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Association of Reported Trimester-Specific Smoking Cessation and Fetal Growth Restriction

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Abstract

Objective—To assess the association of reported smoking cessation at various time points during pregnancy with fetal growth restriction (FGR).

Methods—This was a population-based retrospective cohort study of singleton nonanomalous live births using Ohio birth certificates, 2006–2012. Outcomes of women who reported smoking only in the 3 months before conception and women who reported smoking through the first, second, or third trimester were compared to a referent group of nonsmokers. Multivariate logistic regression assessed the association between smoking cessation at various times in pregnancy and FGR less than the 10th and 5th percentiles.

Results—Of 927,424 births analyzed, 75% did not smoke. Of smokers, 24% smoked preconception only, 10% quit after the 1st trimester, 4% quit after the 2nd trimester, and 59% smoked throughout pregnancy. The rate of FGR less than the 10th and 5th percentiles among non-smokers was 8.1% and 3.6%, respectively. Although smoking only in the preconception period did not significantly increase FGR risk, smoking in any trimester did. The adjOR(95% CI) for FGR less than the 10th and 5th percentiles, respectively, of cessation after the 1st trimester was 1.19(1.13,1.24) and 1.25(1.17,1.33), and 1.67(1.57,1.78) and 1.83(1.68,1.99) for cessation after the second trimester. Women who reported smoking throughout pregnancy had the highest risks of

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FGR, 2.26 (2.22,2.31) and 2.44(2.37,2.51), after accounting for the influence of race, low socioeconomic status, and medical comorbidities.

Conclusions—Smoking of any duration during pregnancy is associated with an increased risk of FGR, with decreasing risk the earlier that cessation occurs. Smoking cessation programs should focus on the benefit of quitting as early in pregnancy as possible.

Introduction

Smoking during pregnancy has been associated with an increased risk of a multitude of adverse outcomes, including fetal growth restriction.^{1,2} As of 2010, 23% of women nationwide smoked tobacco in the 3 months before pregnancy, and just over half (54%) quit during pregnancy.³ In Ohio, a high-prevalence smoking area, only 24% of women who smoked in the 3 months before pregnancy quit before conception and 16% of pregnant women continued to smoke in the 3rd trimester.^{3,4}

Although several studies have examined the effects of smoking cessation in pregnancy on fetal growth restriction, many have been limited in size or ethnic diversity.^{5–8} Limited data exist to assess the association between smoking cessation before pregnancy and in each trimester and risk of fetal growth restriction. Additional knowledge about the benefits of quitting in the preconception or early gestational period would be an added incentive to quit earlier for the women who struggle with this addiction. We aimed to perform a large-scale population-based study of recent US births to quantify the influence of smoking before pregnancy or in any trimester on the risk of fetal growth restriction.

MATERIALS AND METHODS

The protocol for this study was approved by the Human Subjects Institutional Review Board of the Ohio Department of Health and a de-identified data set was provided for this analysis. This study was exempt from review by the Institutional Review Board at the University of Cincinnati, Cincinnati, Ohio

We performed a population-based retrospective cohort study of all live births in Ohio over 7 years (2006–2012) using vital statistics birth certificate records from the Ohio Department of Health. Women were divided into 1 of 5 exposure groups based on their reported smoking status: “non-smokers,” “smoked preconception only” (smoked in the 3 months preconception but not in any trimester), “smoked through 1st trimester” (smoked preconception and the 1st trimester but not 2nd or 3rd), “smoked through 2nd trimester” (smoked preconception and the first 2 trimesters but not the 3rd), and “smoked throughout pregnancy” (smoked before and in all 3 trimesters). For each trimester, women who smoked an average of 1 cigarette a day were considered smokers. We also performed a sensitivity analysis using a threshold of 5 cigarettes per day. We limited analyses to singleton non-anomalous live births between 20 and 42 weeks gestation with available data on smoking history.

The primary outcome was fetal growth restriction less than the 10th and less than the 5th percentiles, as defined by the 1996 Alexander U.S. growth curves reference.⁹ We compared

baseline demographic, socioeconomic, prenatal and behavioral characteristics among all 5 exposure groups. Additionally, a linear regression was performed to assess the dose-response relationship between cigarettes smoked per trimester and birth weight.

Gestational age was defined by the best obstetric estimate variable in the birth record, which combines last menstrual period and ultrasound parameters. BMI was calculated using maternal preconception height and weight, and gestational weight gain was calculated by subtracting maternal weight at delivery from preconception maternal weight.

Comparisons of dichotomous variables were performed with chi squared tests and continuous variables were compared using ANOVA. Multinomial logistic regression estimated the adjusted odds ratio of FGR less than the 10th and less than the 5th percentiles associated with various smoking behaviors after adjusting for maternal age, race, education level, marital status, pregestational hypertension and diabetes, gestational hypertension and diabetes, and BMI. Covariates were selected based on differences noted in univariate comparisons and those with biologic plausibility. Each smoking group was compared to the referent group of nonsmokers. Additionally, a linear regression was performed to assess the dose-response relationship between cigarettes smoked per trimester and birth weight.

Analyses were performed using STATA 12.1 software (StataCorp, College Station, Texas). Results are reported as rates with associated p values and odds ratios with 95% confidence intervals. Comparisons were considered statistically significant if the p value was <0.01 or the 95% confidence interval did not include the null value 1.0.

RESULTS

The total number of live births during the study period was 1,034,552. Following exclusions, there were 927,424 live births included in this analysis (figure 1). There was minimal missing data (<2%) for most variables analyzed; however, gestational age at first prenatal visit was missing in 25% and Body Mass Index (BMI) and Medicaid status were missing in 5% and 4%, respectively. There were few cases (N=13,667, 1.5%) with missing smoking data or smoking behaviors that did not fall within any of the 5 exposure groups. The reference group of non-smokers comprised 75.2% of births during the study period. Nearly 1 in 4 women during the study period smoked cigarettes. Of those, 23.8% smoked preconception only, 9.7% smoked through the first trimester, 3.9% smoked through the second trimester, and the majority (59.2%) smoked throughout the entire pregnancy, Figure 1.

Seventy-six percent of the study population comprised births to non-Hispanic white mothers (N=709,297). Non-Hispanic white mothers were more frequently smokers than non-white mothers (N=188,985, 26.6% vs. N=34,628, 16.0%, p<0.01) and more likely to smoke throughout pregnancy (N=114,230, 16.1% vs. N=18,135, 8.4%, p<0.01). Young mothers age <20 years were more likely to be smokers than women ages 20–34 years (N=29,406, 31.5% vs. N=180,099, 24.9%, p<0.01) and more likely to smoke throughout pregnancy (N=16,883, 18.1% vs N=106,755, 14.8%, p<0.01).

Women who reported quitting smoking in the first trimester were more likely to initiate prenatal care in the first trimester than women who reported smoking throughout pregnancy (N=32,033, 60.0% vs. N=61,947, 46.7%, $p<0.01$). Other maternal characteristics associated with adverse smoking behaviors included low education level, limited prenatal care, late initiation of prenatal care at 20 weeks, unmarried, WIC enrollment, and Medicaid funded delivery, Table I.

Women who reported smoking throughout pregnancy were more likely to be heavy smokers preconception (>20 cigarettes/day) than those who quit smoking early, after the preconception period (N=76,149, 57.5% vs. N=16,595, 31.1%, $p<0.01$), Table 2. However, women who smoked throughout pregnancy reported a reduction in their average cigarettes smoked per day from 17.1 ± 9.9 preconception to 10.0 ± 7.5 in the third trimester, Table 2. In all groups who reported smoking during pregnancy, women most frequently smoked <10 cigarettes/day.

Birth outcomes associated with smoking throughout pregnancy included preterm birth <37 weeks (N=18,053, 13.6% vs. referent N=69,794, 10.0%), low birth weight <2500 g (N=15,052, 11.4% vs. N=39,173, 5.6%), lower average birth weight (3090 g vs. 3340 g), and NICU admission (N=8,298, 6.3% vs. N=34,300, 4.9%), p -values<0.01, Table 3. Absolute rates of other birth outcomes were similar across the various smoking groups, but p values were statistically significant, likely due to the large sample size.

The overall frequency of FGR less than the 10th and 5th percentiles in the study cohort was 9.8% (N=90,613) and 4.6% (N=42,547) respectively. The rate of FGR <10th and <5th percentiles was lowest in non-smokers (8.1%, N=56,666 and 3.6%, N=25,380), followed by those who smoked preconception only (8.4%, N=4,485 and 3.8%, N=2,034). For all groups who smoked in at least 1 trimester of pregnancy, the risk of FGR over non-smokers increased significantly. For women who quit smoking in pregnancy, the adjusted odds ratio (95% CI) of smoking just through the first trimester was 1.19(1.13,1.24) and 1.25(1.17,1.33), and was higher with smoking through the second trimester at 1.67(1.57,1.78) and 1.83(1.68,1.99), respectively for FGR less than the 10th and 5th percentiles, Table 4. Smoking throughout pregnancy carried the highest risk of FGR with over two-fold increase risk for birth weights less than the 10th and 5th percentiles, even after accounting for coexistent influences of maternal age, race, education, marital status, Medicaid funded delivery, pregestational hypertension and diabetes, gestational hypertension and diabetes, and BMI. The attributable risk of smoking throughout pregnancy was 10.2% for FGR less than the 10th percentile and 5.8% for FGR less than the 5th percentile, Table 4.

The dose response analysis showed a significant inverse linear correlation between the number of cigarettes smoked per day and birth weight. Each additional cigarette smoked per day in the first, second and third trimesters was associated with a decrease in birth weight of 12.1, 14.8, and 14.5 grams respectively.

The results of a sensitivity analysis performed after redefining smokers as those who reported 5 or more cigarettes per day produced similar results. Using this definition of smokers, the adjusted odds ratio (95% CI) of smoking just through the first trimester was

1.23(1.16,1.30) and 1.28(1.18,1.39), and was higher with smoking through the second trimester at 1.81(1.67,1.97) and 1.96(1.75,2.19) and third trimester at 2.38(2.33,2.43) and 2.57(2.50,2.65) respectively for FGR less than the 10th and 5th percentiles. The risk of FGR was not increased with smoking only before conception [aOR 1.02(0.98, 1.06) and 1.02 (0.97, 1.05) for FGR <10th and 5th percentiles], again similar to the findings of the original analysis displayed in table 4

DISCUSSION

Smoking during any trimester of pregnancy carries an increased risk of fetal growth restriction over non-smokers. Previous studies showed that women who smoke during pregnancy have double the risk of FGR over women who do not smoke¹ and that roughly ¼ of all growth restriction cases can be attributed to smoking.¹⁰ Fetal growth restriction is a serious pregnancy complication, carrying a 5 to 30-fold increase in infant mortality,¹¹ and an increased risk of preterm birth, necrotizing enterocolitis, and respiratory distress syndrome.¹² Recent evidence also suggests that fetal growth restriction contributes to an increased risk of chronic adult diseases, such as Type II Diabetes Mellitus, hypertension, stroke and coronary heart disease.¹³ In this large population-based cohort study, we found that although preconception smoking was not associated with an increased risk of FGR, smoking during any trimester of pregnancy was associated with FGR risk.

Several studies have concluded that women who quit smoking before the third trimester had similar growth restriction outcomes as those who did not smoke at all during pregnancy.⁶⁻⁸ However, these findings of no significant risk increase in women who smoked but quit earlier in pregnancy may have been limited by smaller sample size (n<11,200) compared to our large cohort of nearly 1 million singleton live births^{5,6,8}. In addition, few similar studies included a population of US women, and the findings of those born in other areas of the world may not be applicable given regional and racial differences in birth weights and smoking patterns across the world.^{7,8} Finally, one other large U.S. cohort study concluded that quitting smoking in the first trimester reduced risk of FGR compared to a referent group of women who smoked throughout pregnancy.¹⁴ This study also drew the conclusion that quitting smoking in the first trimester brought risk of SGA similar to that of non-smokers, but did not use non-smokers as a referent group.¹⁴

Fetal growth is influenced by constitutional, environmental, and genetic factors.¹⁵ The pharmacogenetics of maternal tobacco use and the effects of smoking on fetal growth are complex. Since fetal growth is continuous during pregnancy, early cessation plausibly results in less effect, if the effect is from genetic interaction or direct toxic effects of nicotine.¹⁶ Additionally, the effect of nicotine could theoretically be due to placental-smoking interaction. Decidual invasion occurs during the first trimester. Therefore a critical window of exposure in the first trimester may result in an early pregnancy reversible effect of smoking cessation followed by the remaining gestational period where smoking cessation can no longer salvage normal placentation.^{17,18} Either or both of these mechanisms could hypothetically explain the greater influence earlier cessation has on normalization of fetal growth as our study suggests. We are unaware of any previously published studies

comparing the risk of FGR in women who quit smoking preconception and in each trimester to a referent group of non-smokers.

There are a number of limitations to a study using vital statistics data for research. Some data variables including maternal demographic information and gestational age at birth appear to be very reliably recorded in the birth certificate.¹⁹ However, data on pregnancy complications, and medical comorbid conditions are underreported, which may limit the ability to thoroughly adjust for confounding risk factors for FGR.²⁰ Additionally, smoking may be underreported on birth certificate data when compared to anonymous PRAMS surveys, potentially making the effect of smoking even stronger than reported here.²¹ However, self-reported smoking has been shown to be a valid measure of reproductive smoking behavior, especially when timing of smoking exposure is critical.²² Information regarding alcohol intake, drug use, and second hand smoke exposure was not available in the data set used for this analysis, and thus could not be accounted for as potentially confounding factors.

Our study reinforces prior conclusions that the strongest association between smoking and fetal growth restriction occurs in the third trimester. Additionally, this study provides novel information of an increased risk of FGR with smoking in any trimester of pregnancy, with decreasing risk the earlier smoking cessation occurs. Early initiation of prenatal care may assist women in making the decision to quit smoking early in pregnancy. The only way to achieve the same risk of FGR as non-smoking mothers is by quitting before conception, although quitting at any point is beneficial. Therefore, smoking cessation programs should focus on the benefit of quitting in the preconception period or as early in pregnancy as possible.

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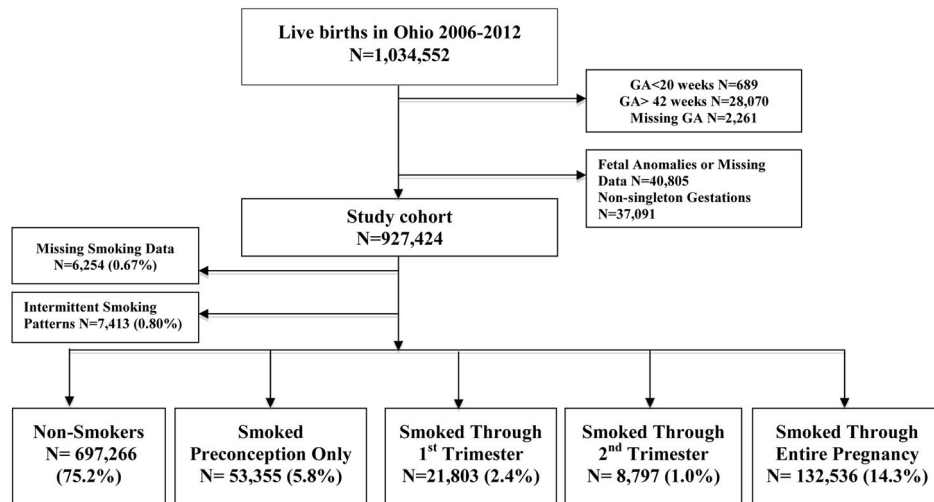


Figure 1.
Flow Diagram of the Study Population

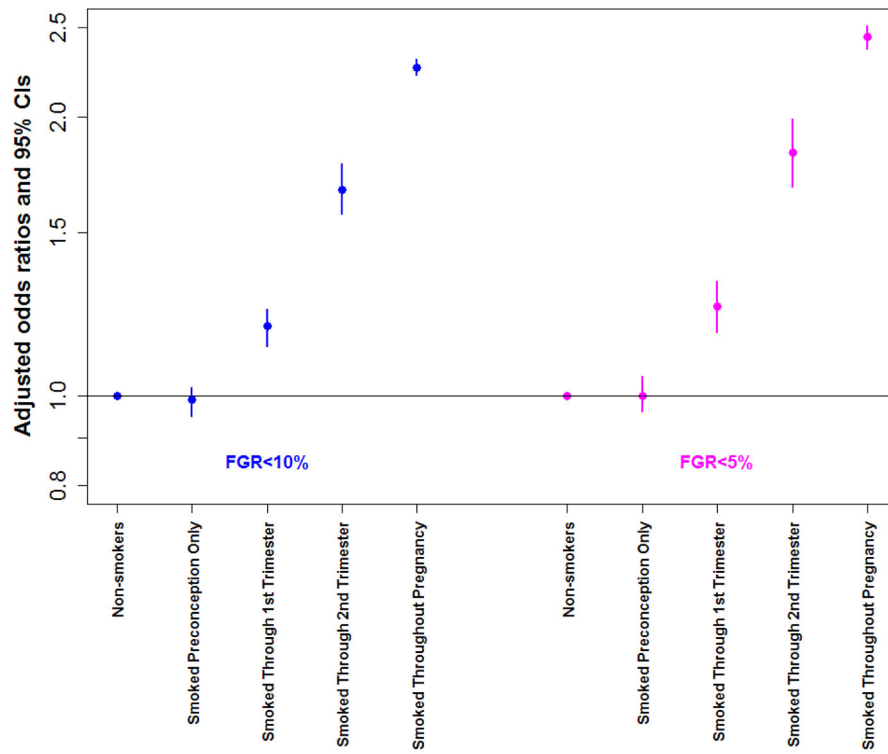


Figure 2. Odds of Fetal Growth Restriction in Singleton Pregnancies by Timing of Smoking Cessation

Odds ratios were adjusted for maternal age, race, education level, Medicaid, marital status, pregestational hypertension and diabetes, gestational hypertension and diabetes, and body mass index. Births with fetal anomalies and multiple gestations were excluded.

Table 1

Baseline Maternal Characteristics

	Non-Smokers N=697,266	Smoked Preconception Only N=53,355	Smoked Through 1 st Trimester N=21,803	Smoked Through 2 nd Trimester N=8,797	Smoked throughout pregnancy N=132,536
Demographic Factors					
Maternal Race					
Non-Hispanic White	517,166 (72.9%)	44,435 (6.3%)	17,728 (2.5%)	7,130 (1.0%)	114,230 (16.1%)
Non-Hispanic Black	120,430 (80.0%)	6,534 (4.3%)	3,123 (2.1%)	1,355 (0.9%)	14,920 (9.9%)
Hispanic	36,657 (86.1)	1,858 (4.4%)	753 (1.8%)	249 (0.6%)	2,564 (6.0%)
Other	21,805 (93.4%)	471(2.0%)	169 (0.7%)	48 (0.2%)	651(2.8%)
Parity	1 (0.2)	0 (0.1)	0 (0.1)	1 (0.2)	1 (0.2)
Maternal Age Mean	27.7 ± 5.9	25.7 ± 5.3	24.6 ± 5.2	24.4 ± 5.3	25.2 ± 5.4
Maternal Age Median and IQR	28 (23,32)	25 (22,29)	24 (21,28)	23 (20,27)	24 (21,29)
Maternal Age	28 (23, 32)	25 (22, 29)	24 (20, 28)	23 (20, 27)	24 (21, 28)
Age Group					
<20	63,110 (67.6%)	6,163 (6.6%)	3,580 (3.8%)	1,524 (1.6%)	16,883 (18.1%)
20–34	538,815 (74.5%)	43,783(6.1%)	17,068 (2.4%)	6,777 (0.9%)	106,755 (14.8%)
35	95,341 (86.3%)	3,409 (3.1%)	1,155(1.1%)	496 (0.5%)	8,898 (8.1%)
Socioeconomic Factors					
Less than High School Diploma	94,378 (13.5%)	7,171(13.4%)	4,243 (19.5%)	2,192 (24.9%)	42,280 (31.9%)
Unmarried	238,063 (34.1%)	29,475 (55.2%)	15,005 (68.8%)	6,533 (74.3%)	94,084 (71.0%)
WIC	239,827 (34.4%)	26,265 (50.2%)	13,141 (60.3%)	5,709 (64.9%)	90,035 (67.9%)
Medicaid	202,044 (29.0%)	23,487 (44.0%)	12,248 (56.2%)	5,662 (64.4%)	90,451 (68.3%)
Prenatal Care					
Limited (< 5 Visits)	49,531 (7.1%)	3,293 (6.2%)	1,700 (7.8%)	976 (11.1%)	16,423 (12.4%)
Early Initiation 12 Weeks Gestation	400,724 (57.5%)	32,033(60.0%)	11,185 (51.3%)	4,054 (46.1%)	61,947 (46.7%)
Late Initiation >20 Weeks Gestation	41,237 (5.9%)	2,709 (5.1%)	1,573 (7.2%)	788 (9.0%)	12,073 (9.1%)
Maternal Health Indicators					
Prior C-Section	90,386 (13.0%)	5,499 (10.3%)	2,245 (10.3%)	1,025 (11.7%)	18,455 (13.9%)

	Non-Smokers N=697,266	Smoked Preconception Only N=53,355	Smoked Through 1 st Trimester N=21,803	Smoked Through 2 nd Trimester N=8,797	Smoked throughout pregnancy N=132,536
Underweight, Prepregnancy BMI < 18.5	23,840 (3.4%)	2,436 (4.6%)	1,274 (5.8%)	610 (6.9%)	9,836 (7.4%)
Obesity, Prepregnancy BMI ≥ 30	153,533 (22.0%)	12,356 (23.2%)	5,197 (23.8%)	2,101 (23.9%)	30,293 (22.9%)
Gestational Weight Gain, pounds	31.2 ± 16.9	36.4 ± 18.8	36.5 ± 19.2	33.6 ± 19.5	30.3 ± 18.9
Chronic Hypertension	13,123 (1.9%)	980 (1.8%)	374 (1.7%)	196 (2.2%)	2,232 (1.7%)
Pre-gestational Diabetes	5,412 (0.8%)	402 (0.8%)	196 (0.9%)	83 (0.9%)	1,188 (0.9%)
Gestational Hypertension/Pre-eclampsia	32,252 (4.6%)	2,754 (5.2%)	1,075 (4.9%)	373 (4.2%)	4,407 (3.3%)
Gestational Diabetes	37,789 (5.4%)	3,076 (5.8%)	1,228 (5.6%)	483 (5.5%)	6,370 (4.8%)

All comparisons are statistically significant at p-value 0.001 for the χ^2 statistic corresponding to the 5 IPI group comparison for each maternal characteristic in this table.

Dichotomous variables are presented as percent of n for corresponding smoking group, except for the categorical variables mother's race and age group, which reflect percentages across rows.

Continuous variables are presented as mean ± standard deviation or median and interquartile range.

Table 2

Smoking Behavior Comparisons

	Non-Smokers N=697,266	Smoked Preconception Only N=53,355	Smoked Through 1 st Trimester N=21,803	Smoked Through 2 nd Trimester N=8,797	Smoked throughout pregnancy N=132,536
Preconception Smoking Behaviors					
Average Number of Cigarettes Smoked per Day	0	11.8±9.6	14.6±10.4	16.1±9.8	17.1±9.9
Heavy Smoking (> 20/day)	0%	16,595 (31.1%)	9,617 (44.1%)	4,644 (52.8%)	76,149 (57.5%)
Smoking Behaviors in Final 3 Months of Smoking					
Average Number of Cigarettes Smoked	0	11.8 ± 9.7	9.0 ± 8.1	7.2 ± 7.2	10.0 ± 7.5
<10	0.0%	20,897 (39.2%)	11,806 (54.2%)	5,832 (66.3%)	56,815 (42.9%)
10–19	0.0%	15,863 (29.7%)	5,901 (27.1%)	1,956 (22.2%)	49,540 (37.4%)
20	0.0%	16,595 (31.1%)	4,096 (18.8%)	1,009 (11.5%)	26,181 (19.8%)

All comparisons are statistically significant at p-value 0.001 for the χ^2 statistic corresponding to the 5 IPI group comparison for each maternal characteristic in this table.

Dichotomous variables are presented as percent of n for corresponding smoking group.

Continuous variables are presented as mean ± standard deviation.

Table 3

Birth Outcomes

	Non-Smokers N=697,266	Smoked Preconception Only N=53,355	Smoked Through 1 st Trimester N=21,803	Smoked Through 2 nd Trimester N=8,797	Smoked throughout pregnancy N=132,536
Maternal					
Vaginal Delivery	456,531 (65.4%)	33,739 (63.2%)	14,007 (64.2%)	5,536 (62.9%)	87,168 (65.8%)
Operative Vaginal Delivery	39,144 (5.6%)	3,392 (6.4%)	1,367 (6.3%)	471 (5.4%)	6,668 (5.0%)
Cesarean Delivery	200,896 (28.8%)	16,178 (30.3%)	6,417 (29.4%)	2,776 (31.6%)	38,555 (29.1%)
Premature Rupture of Membranes	19,704 (2.8%)	1,739 (3.3%)	750 (3.4%)	468 (5.3%)	4,296 (3.2%)
PTB <37 weeks	69,794 (10.0%)	5,096 (9.6%)	2,477 (11.4%)	1,590 (18.1%)	18,053 (13.6%)
Meconium	38,098 (5.5%)	2,833 (5.3%)	1,179 (5.4%)	501 (5.7%)	7,558 (5.7%)
Induction of Labor	220,696 (31.7%)	19,660 (36.9%)	7,977 (36.6%)	2,971 (33.8%)	41,281 (31.2%)
Fetal Intolerance to Labor	44,932 (6.4%)	4,022 (7.5%)	1,516 (7.0%)	688 (7.6%)	7,899 (6.0%)
Newborn					
BW Mean \pm SD	3340.0 \pm 557.8	3339.0 \pm 557.0	3280.0 \pm 589.8	3072.5 \pm 762.9	3090.1 \pm 542.4
LBW <2500 gm	39,173 (5.6%)	3,035 (5.7%)	1,585 (7.3%)	1,306 (14.9%)	15,052 (11.4%)
ELBW <1500 gm	7,391 (1.1%)	535 (1.0%)	309 (1.4%)	541 (6.2%)	1,636 (1.2%)
NICU Admission	34,300 (4.9%)	2,720 (5.1%)	1,260 (5.8%)	930 (10.6%)	8,298 (6.3%)
Infant Transfer	14,234 (2.0%)	1,162 (2.2%)	515 (2.4%)	368 (4.2%)	3,869 (2.9%)
5 min. Apgar score <7	15,610 (2.2%)	1,244 (2.3%)	581 (2.7%)	401 (4.6%)	3,008 (2.3%)

PTB = preterm birth; BW = birth weight; LBW = low birth weight; ELBW = extremely low birth weight; NICU = neonatal intensive care unit

All comparisons are statistically significant at p-value 0.001 for the χ^2 statistic corresponding to the 5 IPI group comparison for each maternal characteristic in this table.

Table 4
Rate of Fetal Growth Restriction In Singleton Pregnancies by Timing of Smoking Cessation

	Non-Smokers N=697,266	Smoked Preconception Only N=53,355	Smoked Through 1 st Trimester N=21,803	Smoked Through 2 nd Trimester N=8,797	Smoked throughout pregnancy N=132,536
FGR <10th Percentile	56,566 (8.1%)	4,485 (8.4%)	2,286 (10.5%)	1,281 (14.6%)	24,182 (18.3%)
Attributable Risk		0.3% (0.25,0.35)	2.4% (2.2,2.6)	6.5% (5.98, 7.02)	10.2% (10.04,10.36)
Crude OR	Ref.	1.04 (1.01, 1.07)	1.33 (1.27, 1.39)	1.93 (1.82, 2.05)	2.53 (2.49, 2.57)
* Adjusted OR	Ref.	0.99 (0.95, 1.02)	1.19 (1.13, 1.24)	1.67 (1.57, 1.78)	2.26 (2.22, 2.31)
FGR <5th Percentile	25,380 (3.6%)	2,034 (3.8%)	1,105 (5.1%)	649 (7.4%)	12,500 (9.4%)
Attributable Risk		0.2% (0.16,0.24)	1.5% (1.34,1.66)	3.8% (3.4,4.2)	5.8% (5.67,5.93)
Crude OR	Ref.	1.05 (1.00, 1.10)	1.41 (1.33, 1.50)	2.11 (1.95, 2.29)	2.76 (2.70, 2.82)
* Adjusted OR	Ref.	1.00 (0.96, 1.05)	1.25 (1.17, 1.33)	1.83 (1.68, 1.99)	2.44 (2.37, 2.51)

* Odds ratios were adjusted for maternal age, race, education level, Medicaid, marital status, pregestational hypertension and diabetes, gestational hypertension and diabetes, and Body Mass Index. Births with fetal anomalies and multiple gestations were excluded.

All comparisons are statistically significant at p-value 0.001 for the χ^2 statistic corresponding to the 5 IPI group comparison for each maternal characteristic in this table.