amounts of insulin in the face of increasing insulin resistance during pregnancy (2). Gestational diabetes mellitus and type 2 diabetes mellitus share common risk factors, such as elevated body mass index, advancing age, and family history of type 2 diabetes mellitus (3, 4). Moreover, women with gestational diabetes mellitus are at increased risk of type 2 diabetes mellitus in later life (5–7).

Smoking appears to affect glucose regulation (8) and, in many studies (9–14), although not all (15–18), has been associated with increased insulin resistance, altered glucose homeostasis, and hyperinsulinemia. Smoking has also been associated with type 2 diabetes mellitus (19–23). For example, in a large prospective study, diabetes mellitus risk for women who smoked was increased by 20–40 percent after adjustment for obesity and other factors, depending on the amount of smoking (20). In a subsequent prospective study, risk among women was elevated by 20–74 percent after adjustment for diet, body mass index, exercise, and other factors (22). In the latter example, the effect was

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confined to those who smoked one or more packs per day. In contrast, no association was noted in several other prospective studies (24–27).

The role of smoking in gestational diabetes mellitus has been studied less often, and it remains uncertain (3, 8, 28–31). Two of the largest epidemiologic studies published to date yielded conflicting findings. Solomon et al. (3), using data from the Nurses’ Health Study II, found a 40 percent increased risk of gestational diabetes mellitus for smokers compared with nonsmokers; Terry et al. (30), using data from the Swedish Birth Registry, found no association between smoking and gestational diabetes mellitus. Other, smaller studies of glucose homeostasis have also produced inconsistent results (28, 29, 31).

The current study was conducted to determine whether smoking during pregnancy is associated with impaired glucose tolerance and increased risk of gestational diabetes mellitus. We used data from a cohort of healthy, nulliparous women interviewed early in pregnancy about their smoking history and monitored for the development of hypertension, proteinuria, and other medical complications.

MATERIALS AND METHODS

Study subjects

For this secondary analysis, data were obtained from the Calcium for Preeclampsia Prevention (CPEP) trial. CPEP was a randomized, double-blind clinical trial of the effects of daily calcium supplementation on the incidence of preeclampsia in nulliparous women. Healthy, normotensive women at 13–21 weeks’ gestation were enrolled at five participating US medical centers and were followed to delivery using a common protocol and identical data collection forms. Subjects known to have preexisting diabetes mellitus were excluded; however, testing for diabetes mellitus was not a prerequisite for study enrollment. Women were routinely screened for gestational diabetes mellitus by administering a 50-g oral glucose challenge and measuring plasma glucose concentration 1 hour later according to the procedures specified at the individual medical centers, typically in the late second or early third trimester. A 3-hour, 100-g oral glucose tolerance test (OGTT) was administered to women with abnormal screening test results. Although all study centers used universal screening for gestational diabetes mellitus, there was no uniform protocol and some practices varied. In one center, for example, the 50-g glucose challenge typically was administered while women were fasting; in the other centers, it was given without regard to time of the last meal. In three centers, the threshold for an OGTT was a glucose concentration of 140 mg/dl 1 hour after a 50-g glucose challenge, but, in two centers, the threshold was 135 mg/dl.

Of the 4,589 women enrolled in the CPEP trial, 4,289 were followed through delivery and were eligible for inclusion in the current analysis, while 300 were excluded for the following reasons: lost to follow-up (n = 253), termination of pregnancy before 20 weeks (n = 21), or absence of data on maternal or neonatal outcomes (n = 22) or smoking history (n = 4). For our study of 1-hour, 50-g glucose screening test results, an additional 514 women were excluded because the 50-g oral glucose challenge was not administered. One woman was also excluded because her results were implausible, leaving data on 3,774 women for analysis. For our study of gestational diabetes mellitus, 596 women were excluded from the eligible group of 4,289 because gestational diabetes mellitus status was indeterminate (refer to the Glucose tolerance paragraphs below). Women who did not undergo a 50-g glucose screening test but had a 3-hour, 100-g OGTT were excluded from our analysis of screening test results but were included in the analysis of gestational diabetes mellitus, and vice versa. Because there was only one gestational diabetes mellitus case in the race/ethnicity category “other/unknown” (n = 91), these women were also excluded to ensure stability of the estimates of odds ratios and confidence intervals. These exclusions left 3,602 women who contributed data for the gestational diabetes mellitus analysis.

The CPEP study protocol was approved by the institutional review boards at the five participating medical centers, and all women gave written informed consent. The design, methods, and primary outcomes of this trial have been described in greater detail elsewhere (32–34).

Smoking history

At study enrollment, women were asked whether they had ever smoked regularly (every day or almost every day). Women responding yes were asked whether they still smoked and, if so, how many cigarettes they had smoked per day on average since their last menstrual period. Those who no longer smoked were asked whether they had stopped smoking before or after their last menstrual period. All women who had ever smoked were asked how many cigarettes they had smoked per day on average over their lifetime smoking history. Women were not asked at subsequent study visits about smoking status.

Glucose tolerance

We assessed glucose tolerance by analyzing the results of the 1-hour, 50-g oral glucose screening test and the 3-hour, 100-g OGTT. Gestational diabetes mellitus was defined as a plasma glucose concentration of ≥200 mg/dl 1 hour after administration of a 50-g glucose challenge in the absence of a 3-hour, 100-g OGTT or two or more abnormal plasma glucose values in a 3-hour, 100-g OGTT. Thresholds were based on conversion of O’Sullivan and Mahan criteria (35) proposed by the National Diabetes Data Group (≥105 mg/dl fasting, ≥190 mg/dl at 1 hour, ≥165 mg/dl at 2 hours, or ≥145 mg/dl at 3 hours) (36). Gestational diabetes mellitus status was indeterminate for women whose 1-hour plasma glucose concentration was between 140 mg/dl and 200 mg/dl and who had no 3-hour OGTT, and for women who had neither a 1-hour glucose screening test nor a 3-hour OGTT. Because the conversion of O’Sullivan and Mahan criteria for gestational diabetes mellitus proposed by Carpenter and Coustan (37) has also been supported by expert panels (38), analyses of gestational diabetes mellitus were repeated using these
threshold values (≥295 mg/dl fasting, ≥180 mg/dl at 1 hour, ≥155 mg/dl at 2 hours, or ≥140 mg/dl at 3 hours).

The percentage of women excluded because of indeterminate gestational diabetes mellitus status did not differ substantially by smoking exposure (13 percent for never smokers, 16 percent for women who quit before pregnancy, 16 percent for women who quit during pregnancy, and 14 percent for women who smoked at study enrollment).

Fasting glycemia

Impaired fasting glycemia may reflect more severe gestational diabetes mellitus (2) or undiagnosed, preexisting diabetes mellitus (39). Therefore, fasting glucose concentration was examined in those women who attended a single medical center where fasting values were routinely measured as part of the 1-hour, 50-g glucose screening test (n = 1,209).

Statistical analysis

Women were classified into four mutually exclusive categories of tobacco exposure based on their smoking history reported at study enrollment: 1) never smoked, 2) quit before pregnancy (before the last menstrual period), 3) quit during pregnancy (after the last menstrual period but before study enrollment), and 4) smoked at enrollment. Exposure level during pregnancy (for those who smoked at enrollment) was based on the average number of cigarettes smoked per day since the last menstrual period and was categorized as light (1–9 cigarettes/day), moderate (10–19 cigarettes/day), or heavy (≥20 cigarettes/day). Lifetime exposure (for all women who had ever smoked) was based on the average number of cigarettes smoked per day over the lifetime smoking history and was categorized similarly. Lifetime exposure was also estimated by using the number of pack-years of smoking, calculated by multiplying the average number of packs of cigarettes smoked per day (the average number of cigarettes smoked per day in the lifetime smoking history divided by 20) by the number of years of smoking. Pack-years of smoking were divided into three categories that approximated tertiles: less than 3.0, 3.0–5.9, and 6.0 or more.

Chi-square tests and t tests were used in unadjusted analyses to compare categorical variables or continuous variables, respectively. Analysis of covariance was used to generate adjusted mean 1-hour plasma glucose concentrations for women in each tobacco exposure category; pairwise comparisons were made by using independent t tests. Where multiple comparisons were made, analyses were repeated by using post hoc Dunnett’s two-tailed t test. For women who underwent two or more 1-hour screening tests, we selected the test conducted nearest to the median gestational age at testing for those women who had never smoked (191 days). Variables considered as possible confounders were those potentially associated with both blood glucose and smoking status, including maternal race/ethnicity (African American; White, non-Hispanic; White, Hispanic; or other/unknown), age at study enrollment (<17, 17–24, 25–29, or ≥30 years), education (high school graduate or not), body mass index at enrollment (<19.8, 19.8–25.9, 26–34.9, or ≥35 kg/m²), previous pregnancy loss at less than 20 weeks (none or ≥1), private health insurance (yes or no), study center, and gestational age at the time of blood collection. Variables associated with both smoking status and 1-hour plasma glucose concentration in crude analyses (p ≤ 0.20) were included in initial adjustment models. Those variables not associated in adjustment models with glucose concentration (p > 0.05) were then excluded. To determine whether glucose tolerance was altered in women without gestational diabetes mellitus, analyses were repeated after excluding those with gestational diabetes mellitus or of indeterminate gestational diabetes mellitus status. All reported p values are two-tailed.

To evaluate the contribution of lifetime smoking exposure to glucose tolerance relative to that of exposure during pregnancy, two approaches were taken. First, we used analysis of covariance to generate adjusted mean 1-hour plasma glucose concentrations for women who smoked at enrollment by exposure level over lifetime smoking history (light, moderate, or heavy) and, in a separate analysis, by number of pack-years of smoking (<3.0, 3.0–5.9, or ≥6.0). Results were adjusted for number of cigarettes smoked per day during pregnancy and for factors described previously. Second, data on women who smoked at enrollment were stratified by exposure level over lifetime smoking history (light, moderate, or heavy) and then again by exposure level during pregnancy (light, moderate, or heavy). The adjusted mean 1-hour glucose concentration in women who, by study enrollment, had reduced their cigarette use to a lower level (from heavy to moderate or light exposure, or from moderate to light exposure) was compared with that of women whose cigarette use did not change.

Multiple logistic regression models were used to calculate the adjusted odds ratios and 95 percent confidence intervals for gestational diabetes mellitus for women in each category of tobacco exposure. For consistency, the same adjustment variables were included as in models for 1-hour plasma glucose concentration, with the exception of gestational age at the time of blood collection, which was not included in gestational diabetes mellitus analyses. Odds ratios for gestational diabetes mellitus were then recalculated by using conversion thresholds proposed by Carpenter and Coustan (37), as described previously.

RESULTS

Study subjects

Demographic characteristics of study subjects varied by smoking exposure (table 1). Compared with women who had never smoked, women who smoked at enrollment and women who had quit smoking before or during pregnancy were more often White and less often African American. Women who had quit smoking before pregnancy were older and were more likely to have private health insurance. Women who smoked at enrollment were older, had a greater body mass index, and were less likely to have a high school education than women who had never smoked.
TABLE 1. Characteristics of the study population by smoking exposure among women for whom a 1-hour, 50-g glucose screening test was completed \( (n = 3,774) \), Calcium for Preeclampsia Prevention trial, United States, 1992–1995

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Never smoked* ( (n = 2,658) )</th>
<th>Quit before pregnancy ( (n = 286) )</th>
<th>Quit during pregnancy ( (n = 382) )</th>
<th>Smoked at study enrollment ( (n = 448) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race/ethnicity (no. (%))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>1,679 (63.2)</td>
<td>45 (15.7)†</td>
<td>44 (11.5)†</td>
<td>42 (9.4)†</td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>543 (20.4)</td>
<td>169 (59.1)†</td>
<td>252 (66.0)†</td>
<td>353 (78.8)†</td>
</tr>
<tr>
<td>White, Hispanic</td>
<td>373 (14.0)</td>
<td>64 (22.4)†</td>
<td>70 (18.3)†</td>
<td>47 (10.5)†</td>
</tr>
<tr>
<td>Other, unknown</td>
<td>63 (2.4)</td>
<td>8 (2.8)†</td>
<td>16 (4.2)†</td>
<td>6 (1.3)†</td>
</tr>
<tr>
<td>High school or greater education (no. (%))</td>
<td>1,518 (57.2)</td>
<td>178 (62.2)</td>
<td>211 (55.5)</td>
<td>230 (51.3)†</td>
</tr>
<tr>
<td>Private insurance (no. (%))</td>
<td>208 (7.8)</td>
<td>34 (11.9)‡</td>
<td>31 (8.1)</td>
<td>30 (6.7)</td>
</tr>
<tr>
<td>Maternal age in years (mean (SD))</td>
<td>20.5 (4.1)</td>
<td>22.3 (5.2)†</td>
<td>20.8 (4.1)</td>
<td>22.0 (4.7)†</td>
</tr>
<tr>
<td>Body mass index in kg/m² (mean (SD))</td>
<td>25.8 (6.2)</td>
<td>25.5 (5.2)</td>
<td>25.5 (5.3)</td>
<td>26.4 (6.1)†</td>
</tr>
<tr>
<td>Gestation in days at 1-hour screening¶ (mean (SD))</td>
<td>190.4 (17.5)</td>
<td>191.9 (15.7)</td>
<td>192.3 (14.1)</td>
<td>192.4 (13.3)</td>
</tr>
<tr>
<td>No. of years of smoking (mean (SD))</td>
<td>4.0 (3.7)</td>
<td>5.2 (3.7)†</td>
<td>7.2 (4.0)†</td>
<td></td>
</tr>
<tr>
<td>No. of cigarettes smoked per day over lifetime smoking history (mean (SD))</td>
<td>8.4 (8.3)</td>
<td>11.5 (8.0)†</td>
<td>16.2 (9.1)#</td>
<td></td>
</tr>
<tr>
<td>No. of pack-years of smoking (mean (SD))</td>
<td>2.1 (3.5)</td>
<td>3.3 (3.6)†</td>
<td>6.1 (5.4)†</td>
<td></td>
</tr>
<tr>
<td>No. of cigarettes smoked per day during pregnancy (mean (SD))</td>
<td>8.0 (5.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Reference group for statistical comparisons except for comparisons within ever smokers, when “quit before pregnancy” was the reference group.
† Significant at \( p < 0.001 \).
‡ Significant at \( p < 0.05 \).
§ SD, standard deviation.
¶ If two or more 1-hour screening tests were performed, the test nearest to the median gestational age at testing among women who had never smoked (191 days) was selected.
# Significant at \( p < 0.01 \).

**One-hour, 50-g glucose screening test**

Daily maternal calcium supplementation was not significantly associated with smoking status or results of the 1-hour, 50-g glucose screening test. Therefore, for this analysis, we combined data on women who had received calcium with those who had received placebo supplements. In adjustment models, factors independently associated with plasma glucose concentration were study center (\( p < 0.001 \)), race/ethnicity (\( p < 0.001 \)), maternal age (\( p < 0.001 \)), body mass index (\( p < 0.001 \)), and gestational age at time of blood collection (\( p = 0.03 \)). Education, previous pregnancy loss, and private health insurance did not contribute significantly to final adjustment models (inclusion of these variables changed adjusted mean glucose values by ≤0.2 percent, and all \( p \) values were ≥0.4) and were dropped; all other adjustment variables were retained.

Adjusted mean 1-hour plasma glucose concentration was lowest in women who had never smoked and highest in women who smoked at study enrollment (\( p < 0.01 \)). Glucose concentrations in women who had quit before or during pregnancy were not significantly different from those in women who had never smoked (table 2). Among women who smoked at enrollment, glucose concentration increased with increasing level of tobacco exposure during pregnancy (table 3). On average, plasma glucose concentration increased by 0.5 mg/dl for each cigarette smoked per day (\( p = 0.01 \)). Similar relations were observed after excluding women with gestational diabetes mellitus or of indeterminate gestational diabetes mellitus status: compared with that in women who had never smoked, adjusted mean plasma glucose concentration (mg/dl) remained significantly higher in women who smoked at study enrollment (105.6, 95 percent confidence interval (CI): 104.2, 107.0 vs. 109.2, 95 percent CI: 106.8, 111.6; \( p < 0.01 \)). Among women who smoked at enrollment, glucose concentration increased on average 0.3 mg/dl for each cigarette smoked per day, although this association was not significant (\( p = 0.09 \)).

The contribution of lifetime smoking exposure to glucose tolerance was assessed among women who smoked at study enrollment (table 3). No association was observed between 1-hour plasma glucose concentration and average number of cigarettes smoked per day over lifetime smoking history or pack-years of smoking. Women with heavy exposure to smoking over their lifetime history who had reduced their exposure to moderate or light levels by study enrollment had lower adjusted mean 1-hour glucose concentrations than heavy smokers who had not reduced their exposure (table 4). A similar pattern was observed among moderate smokers who reduced their levels to light exposure. The comparison between women who reduced their exposure from heavy to light levels and women who remained at heavy exposure levels was statistically significant.
Among women who attended the single medical center where fasting glucose concentration was obtained as part of the 50-g glucose screening test \((n = 1,209)\), fasting plasma glucose concentrations were similar in all tobacco exposure groups. Respective adjusted mean glucose concentrations (mg/dl) were 76.1 (95 percent CI: 72.6, 79.6), 75.2 (95 percent CI: 70.9, 79.5), 75.5 (95 percent CI: 71.4, 79.6), and 76.5 (95 percent CI: 72.6, 80.4) for women who had never smoked, who quit before pregnancy, who quit during pregnancy, and who smoked at study enrollment.

### Three-hour OGTT

The proportion of women developing gestational diabetes mellitus was lowest among those who had never smoked (1.8 percent), intermediate among women who had quit before or during pregnancy (1.9 percent and 2.5 percent, respectively), and highest among those who smoked at study enrollment.
(4.4 percent) (table 5). After adjustment, the association between smoking and gestational diabetes mellitus was significant (adjusted odds ratio = 1.9, 95 percent CI: 1.0, 3.6). The odds ratio for women who quit during pregnancy was greater than 1 but not statistically significant. Of the women who smoked at enrollment, the odds ratio for gestational diabetes mellitus was highest for moderate smokers and lowest for light smokers (table 5). If we assume that the odds ratio is a reasonable estimate of relative risk (which should be appropriate in this case given that gestational diabetes mellitus is a rare outcome) and if the association between smoking and gestational diabetes mellitus is causal, then 47 percent of gestational diabetes mellitus in smokers and 10 percent in all women in our study population could potentially be attributed to tobacco exposure.

When the lower cutoff points for gestational diabetes mellitus proposed by Carpenter and Coustan (37) were used, there were 65 cases of gestational diabetes mellitus among women who never smoked, seven cases among women who quit before pregnancy, 15 cases among women who quit during pregnancy, and 23 cases among women who smoked at study enrollment. The association between smoking at enrollment and gestational diabetes mellitus was not significant (adjusted odds ratio = 1.4, 95 percent CI: 0.8, 2.5). Adjusted odds ratios for women who quit before or during pregnancy were 0.7 (95 percent CI: 0.3, 1.7) and 1.4 (95 percent CI: 0.8, 2.6), respectively.

**DISCUSSION**

Nulliparous women who reported at 13–21 weeks’ gestation that they were active smokers had an increased plasma glucose concentration 1 hour after a 50-g oral glucose challenge and an increased risk of gestational diabetes mellitus compared with women who reported that they had never smoked. There was a clear dose-response relation between reported number of cigarettes smoked per day during pregnancy and results of the 50-g glucose screening test. Women who smoked 10 or more cigarettes per day appeared to have a greater risk of gestational diabetes mellitus than women who smoked less. Together, these findings suggest that smoking may play a role in glucose tolerance during pregnancy.

Although our power to evaluate glucose tolerance in women who quit smoking during pregnancy was limited, we found that women who quit smoking before becoming pregnant were not at increased risk of gestational diabetes mellitus and that heavy smokers who reduced their exposure had a lower mean 1-hour glucose concentration than those who did not. Furthermore, in the subgroup of women for whom data were available, we found no difference in fasting plasma glucose concentration between those who never smoked and those who smoked at study enrollment, making it unlikely that there was an excess of women with undiagnosed, chronic diabetes mellitus among smokers. Although this lack of an association between fasting glucose concentration and smoking status could be interpreted as evidence against an association between smoking and type 2 diabetes mellitus, it is also possible that screening procedures were effective and that few women with preexisting diabetes mellitus were enrolled in the CPEP trial.

The relation between smoking and glucose tolerance has been studied extensively in nonpregnant populations. Observational studies of smoking status and risk of type 2 diabetes mellitus are challenging because of the potential for confounding: smoking tends to be correlated with several risk factors for diabetes mellitus, such as suboptimal diet and sedentary lifestyle (9). However, smoking has been found to be associated with elevated hemoglobin A1c and/or increased insulin resistance in many studies (10–13, 40), although not all (16–18, 41). In addition, some studies suggest that the effects of smoking on insulin resistance may be reversible (15, 42). Among pregnant women, the role of smoking in glucose tolerance is uncertain. In a study of glucose tolerance among women in their third trimester, Goldman and Schechter (29) found that, after administration of an intravenous glucose tolerance test, mean glucose half-life in 54 smokers was longer than that in 54 nonsmokers. However, information about potential confounders, such as maternal age, body mass index, and gestational age at testing, was not provided. Zaren et al. (31) similarly found that, at 37 weeks of gestation, heavy smokers were twice as likely as

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**TABLE 4.** Results of a 1-hour, 50-g glucose screening test (adjusted* mean glucose concentration (mg/dl)) by smoking status before and during pregnancy among women who smoked at study enrollment, Calcium for Preeclampsia Prevention trial, United States, 1992–1995

<table>
<thead>
<tr>
<th>No. of cigarettes smoked per day over lifetime smoking history</th>
<th>No. of women</th>
<th>Mean 95% CI†</th>
<th>No. of women</th>
<th>Mean 95% CI</th>
<th>No. of women</th>
<th>Mean 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–9</td>
<td>76</td>
<td>111.6‡</td>
<td>104.1, 119.1</td>
<td>5</td>
<td>123.1</td>
<td>101.0, 145.2</td>
</tr>
<tr>
<td>10–19</td>
<td>91</td>
<td>111.5</td>
<td>104.2, 118.8</td>
<td>61</td>
<td>114.6‡</td>
<td>106.6, 122.6</td>
</tr>
<tr>
<td>≥20</td>
<td>93</td>
<td>107.3‡</td>
<td>99.8, 114.8</td>
<td>85</td>
<td>115.6</td>
<td>108.0, 123.2</td>
</tr>
</tbody>
</table>

* Results were adjusted for clinical center, race/ethnicity, maternal age, body mass index, and gestational age at time of testing.
† CI, confidence interval.
‡ Reference groups for statistical comparisons within rows.
§ p = 0.01.
nonsmokers to have a glucose value in the gestational diabetes mellitus range after administration of an OGTT. Similarly, in the large, prospective Nurses’ Health Study II, Solomon et al. (3) found a positive association between self-reported pregravid smoking status and gestational diabetes mellitus, with an odds ratio of 1.4 (95 percent CI: 1.1, 1.8).

Limitations of this study were that smoking status was not assessed during pregnancy and gestational diabetes mellitus status was based on self-report.

In contrast, in a study in which 15 smoking and 37 nonsmoking, nondiabetic, primiparous women were given intravenous glucose tolerance tests in week 37 of pregnancy, Langhoff-Roos et al. (28) found that smokers had lower mean fasting blood glucose concentrations and a shorter glucose half-life than nonsmokers did. In this study, participants refrained from smoking for 8 hours prior to testing, which could have temporarily improved their glucose tolerance. Likewise, smoking was unrelated to risk of gestational diabetes mellitus in two large studies, one using birth certificate data (43) and one using a computerized database drawn from medical records (44). Most recently, Terry et al. (30) found no association between smoking and gestational or pregestational diabetes mellitus in an analysis of data from the Swedish Birth Registry.

It is not clear why studies of smoking and gestational diabetes mellitus have yielded inconsistent findings. Possible explanations are that residual confounding by factors such as diet and exercise has led to the erroneous identification of an association between smoking and gestational diabetes mellitus, or that factors such as smoking exposure misclassification and low power have led to the erroneous conclusion that no association exists. As in previous studies, our analysis was limited by insufficient data on diet and exercise. However, our finding that smoking during pregnancy was associated with both results of the 50-g glucose screening test and risk of gestational diabetes mellitus adds support to the findings of Solomon et al. (3), Zaren et al. (31), and Goldman and Schechter (29). We also noted a dose-response relation between smoking and gestational diabetes mellitus when National Diabetes Data Group

<table>
<thead>
<tr>
<th>Maternal tobacco exposure status and demographic characteristics</th>
<th>Gestational diabetes mellitus</th>
<th>Crude</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smoked (n = 2,544)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quit smoking before pregnancy (n = 267)</td>
<td>45</td>
<td>1.8</td>
<td>Reference</td>
</tr>
<tr>
<td>Quit smoking during pregnancy (n = 360)</td>
<td>9</td>
<td>2.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Smoked at study enrollment (n = 431)</td>
<td>19</td>
<td>4.4</td>
<td>2.6</td>
</tr>
<tr>
<td>1–9 cigarettes per day (n = 253)</td>
<td>9</td>
<td>3.6</td>
<td>2.0</td>
</tr>
<tr>
<td>10–19 cigarettes per day (n = 144)</td>
<td>8</td>
<td>5.6</td>
<td>3.3</td>
</tr>
<tr>
<td>≥20 cigarettes per day (n = 34)</td>
<td>2</td>
<td>5.9</td>
<td>3.5</td>
</tr>
<tr>
<td>Age‡</td>
<td>1.1</td>
<td>1.1, 1.2</td>
<td>1.1, 1.1</td>
</tr>
<tr>
<td>Body mass index§</td>
<td>1.1</td>
<td>1.1, 1.1</td>
<td>1.1, 1.1</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American (n = 1,779)</td>
<td>31</td>
<td>1.7</td>
<td>Reference</td>
</tr>
<tr>
<td>White, non-Hispanic (n = 1,283)</td>
<td>38</td>
<td>3.0</td>
<td>1.7</td>
</tr>
<tr>
<td>White, Hispanic (n = 540)</td>
<td>9</td>
<td>1.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Clinical center</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albuquerque, New Mexico (n = 619)</td>
<td>9</td>
<td>1.5</td>
<td>Reference</td>
</tr>
<tr>
<td>Birmingham, Alabama (n = 1,210)</td>
<td>22</td>
<td>1.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Cleveland, Ohio (n = 562)</td>
<td>16</td>
<td>2.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Memphis, Tennessee (n = 757)</td>
<td>14</td>
<td>1.9</td>
<td>1.3</td>
</tr>
<tr>
<td>Portland, Oregon (n = 454)</td>
<td>17</td>
<td>3.7</td>
<td>2.6</td>
</tr>
</tbody>
</table>

* Each variable was adjusted for all other variables in the table; results reflect a model in which smoking at enrollment was treated as yes or no. A separate model was run to generate adjusted odds ratios for smoking at enrollment by number of cigarettes smoked per day.
† CI, confidence interval.
‡ Odds ratios for age are for increments of 1 year.
§ Odds ratios for body mass index are for increments of 1 kg/m².
criteria were used, we were not able to demonstrate a significant association by using the criteria of Carpenter and Coustan (37). One possible explanation for this discrepancy is that decreased specificity and increased potential for disease misclassification may have occurred when lower threshold values were used for diagnosis. Finally, we observed that fasting glucose levels did not vary by tobacco exposure, which may indicate that the effects of smoking are specific to postprandial glucose homeostasis and that smoking may not have direct effects on endogenous glucose production. This finding is consistent with a previous study in which cigarette smoking increased circulating free fatty acid levels but did not affect hepatic glucose production (45).

Our study has several limitations. Screening and diagnostic testing for gestational diabetes mellitus were not performed according to a uniform protocol, and some cases of gestational diabetes mellitus may have gone undetected. Smoking status was determined by self report, and maternal misreporting of smoking status would have resulted in exposure misclassification. However, self-reported smoking status in the CPEP trial appears to be accurate except for women who reported that they quit during pregnancy. A large proportion of these women may have been active smokers (46). Misclassification of smoking status could have led to overestimation of the odds ratios for gestational diabetes mellitus in this group. Likewise, if some women who smoked at study enrollment quit by the time of screening and diagnostic testing for gestational diabetes mellitus, we could have underestimated the risk of gestational diabetes mellitus in smokers. Because gestational diabetes mellitus is an uncommon complication of pregnancy (in our study, there were only 19 cases of gestational diabetes mellitus in smokers and only 14 cases in quitters), it is difficult to confirm and quantify with certainty the excess risk from smoking, even in a large trial such as CPEP. However, our finding that smoking was associated with results of the 50-g glucose screening test provides additional support for an association between smoking and glucose tolerance.

Finally, as stated previously, we cannot be certain that our findings do not reflect differences between smokers and nonsmokers in other factors such as diet or exercise. Prospective studies of the effects of smoking on glucose tolerance are needed to determine with certainty that smoking itself impairs glucose tolerance and increases gestational diabetes mellitus risk and, if so, whether this effect is reversible, and to determine whether smoking status might be a useful criterion for selective screening for gestational diabetes mellitus.

In conclusion, we found that smoking during pregnancy was associated with decreased glucose tolerance and an increased risk of gestational diabetes mellitus. Smoking may be an important modifiable risk factor for gestational diabetes mellitus.

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REFERENCES


