

Cigarette Smoking and the Risk of Gestational and Pregestational Diabetes in Two Consecutive Pregnancies

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OBJECTIVE — Cigarette smoking during pregnancy may increase the risk of gestational diabetes mellitus (GDM) or pregestational diabetes mellitus (PDM). Smoking has been associated positively with hyperinsulinemia and insulin resistance in experimental studies, although the association with diabetes remains unclear. To further explore this issue, we examined the association with smoking in the largest prospective cohort study of GDM and PDM to date.

RESEARCH DESIGN AND METHODS — The study population comprised 212,190 women in the population-based Swedish Birth Registry who had their first and second deliveries between January 1987 and December 1995. Maternal characteristics were recorded in a standardized manner at the first prenatal visit, followed by a clinical examination and a standardized in-person interview to assess lifestyle habits. Women were categorized as nonsmokers, light smokers (one to nine cigarettes per day), or moderate-to-heavy smokers (at least 10 cigarettes per day).

RESULTS — Women with GDM in their first pregnancy experienced an eight- to ninefold increased risk of GDM or PDM in their second pregnancy. Cigarette smoking was not associated with increased risk of these conditions. Neither women who smoked during their first and second pregnancies nor those who commenced smoking between pregnancies had a higher risk of GDM or PDM than nonsmokers.

CONCLUSIONS — Our findings do not support an association between cigarette smoking and risk of GDM or PDM in young women of childbearing age.

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Gestational diabetes mellitus (GDM) is defined as the onset or recognition of glucose intolerance during pregnancy (1). GDM has been associated with pre-eclampsia and perinatal conditions such as macrosomia, fetal hyperinsulinemia, and perinatal mortality (1,2). Women with GDM also have an increased risk of developing overt diabetes later in life (2). Thus, glucose control in

pregnancy is an important way of reducing the risk of maternal and fetal complications.

Cigarette smoking has been associated positively with HbA_{1c} levels, which reflect long-term glucose levels in some (3–5) but not all (6,7) studies to date. Cigarette smoking also has been associated positively with hyperinsulinemia and insulin resistance in some (but not all) stud-

ies (8), including those that have compared the glucose response of smokers and nonsmokers in glucose tolerance tests. Nevertheless, the association between smoking and GDM itself remains unclear (8). The Nurses' Health Study (9), which is the only cohort study that has examined this association previously, found a statistically significant 40% increased risk of GDM among 1,433 current smokers compared with 10,288 never smokers. Supporting these findings, recent cross-sectional data among pregnant women in Scandinavia suggest that smoking ≥ 10 cigarettes per day affects glucose homeostasis in the direction of GDM (10). In contrast, no association between cigarette smoking and GDM was observed in a cross-sectional study of 10,000 maternity patients in New York City (11) or in a cross-sectional study of 422 patients with GDM and 856 nondiabetic women in the state of Washington (12). The results of a case-control study in Canadian and North American Indian women were mostly null, although some analyses in the Canadian women showed an increased risk of GDM among current smokers compared with nonsmokers (13).

As with GDM, the relation between cigarette smoking and pregestational diabetes mellitus (PDM) is unclear, although the results of studies to date are suggestive (14). Whereas several epidemiological studies have not found a clear association between cigarette smoking and risk of type 2 diabetes (8) or have found an inverse association (15), nearly as many other studies (8,14), including the Nurses' Health Study (16), have found that current smokers had an elevated risk relative to nonsmokers. In the nurses, for example, there was a statistically significant 40% increased risk among the heaviest smokers compared with never smokers. With few exceptions, however, nearly all of these studies have examined the association primarily among middle-aged individuals and most often among men; studies conducted among younger women have been scarce. In addition, the

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Abbreviations: GDM, gestational diabetes mellitus; PDM, pregestational diabetes mellitus; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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association with type 2 diabetes has not always been evident among women, even in populations in which a positive association has been observed among men (6,17,18). Cigarette smoking is common in pregnant and nonpregnant women (8), and even a modest association with GDM or PDM among women of childbearing age would be of public health importance. Therefore, given the paucity of prospective data, especially among young women, we examined the association between cigarette smoking during pregnancy and risk of GDM and PDM in the largest prospective cohort study of singleton births to date.

RESEARCH DESIGN AND METHODS

Study population

The population-based Swedish Birth Registry recorded the births of ~1.2 million singleton infants between 1983 and 1995. Our study population was restricted to the 212,190 women who had their first and second deliveries between January 1987 and December 1995 due to the implementation of the ninth revision of the *International Classification of Diseases* (ICD-9) in 1987. The ICD-9 was the first revision that distinguished GDM from PDM. This study was also restricted to women born in the Nordic countries.

In Sweden, maternal characteristics are recorded in a standardized manner at the first prenatal visit, which occurs before the 15th week of gestation in >95% of all pregnancies (19). At the time of registration for antenatal care, a midwife conducts a clinical examination and an in-person interview. The standardized interview focuses on smoking habits, previous obstetric history, maternal diseases, and heredity of chronic diseases (such as diabetes) among first-degree relatives. Weight is recorded in kilograms and height in centimeters. During each interview, women were categorized as nonsmokers, light smokers (one to nine cigarettes per day), or moderate-to-heavy smokers (at least 10 cigarettes per day). Blood glucose screening for GDM is recommended four times during the pregnancy in women with certain characteristics, such as diabetes heredity, previous GDM, overweight (+120%), or those who had previously given birth to child weighing >4.5 kg. In these women, the first blood glucose test was performed at

the first prenatal visit followed by three additional tests at regular intervals during the second and third trimester. In addition, blood glucose screening was done in the presence of signs of augmented fetal growth or polyhydramnios. In most Swedish obstetric clinics, a random blood glucose value exceeding 7.0 mmol/l enforced an oral glucose tolerance test (OGTT) with 75 g glucose in accordance with the recommendations of the World Health Organization (20).

Case definition and ascertainment

Complications during pregnancy and delivery were assessed at the time of discharge from the hospital. This information is routinely included in the obstetrical record, a copy of which is forwarded to the Birth Register. GDM, PDM, and other conditions for which patients are routinely assessed were diagnosed by physicians and recorded on a standardized checklist that included descriptions of each condition and its corresponding ICD-9 code. The Swedish ICD-9 codes 648W and 648A were used for GDM and PDM, respectively. According to results of the OGTT, GDM was defined based on fasting venous plasma glucose concentration ≥ 7.8 mmol/l (corresponding to capillary blood glucose ≥ 6.7 mmol/l), or a 2-h value > 9.0 mmol/l (both venous plasma and capillary blood). During the period 1987–1991, however, some clinics used the cut-off level of > 8 mmol/l for the 2-h value in OGTT for diagnosis of GDM. Women with PDM were diagnosed before the onset of pregnancy according to the ICD-9 codes provided in the medical records. The interpregnancy interval was defined as the time elapsed between the birth of the first child and the conception of the following child, which was estimated by subtracting the duration of gestation in days (-14 days) from the date of the second birth. Information regarding the duration of gestation and the date of birth was obtained from the standardized pediatric record, which is routinely filled out immediately after delivery.

Statistical analysis

Multiple logistic regression models were used to estimate odds ratios (ORs) and 95% CIs for the association between cigarette smoking and GDM and PDM in the successive pregnancies. Multivariate models included maternal age, whether

the mother was living with the infant's father, and the interpregnancy interval. In the analyses of smoking habits in relation to GDM or PDM in the second pregnancy, statistical adjustments were also made for GDM status during the first pregnancy.

RESULTS — The baseline characteristics of the cohort are shown in Table 1. Approximately 0.4% of the women had been diagnosed with GDM in first pregnancy and ~0.6% had been diagnosed with GDM in the second pregnancy. Approximately 28% of women who had GDM in their first pregnancy also had a second pregnancy complicated by GDM compared with 0.5% of the women who were not diagnosed with GDM in their first pregnancy.

Cigarette smoking was not associated with risk of GDM. During the first pregnancy, women who smoked one to nine cigarettes per day had an OR of 1.10 (95% CI 0.81–1.49) for GDM compared with nonsmokers. The corresponding OR for women who smoked ≥ 10 cigarettes per day was 1.08 (0.71–1.63). During the second pregnancy, women who smoked ≥ 10 cigarettes per day had an OR of 0.68 (0.46–1.00) for GDM compared with nonsmokers (Table 2). Similarly, women who commenced smoking cigarettes during the second pregnancy or interpregnancy interval were not more likely to experience PDM than nonsmokers. However, women who ceased smoking after their first pregnancy were more likely to experience GDM in their second pregnancy than those who continued to smoke. Statistically significant higher risks of GDM in the second pregnancy were also observed among women with high (> 35 years) compared with low (< 24 years) maternal age, short (< 163 cm) compared with tall (> 170 cm) stature, low (< 4.00 months) compared with high (> 36 months) interpregnancy intervals, and high (> 30 kg/m²) compared with low (< 20 kg/m²) BMI. Age-adjusted results for the effects of cigarette smoking were similar to those obtained from multivariate models (data not shown). The results were also similar after additional adjustment for the effects of BMI and education. As expected, women who had GDM in their first pregnancy had an eight- to ninefold increased risk of a subsequent GDM or PDM compared with those who did not have GDM in their first pregnancy (Table 2).

Table 1—Characteristics of 212,190 Swedish women who twice gave birth from 1987 through 1995 and univariate associations with the risk of GDM and PDM in the second pregnancy*

Characteristic	Second pregnancy		
	All	Gestational diabetes	Pregestational diabetes
<i>n</i>		1,256	304
Gestational diabetes in the first pregnancy			
No	211,344	1,019 (0.5)	255 (0.1)
Yes	846	237 (28)	49 (5.8)
Smoking in successive pregnancies			
Yes-yes	29,749	157 (0.5)	40 (0.1)
Yes-no	11,845	101 (0.8)	12 (0.1)
No-no	143,026	814 (0.6)	188 (0.1)
No-yes	4,798	30 (0.6)	9 (0.2)
Data missing	22,772	154 (0.7)	55 (0.2)
Maternal age at second pregnancy			
≤24 years	44,058	176 (0.4)	63 (0.1)
25–29 years	95,853	498 (0.5)	126 (0.1)
30–34 years	56,876	412 (0.7)	85 (0.1)
≥35 years	15,335	170 (1.1)	29 (0.2)
Data missing	68	0 (0)	1 (1.5)
Living with the baby's father			
Yes	189,660	1,125 (0.6)	268 (0.1)
No	4,347	22 (0.5)	2 (0.05)
Data missing	18,183	109 (0.6)	34 (0.2)
Mothers' height (cm)			
<163	39,486	304 (0.8)	75 (0.2)
163–166.99	39,565	254 (0.6)	52 (0.1)
167–169.99	33,932	202 (0.6)	29 (0.08)
170+	55,899	264 (0.5)	70 (0.1)
Data missing	43,308	232 (0.5)	78 (0.2)
Interpregnancy interval (months)			
≤4.00	2,201	26 (1.2)	5 (0.2)
4.01–8.00	12,599	74 (0.6)	18 (0.1)
8.01–36.00	167,904	921 (0.5)	206 (0.1)
>36.00	28,675	232 (0.8)	75 (0.3)
Data missing	811	3 (0.4)	0 (0)
BMI, second pregnancy (kg/m ²)		701	170
<20	14,745	35 (0.2)	11 (0.07)
20–24.9	65,763	282 (0.4)	88 (0.1)
25–29.9	22,897	217 (0.9)	48 (0.2)
30+	7,384	167 (2.3)	23 (0.3)
Data missing	101,400	555 (0.5)	134 (0.1)

Data are presented as *n* (%). *Women with PDM in the first pregnancy (*n* = 502) were excluded.

CONCLUSIONS— Consistent with the findings of previous studies (21), we found that women with GDM in their first pregnancy experienced an eight- to nine-fold increased risk of a subsequent GDM or PDM. However, cigarette smoking was not associated with increased risk of these conditions. Neither women who smoked before their first and second pregnancies nor those who commenced smoking during the interpregnancy interval had a

higher risk of GDM or PDM than nonsmokers.

There was a moderate increase in risk of GDM among women who ceased smoking during the interpregnancy interval compared with women who smoked during both pregnancies. This finding may be explained by the fact that smokers gain less weight during pregnancy than nonsmokers (8), and weight gain is positively associated with GDM (9). The

higher incidence rate of GDM among quitters than current smokers may also be due to confounding. For example, smoking cessation may be more common among women whose health was impaired during the interpregnancy interval, which in turn may affect the risk of GDM in a subsequent pregnancy. The higher incidence rate of GDM among former smokers may also have been influenced by ascertainment bias. For example, if women who ceased smoking subsequently had higher maternal weight gain and increased fetal growth than those who continued to smoke, the former may have been screened for GDM more frequently than the latter. In our data, however, there was no evidence for a greater change in BMI during the interpregnancy interval among women who ceased smoking compared with those who continued to smoke.

The Nurses' Health Study (9) is the only previous cohort study that examined the association between lifestyle factors (including cigarette smoking) and GDM. As with that study, the present study found positive associations with maternal age and BMI. However, in contrast with our findings, the Nurses' Health Study also found a statistically significant 40% increased risk of GDM among current smokers compared with never smokers. There are several possible explanations for the inconsistent findings with respect to smoking. Some studies have found an increased risk of diabetes only with long-term or high-intensity smoking, such as ≥20 pack-years of consumption, suggesting that a positive association with smoking may be limited to long-term smokers or smokers of high intensity. Because the nurses were older at baseline than women in our cohort (the approximate mean ages of the cohorts at baseline were 31 years and 24 years, respectively), the former, by virtue of their age, were more likely than the latter to have been long-term smokers. Furthermore, there may have been a greater percentage of heavy smokers among the nurses, for example, those who smoked one packet of cigarettes per day or more, than among women in our cohort. This possibility is suggested by the relatively low percentage of very heavy smokers typically observed among Swedish women (22). However, consistent with the findings of our study, two cross-sectional studies conducted in the U.S. (11,12), including one study with an

Table 2—OR and 95% CI for developing GDM in the second pregnancy according to changes in smoking habits during the interpregnancy interval

	Second pregnancy			
	GDM		PDM	
	Age adjusted	Multivariate*	Age adjusted	Multivariate*
Gestational diabetes in the first pregnancy				
No	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Yes	8.82 (7.89–9.86)	8.19 (7.27–9.22)	8.68 (7.07–10.66)	8.80 (7.12–10.88)
Smoking during second pregnancy†				
No	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1–9 cigarettes/day	1.09 (0.86–1.38)	0.97 (0.75–1.25)	0.99 (0.61–1.63)	0.92 (0.55–1.54)
10+ cigarettes/day	0.97 (0.69–1.37)	0.68 (0.46–1.00)	1.05 (0.55–2.00)	0.82 (0.41–1.64)
Smoking in successive pregnancies‡				
No-no	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
No-yes	1.20 (0.72–2.01)	0.94 (0.74–1.21)	1.76 (0.77–4.01)	1.32 (0.53–3.31)
Yes-yes	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Yes-no	1.44 (1.04–1.99)	1.64 (1.16–2.33)	1.05 (0.48–2.33)	1.00 (0.43–2.31)

Data are presented as OR (95% CI). *Multivariate models adjusted for maternal age (continuous), cohabitation with the child's father (yes or no), maternal height in centimeters (163, 163–169, 170+), BMI (kg/m²) in the second pregnancy (<20, 20–24.9, 25–29.9, 30+), and interpregnancy interval (four groups). †Also adjusting for smoking and GDM in the first pregnancy in the multivariate analysis. ‡Additional adjustment for GDM in the first pregnancy in the multivariate analysis.

age range similar to that of the Nurses' Health Study (11) and one with a somewhat younger population (12), found no association between smoking and GDM. Comparisons among the studies of type 2 diabetes are also complicated by methodological considerations, including the examination of populations with varying characteristics, such as age range, ethnic composition, number of study participants and case subjects, percentage of long-term or heavy smokers, and other factors that might modify the association between smoking and diabetes, such as the smoking habits of the mothers of the study subjects (23), the participation status of subjects eligible for recruitment into epidemiological studies (24), and the prevalence of potentially effect-modifying genetic polymorphisms, such as the CYP1A1 MspI polymorphism (25).

The strengths of our study include the large sample size and the ability to examine changes in smoking habits between successive pregnancies. The completeness of follow-up of the cohort reduces the likelihood that our results reflected bias due to differential follow-up of exposed compared with unexposed women. Potential bias due to confounding was mitigated by the standardized antenatal and obstetrical care in Sweden, the relatively homogenous Swedish population, and statistical adjustment for potentially confounding variables. The wide-scale

screening for diabetes during prenatal care in Sweden helps to eliminate bias that stems from greater surveillance of smokers or ascertainment bias. On the other hand, we cannot exclude the possibility of confounding by uncontrolled factors, such as family history of diabetes and physical activity. Nonetheless, these latter factors were not confounding variables in the Nurses' Health Study (9).

It is possible that some former smokers, particularly those who ceased smoking before their first pregnancy, were misclassified as nonsmokers, which may have attenuated the association between smoking and risk of GDM in our data. However, the diabetogenic effect of tobacco use seems to be related to the acute stimulatory effect of plasma catecholamine levels, which may cause glucose intolerance by action on the liver as well as on pancreatic β -cells, the latter particularly in men (17). This acute effect could be mediated by a stimulation of the sympathetic nervous system by nicotine, leading to enhanced catecholamine levels and insulin resistance. Indeed, long-term use of nicotine-containing chewing gum has been associated with insulin resistance (26), and some studies indicate that acute administration of nicotine induces insulin resistance (27). However, transient acute smoking does not appear to affect insulin secretion (27), and the long-term effects of tobacco use on insulin secretion remain

unclear. In the Stockholm Diabetes Prevention study (28), a cross-sectional study of 3,129 middle-aged Swedish men, the risk of diabetes was increased in current smokers compared with former smokers. Hence, we can speculate that former smokers may not be exposed to such accentuated catecholamine levels and should not, therefore, have an increased risk of diabetes relative to nonsmokers.

Our data are also limited by the possibility of nondifferential misclassification with respect to cigarette smoking. Nondifferential misclassification tends to attenuate true associations, and in the present study it may have resulted from unmeasured cessation of smoking during pregnancy (29) or the underestimation of smoking prevalence. Among the women who stated that they smoked in early pregnancy, ~20% had ceased smoking later in the pregnancy (29). Moreover, the pregnancy-related risks associated with smoking are well known, and self-reported statements about smoking may underestimate the true smoking prevalence (30). It is also possible that undiagnosed (e.g., nonsymptomatic) cases of PDM were misdiagnosed as GDM, which would have inflated the observed association between GDM in a first pregnancy and PDM in the second. Finally, the interval between the two pregnancies was often <3 years, which is a relatively short

follow-up time with respect to diabetes incidence, especially in a population of young women.

In conclusion, a diagnosis of GDM in a first pregnancy is a strong risk factor for developing GDM or PDM in the subsequent pregnancy. The results of the present study do not support an association between cigarette smoking and risk of GDM or PDM in women of childbearing age. However, the relative youth of our study population precluded the examination of very long-term smoking, and our findings may not be applicable to older populations or those in which individuals generally have had a greater opportunity for long-term exposure. Regarding GDM in particular, prospective cohort studies are scarce, and further investigations are warranted.

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