Journal of Perinatology (2010) 30, 319–323

www.nature.com/jp

ORIGINAL ARTICLE

The impact of tobacco smoking on perinatal outcome among patients with gestational diabetes

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Objective: To determine the effects of tobacco use on perinatal outcomes among patients with gestational diabetes (GDM).

Study Design: This was a retrospective cohort study of singleton pregnancies with GDM and live births from 2003 to 2006. The primary outcome, large for gestational age (LGA) infants, was compared between smoking and nonsmoking groups. Secondary outcomes included cesarean deliveries, shoulder dystocia, birth trauma, peripartum complications, macrosomia, 5-min Apgar score $\leqslant 3$, birth defects, and neonatal intensive care unit (NICU) admissions. χ^2 and Student *t*-tests compared the two groups; a *P*-value <0.05 was statistically significant and odds ratios (OR) were reported with 95% confidence intervals (CI). A multivariate logistic regression analysis controlled for variables known to affect outcomes in GDM.

Result: We identified 915 patients with GDM, of which 130 (14.2%) smoked during pregnancy. Women who smoked during pregnancy were less likely to have LGA infants (22.4 vs 31.2%; OR, 0.61; 95% CI, 0.39 to 0.95). In a logistic regression analysis, the inverse relationship between smoking and LGA persisted (OR, 0.59; 95% CI, 0.36 to 0.97) after controlling for maternal age, multiparity, ethnicity, weight status before pregnancy, weight gain during pregnancy, and male gender. Preterm labor, preeclampsia, Cesareans, shoulder dystocia, and birth trauma were similar in both groups. PPROM was more likely to occur in nonsmokers (0 vs 4%, $P=0.03$), but postpartum hemorrhage was more common among smokers (OR, 2.3; 95% CI, 1.02 to 5.31). Macrosomia, low 5-min Apgar score, birth defects, and NICU admissions were similar between the groups.

Conclusion: Patients with GDM who smoke during pregnancy were 40% less likely to have LGA infants. However, smoking was not protective of other common morbidities associated with GDM.
Journal of Perinatology (2010) **30,** 319–323; doi:10.1038/jp.2009.175; published online 12 November 2009

Keywords: gestational diabetes; tobacco smoking; large for gestational age infants

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Received 8 June 2009; revised 5 September 2009; accepted 7 September 2009; published online 12 November 2009

Introduction

Tobacco smoking is an independent, modifiable, and dose-dependent risk factor for diabetes mellitus (DM).[1,2] Despite its association with type II DM, tobacco smoking as a risk factor for GDM has not been well described. Several studies have shown a positive correlation between tobacco smoking and GDM with odds ratios (OR) from 1.4 to 1.9.[3–5] In contrast, a large prospective cohort study from the Swedish Birth Registry found that smoking did not increase the risk for GDM.[6]

An association between GDM and smoking would have important clinical consequences. Given that GDM increases the risk of LGA (large for gestational age) infants and smoking has the opposite effect on birth weight, the restricting effect of smoking on fetal growth might abolish the growth-stimulating effect of diabetes. This could impact outcomes such as cesarean deliveries, shoulder dystocia, and birth trauma among gestational diabetics who smoke. The purpose of this study is to determine the effects of smoking on pregnancy outcome, primarily infant birth weight, among women with GDM.

Methods

This was a retrospective cohort study of all singleton pregnancies diagnosed with GDM and delivered at two inner-city hospitals during 2003 to 2006. The dietician's registry identified patients with GDM at one hospital, whereas a keyword search of the Watch Child Database (an electronic obstetrical database) identified the cohort for the other hospital. Exclusion criteria were pregestational diabetes or multiple gestations. Data were abstracted from both an electronic database (CareWeb) and medical records (preprinted prenatal template). Smoking status was determined based on the number of cigarettes smoked before and during each of the trimesters of pregnancy. The exposed group (smokers) included those patients who smoked tobacco at any time during the pregnancy. The unexposed group (nonsmokers) included those who never smoked or stopped smoking before pregnancy. Demographic data including alcohol and illicit drug use were collected for all patients. A prepregnancy body mass index (BMI) $\geqslant 30\,kg/m^2$ defined obesity. Diabetes that began or was first

recognized in pregnancy defined GDM. Either a 50-g 1 h glucose challenge test (glucola) result >200 mg per 100 ml or an abnormal 100-g 3 h oral glucose tolerance test based on the Carpenter and Coustan criteria confirmed GDM.

The primary outcome, the proportion of LGA infants (birth weight >90th% according to a standard infant growth chart),[7] was compared between the smokers and nonsmokers. A birth weight >4000 g defined macrosomia. The following secondary outcomes were compared between the two groups: labor induction, delivery route, cesarean indication, presence of perineal laceration, estimated blood loss, and shoulder dystocia. Postpartum hemorrhage was as an estimated blood loss >500 or >1000 ml for vaginal or cesarean deliveries, respectively. The following neonatal outcomes were also compared—preterm delivery (<37 weeks), neonatal gender, meconium staining, Apgar scores, birth defects, birth trauma (brachial plexus palsy, clavicular fracture, and cephalohematoma).

Statistical analysis was performed with SPSS software, version 15.0 (Chicago, IL, USA). χ^2 tests compared categorical data and OR with 95% confidence intervals (CI) were reported. Continuous data, reported as mean ± s.d., were compared with the Student's *t*-test. All *P*-values were two-sided and a value <0.05 was considered statistically significant. A multiple logistic regression analysis controlled for available demographic and clinical variables known to influence pregnancy outcomes in patients with GDM. These include maternal age >25 years, multiparity, race/ethnicity, weight status before pregnancy, weight gain during pregnancy, and neonatal gender. The Indiana University-Purdue University, Indianapolis/Clarian Institutional Review Board granted permission to conduct this study.

Table 1 Maternal charateristics of women with gestational diabetes by tobacco use

Characteristics	*Nonsmokers (n = 785)*	*Smokers (n = 130)*	P
Maternal age (years)	29 ± 6	28 ± 6	0.065
⩾25 years	555 (71)	79 (61)	0.030
Multiparity	537 (68)	90 (69)	0.948
Ethnicity			<0.001
White	234 (30)	87 (67)	
Black	208 (27)	35 (27)	
Hispanic	298 (38)	7 (5)	
Other	43 (5)	1 (1)	
Marital status			<0.001
Single/divorced	341 (49)	86 (73)	
Married	352 (51)	31 (27)	
Prepregnancy weight (kg)	80 ± 22	79 ± 23	0.886
BMI (kg/m^2)	31 ± 7	30 ± 8	0.090
BMI (kg/m^2) categories			<0.001
Underweight	17 (2)	2 (2)	
Normal BMI	199 (26)	37 (29)	
Overweight	356 (47)	32 (25)	
Obese	182 (24)	56 (44)	
Mean weight gain (kg)	12 ± 7	14 ± 9	0.024
>18 kg weight gain	138 (19)	38 (31)	0.004
Alcohol intake	13 (2)	12 (9)	<0.001
Illicit drug use	24 (3)	33 (25)	<0.001

Abbreviation: BMI, body mass index.
Data are presented as mean ± s.d. or *n* (%).

Results

The entire cohort, 915 singleton pregnancies, was composed mostly of women >25 years (69%), multiparous (69%) and overweight (65%) patients. The control group included 785 (85.8%) patients, of these, 745 (94.9%) never smoked and 40 (5.1%) quit before pregnancy. There were 130 (14.2%) patients who smoked tobacco during the pregnancy. Table 1 presents the maternal demographics. Of note, the smokers were more likely to be white, single/divorced, obese, gain more weight during the pregnancy, and use other substances such as alcohol or other illicit substances, $P<0.01$.

The mean gestational age at the diagnosis of GDM was 28 ± 5 weeks. There was no difference with respect to the treatment modality for GDM as nearly 80% were treated with diet alone. The mean infant birth weight of the entire cohort was 3399 ± 616 g and was not significantly different between the two groups. LGA infants comprised 28.4% of the entire cohort, 89.2% of which were infants of nonsmokers. Infants of gestational diabetics who smoked during pregnancy were less often LGA compared with those of nonsmokers (31.2 vs 21.6%; OR, 0.61; 95% CI, 0.387 to 0.952).

There were significant differences in some demographic and behavioral characteristics between those who were smoking during pregnancy compared with the nonsmokers, as shown in Table 1. Differences were found in age, race/ethnicity, marital status, BMI category, weight gain, and substance use. These differences may affect the relationship between smoking and having an LGA infant when the mother has gestational diabetes. However, in the multiple logistic regression, the association between maternal smoking and LGA infants remained significant after adjusting for confounding factors (OR, 0.59; 95% CI, 0.357 to 0.972) (Table 2). Obesity was the greatest predictor of an LGA infant. Overall, 86.7% of the patients delivered at term. Tables 3 and 4 summarize the delivery and neonatal outcomes, respectively. Shoulder dystocia and birth

Table 2 Multiple logistic regression analysis for prediction of large for gestational age infants

Independent variable	*Unadjusted odds ratio*	*Adjusted odds ratio*	*95% CI*
Maternal age (⩾25 years old)	0.642	1.006	0.977–1.035
Multiparity	1.035	1.693	1.163–2.463
African-American	1.018	0.722	0.476–1.093
Hispanic	0.093	1.018	0.691–1.500
Overweight	0.377	2.191	1.359–3.532
Obese	2.479	2.863	1.817–4.512
Weight gain in pregnancy (>18 kg)	1.911	1.069	1.045–1.094
Male gender	0.850	1.714	1.283–2.290
Smoking	0.610	0.589	0.369–0.997

Table 3 Pregnancy outcomes among patients with gestational diabetes

	Nonsmokers (n = 785)	*Smokers (n = 130)*	P
Gestational age at delivery (weeks)	38.5 ± 2.1	38.8 ± 1.9	0.156
Induction of labor	264 (34)	50 (39)	0.298
Delivery route			0.96
Spontaneous vaginal	443 (58)	74 (58)	
Operative vaginal	28 (4)	4 (3)	
Cesarean	297 (39)	49 (39)	
Cesarean indication			
Labor dystocia	79 (27)	10 (20)	0.458
Nonreassuring fetal heart rate	40 (13)	9 (18)	0.490
Repeat	131 (44)	19 (39)	0.588
Elective for macrosomia	12 (4)	4 (8)	0.365
Lacerations	269 (57)	36 (46)	0.093
Shoulder dystocia	22(2)	2 (2)	0.586
Birth trauma	5 (1)	3 (2)	0.942
Pregnancy complications			
Oligohydramnios	28 (4)	6 (5)	0.738
Polyhydramnios	8 (1)	2 (2)	0.942
Preeclampsia/PIH	40 (5)	8 (6)	0.773
Chronic hypertension	32 (4)	8 (6)	0.400
Preterm labor	34 (4)	6 (5)	1.000
PPROM	33 (4)	0 (0)	0.033
Peripartum complications			
Chorioamnionitis	16 (2)	1 (1)	0.521
Abruption	4 (1)	1 (1)	1.000
Postpartum hemorrhage	20 (3)	8 (7)	0.083

Abbreviations: PIH, pregnancy-induced hypertension; PPROM, preterm premature rupture of membranes.
Data are presented as mean ± s.d. or *n* (%).

Table 4 Neonatal outcome among infants of gestational diabetics

	Nonsmokers (n = 785)	*Smokers (n = 130)*	P
Birth weight (g)	3410 ± 620	3331 ± 589	0.1863
Large for gestational age	232 (31)	27 (22)	0.038
Male gender	395 (52)	70 (56)	0.460
Macrosomia	115 (15)	16 (13)	0.567
Meconium stained amniotic fluid	96 (12)	24 (18)	0.070
5 min Apgar score <3	4 (1)	1 (1)	1.000
Congenital anomalies	47 (6)	11 (8)	0.380
Neonatal intensive care unit (NICU) admission	128 (16)	25 (19)	0.408

Data are presented as mean ± s.d. or *n* (%).

trauma did not differ between the two groups. All other pregnancy complications (preeclampsia, chorioamnionitis, abruption, postpartum hemorrhage) were similar in both groups. The occurrences of the various neonatal complications were similar in both groups.

Discussion

Maternal smoking has a negative influence on fetal growth. It has been associated with at mean reduction of 150 to 200 g in infant birth weight. Vasoconstriction, nutritional deprivation, and direct toxic effects are the main mechanisms by which tobacco decreases birth weight. Although birth weight decreases as tobacco exposure increases, this relationship is not linear. Two studies have shown that a sharp decline in birth weight occurs at low levels of tobacco exposure.[8,9] Smoking cessation during pregnancy has been associated with a lowered risk of delivering a small for gestational age infant similar to a nonsmoker.[10]

Maternal diabetes, on the other hand, is associated with macrosomia and LGA infants. Hyperinsulinemia results in fetal hyperglycemia which in turn causes stimulation of insulin and other growth factors causing fetal growth and deposition of fat and glycogen. As such, optimal glycemic control is a key element to improving pregnancy outcome. Although smoking and GDM have opposite effects on fetal growth, both are modifiable risk factors for potential adverse neonatal outcomes.

This study showed that tobacco use during pregnancy in patients with GDM reduces the risk of having an LGA infant by 40%. We did not find a difference in the occurrence of other adverse pregnancy and neonatal outcomes related to LGA infants. The study, however, was not powered for these less frequent outcomes. Earlier studies report that LGA infants of women with GDM have increased fat mass and decreased lean body mass compared with women with normal glucose tolerance.[11] Conversely, infants of smokers have decreased lean body mass but similar fat mass compared with nonsmokers.[12] It is possible that

the fewer LGA infants in this study among the smokers is secondary to the combined effect of smoking and GDM on lean body mass. No study has previously described this observation. Clearly, the relationship between GDM, smoking, and infant body weight is a complex one. The mechanism by which tobacco smoking and gestational diabetes influence birth weight may be independent of each other.

In general, patients with GDM are more likely to be older, obese, non-Caucasian, or have a family/personal history of type II DM or GDM. Our study population exhibited most of these characteristics. Furuno *et al*.[13] showed that smoking during pregnancy is associated with decreased weight gain. In contrast, smokers in our study gained more weight during pregnancy than nonsmokers. Whether this observation is dependent on other factors besides smoking is uncertain. Smokers also differed in the composition of race, marital status, BMI, and use of alcohol and illicit substances compared with nonsmokers. Some of these differences can be explained by the decreased prevalence of smoking in Hispanics and common association of tobacco smoking with drinking alcohol.

The cesarean delivery rate is higher among patients with GDM than the general population.[14,15] This difference is even more exaggerated if GDM is untreated or when glycemic control is poor.[16] Although dystocia is a more common indication for cesarean delivery among GDM patients,[14] fetal distress is a more common indication among smokers.[17] The constricting effect of uterine contractions and nicotine both contribute to fetal hypoxia. In this study, smokers and nonsmokers had the same cesarean rate, albeit higher than earlier reports, despite the less frequent occurrence of LGA infants among smokers. There was a trend toward decreased cesarean deliveries for dystocia among smokers. This may in part be due to the fewer LGA infants. Similar to the study by Guirgis *et al*.,[17] cesareans for fetal distress were more common among those who smoked during pregnancy. As a nonreassuring fetal heart rate is more worrisome than dystocia, emergent cesarean deliveries are more likely to occur among smokers. This aspect, however, was not analyzed in this study.

An inverse relationship between cigarette smoking during pregnancy and preeclampsia was reported in a systematic review, with a 32% reduction in the incidence of preeclampsia among smokers.[18] In contrast, GDM increases the risk for preeclampsia. As the occurrence of preeclampsia was similar between smokers and nonsmokers in our study and similar to that of the general population (5 to 8%), it is possible that GDM and other factors superseded the 'protective' effect of smoking on preeclampsia.

This study involved a large number of patients from two different institutions. The population demographics were similar to earlier studies of GDM. Other strengths included strict criteria to confirm the diagnosis of GDM and a single investigator performed the data collection. However, there were several limitations to our study. First, we did not address other risk factors for LGA infants including a history of an LGA/macrosomic infant and adequacy of glucose control during the pregnancy. As our population included women with GDM only, glycosylated hemoglobin values were not routinely monitored. Second, we did not study the impact of smoking cessation during pregnancy on perinatal outcome. This is worth investigating as studies have shown that the effect of smoking on glucose tolerance is reversible. Finally, given the retrospective nature of the study, there are likely some inaccuracies in the patient reporting of tobacco use, as it is common to underestimate tobacco exposure and recall biases have a function as well. Underreporting of smoking behavior during pregnancy means that some of the women in the nonsmoking group should have been correctly placed in the smoking group, if the tobacco use data were accurate. The misclassification dilutes the true impact of tobacco use during pregnancy on the birth outcome. Studies that use urine and plasma biomarkers of tobacco metabolites would be able to more precisely ascertain the impact of smoking on birth outcomes. In a study that explored the relationship of self-reported exposure to tobacco smoke and cotinine levels in urine and blood of pregnant women, cotinine was a sensitive measure of tobacco exposure. However, if biochemical analysis was not available and/or convenient for pregnant women, then reported exposure to tobacco could provide a good estimate if a well-trained interviewer collected the information in a structured way. To more accurately assess risk in pregnancy, careful histories with respect to exposures such as tobacco should be taken.[19]

This study showed that patients with GDM who smoke during pregnancy were less likely to have LGA infants, even after controlling for confounding factors. Despite this, smoking did not prevent the serious co-morbidities associated with GDM; however, the study was not powered for these less frequent outcomes. Although tobacco use has some protective effect for adverse pregnancy outcome,[18] we do not recommend tobacco use to decrease the frequency of LGA infants in patients with GDM. The impact of smoking during pregnancy identified in this and other studies do not justify its use. The adverse health effects of smoking during pregnancy on the mother and baby are significant and well documented in the literature. Providers are encouraged to screen their pregnant patients for tobacco use and urge them to quit regardless of the patients' other clinical characteristics. Clinicians should also be aware that patients who smoke during pregnancy continue to be at risk for birth trauma such as a shoulder dystocia.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

We gratefully acknowledge the significant contributions of Barbara Amerman, Dietician, Wishard Health Services; Carol Denny RHIT, and the personnel of the Health Information Management at Methodist Hospital of Indiana.

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