Relationship of trimester specific smoking patterns and risk of preterm birth

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Abstract

Background—In 2011, the US national rate of smoking early in pregnancy was 11.5%. Unfortunately, our home state of Ohio had a rate twice as high at 23%. Smoking in pregnancy remains one of the most important modifiable risk factors for pregnancy complications, specifically preterm birth.

Objective—To quantify the preterm birth risk to various trimester-specific smoking behaviors.

Study Design—Population-based retrospective cohort study of singleton non-anomalous live births utilizing Ohio birth records 2006–2012. Preterm birth rates were compared between non-smokers, and women who smoked in the preconception period only, those who quit smoking after the 1st and 2nd trimesters and those who smoked throughout pregnancy. Multivariate logistic regression quantified the risk of smoking with cessation at various times in pregnancy and preterm birth risk, adjusted for maternal race, education, age, Medicaid use, marital status, and parity.

A stratified analysis was performed based on preterm birth subtype: spontaneous preterm birth versus indicated preterm birth. We also performed an additional analysis stratifying for maternal race using the 2 largest categories of race (non-Hispanic white and non-Hispanic black).

Results—Of the 913,757 birth records analyzed, nearly 1/4 of the women reported some smoking behavior on the birth certificate data. Of smokers, less than half quit during pregnancy (38.8% vs 61.2% smoked throughout pregnancy). Early quitters had a similar preterm birth rate compared to non-smokers. Women who smoked through the 1st trimester only did not have a significant increase in their overall preterm birth odds ratio <37 weeks; however it did increase the

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odds of extreme preterm birth <28 weeks by 20%; adjusted odds ratio 1.20 (95% Confidence interval 1.02, 1.40). Quitting late in pregnancy resulted in the highest odds ratio increase, 70% for preterm birth <37 wks, adjusted odds ratio 1.70 (CI 1.60, 1.80), even after adjustment for the confounding influences.

Quitting smoking early in pregnancy after the 1st trimester did not increase the overall risk of spontaneous or indicated preterm birth <37 weeks significantly. However, quitting after the 1st trimester was associated with a significant increase in risk of extreme spontaneous preterm birth <28 weeks, an effect not seen with indicated preterm birth <28 weeks. Delaying cessation until late in pregnancy – after the 2nd trimester - was associated with the highest risk increases, 65% increased odds of spontaneous and 78% increase in odds of indicated preterm births. The rate of preterm births to non-Hispanic black mothers was increased in all categories over those of non-Hispanic white mothers. The relative influence of smoking cessation in pregnancy was similar in black compared to white mothers. The effect modification in the regression model was analyzed and revealed no significant interaction between race and smoking patterns on preterm birth risk.

Conclusions—Smoking throughout pregnancy is associated with an increased risk of preterm birth. However, quitting early in pregnancy negates this risk. Widespread programs aimed at smoking cessation early in pregnancy could have a significant impact on reducing the rate of preterm birth nationally.

Condensation

Smoking throughout pregnancy is associated with an increased risk of preterm birth. However, quitting early in pregnancy negates this risk.

Introduction

Both tobacco smoking and preterm birth are significant global health problems.[1,2] Recent estimations in high income countries suggest implementation of maternal smoking cessation along with other effective preventive approaches such as progesterone supplementation, cervical cerclage placement, decreasing non-medically indicated cesarean section and labor induction, and limiting multiple embryo transfer in assisted reproductive technology may reduce the rate of preterm birth by as much as 5% by the end of 2015.[3] Preterm birth <37 weeks is a strong predictor of perinatal and infant mortality in the United States and also contributes to serious long-term morbidities including neurological handicaps as well as financial burdens on families and health care systems.[4–6]

Smoking is one of the most important modifiable risk factors for the reduction of pregnancy complications. In 2011, the prevalence of smoking early in pregnancy in Ohio was 23%, twice as high compared to the US national rate of 11.5%.[7] This high rate has been attributed to a variety of factors; however public health programs have been put in place to target pregnant smokers.[8,9] Because of the high rate of smoking in pregnancy in our home state, we aim to quantify the influence of quitting smoking at various times in pregnancy on preterm birth risk. These data may be used to assist in smoking cessation counseling in pregnancy.

Materials and Methods

The Human Subjects Institutional Review Board of the Ohio Department of Health approved the protocol for this study and provided a de-identified set of data for analysis which included birth certificate data on 1,034,552 live births that occurred in Ohio over a 7 year period (2006–2012). This study was exempt from review by the Institutional Review Board at the University of Cincinnati, Cincinnati, Ohio. All Ohio birth records utilized the newest (2003) version of the national birth certificate beginning in 2006.[10]

We performed a population based retrospective cohort study aimed to compare various trimester specific maternal self-reported smoking behaviors during pregnancy with preterm birth rates. The U.S. birth certificate contains data on maternal tobacco smoking during four time periods: "three months before pregnancy", "first three months of pregnancy", "second three months of pregnancy", and "third trimester of pregnancy".[8] From this data study subjects were categorized into one of five exposure groups based on their smoking behaviors: "non-smokers", "smoked preconception only" (smoked only in the 3 months prior to conception but not in any trimester), "smoked through 1st trimester" (smoked preconception and the 1st trimester, but not in the 2nd or 3rd trimester), "smoked through 2nd trimester" (smoked preconception and the first 2 trimesters, but not the 3rd trimester), and "smoked throughout pregnancy" (smoked preconception and in all trimesters). Smoking 1 cigarette per day was considered a smoker for the purpose of this study. We performed additional sensitivity analyses defining smokers using a threshold of 5 cigarettes per day. Non-smokers comprised the referent group for exposure group comparisons.

Our analyses were limited to singleton, non-anomalous live births between 20 and 42 weeks gestation with available data on maternal smoking during pregnancy. Gestational age was defined using the US vital statistics birth certificate variable gest_comb, which is the clinician's best estimate of gestational age using a combination of the last menstrual period and earliest ultrasound measurement.[11] The primary outcome of this study was preterm birth <37 weeks. We then stratified the outcomes into subcategories of preterm birth: extremely preterm (20–27 weeks) and preterm (28–36 weeks). Term births, 37–42 weeks, comprised the referent group for outcome comparisons.

We performed a stratified analysis based on preterm birth subtype: spontaneous preterm birth (SPTB) versus indicated preterm birth (IPTB). Indicated PTB included births at <37 weeks complicated by intrauterine growth restriction (IUGR), preeclampsia, eclampsia, or births that occurred <37 weeks following induction of labor as recorded in the birth certificate. IUGR was defined as birthweight less than the 10th percentile based on a widely used US reference.[12] Preterm births not categorized as indicated were considered spontaneous preterm births for the purposes of this study. We also performed an additional analysis stratifying for maternal race using the 2 largest categories of race (non-Hispanic white and non-Hispanic black). Additionally, we tested for effect modification and found no significant interaction between race and smoking patterns in preterm birth risk.

Following exclusions of birth <20 or >42 weeks, missing gestational age, fetal anomalies, and twins or higher order multiples the cohort used for this analysis was comprised of

927,424 live births. Of the other variables that were analyzed (maternal age, race, educational attainment, and smoking habits), there was minimal missing data (<2%). Medicaid enrollment had slightly higher amounts of missing data 4%. Smoking behavior was largely reported; only 0.7% (n=6,254) of birth records in Ohio had missing data on smoking and 0.8% (n=7,413) of the subjects had intermittent smoking habits that did not correspond with one of the 5 exposure categories defined for this study. Those cases were not included in this analysis.

Comparisons of dichotomous variables were performed with chi-square tests and continuous variables were compared using ANOVA. Multivariate logistic regression quantified the odds of preterm birth among each of the smoking behavior groups compared to non-smokers (referent) after adjustment for the confounding influences of maternal race, maternal age, maternal education, marital status, Medicaid funded delivery, and parity. Covariates for the adjusted models were selected based on significant differences noted among exposure groups as well as biologic plausibility. Analyses were performed using STATA 12.1 software (StataCorp, College Station, Texas). Comparisons were considered statistically significant if p-value was <0.05.

Results

Of the 913,757 birth records included in this study, nearly a quarter (n=216,491, 23.7%) of the women in our study population reported some smoking behavior on the birth certificate data. Women who smoked preconception only comprised of 5.8% (n=53,355) of the study cohort, 2.4% (n=21,803) smoked through the 1st trimester, 1.0% (n=8,797) smoked through the 2nd trimester, and 14.3% (n=132,536) smoked throughout pregnancy. Of women who smoked, less than half quit smoking during pregnancy (n=83,955; 38.8% vs 132,536 who smoked throughout pregnancy; 61.2%). Of quitters, more women quit early in pregnancy compared to quitting in the 2nd or 3rd trimester (p<0.01). Summary statistics regarding quantity of smoking among this population are reported elsewhere.[13]

Women who smoked throughout pregnancy were more likely of non-Hispanic white race, maternal age <20, low educational attainment, were unmarried, and had Medicaid funded medical care. Women who smoked through the 2nd trimester had significant increases in rates of preterm birth, most notably among the following high risk groups: non-Hispanic black race (23.9%), maternal age >35 (29.4%), and low educational attainment (21.8%); where the percentage equals the percent of preterm birth rates for the corresponding high risk group. Woman of advanced maternal age (>35 yrs) had nearly a 3 fold increase risk of preterm birth if they smoked through the 2nd trimester compared to non-smoking women of the same age group, table 1.

The preterm birth (PTB) rate in non-smokers among our study cohort of singleton non-anomalous births was 10%. Early quitters (smoked preconception only) had a similar PTB rate compared to non-smokers, 9.6%, although statistically significant at p<0.01. Women who smoked through the 1st trimester only then quit did not have a significant increase in their overall PTB risk <37 weeks (11.4%), compared to non-smokers, adj OR 1.02 (0.98, 1.07); however it did increase the risk of extreme preterm birth <28 weeks by 20%; adj OR

1.20 (1.02, 1.40). Smoking through the 2nd trimester then quitting late in pregnancy resulted in the highest risk increase, 70% for PTB <37 wks (adj OR 1.70; 95% CI 1.60, 1.80) compared to non-smokers, even after adjustment for the confounding influences of maternal race, maternal age, maternal education, Medicaid funded medical care, marital status, and parity, Table 2.

After redefining smokers as those who reported using 5 cigarettes or more per day, we performed a sensitivity analysis which generated similar results. Using this new definition, the rate of PTB in early quitters and those who quit after the 1st trimester were nearly identical to the original analysis (9.4% and 11.5%, respectively), which did not significantly increase their PTB risk from the non-smokers (adj OR 1.03; CI 0.98, 1.09). Women who smoked 5 cigarettes per day and did not quit smoking until after the 2nd trimester had an increased risk of PTB <37 weeks of 90% (adj OR 1.90; CI 1.76, 2.04), again similar to our initial analysis defining smokers as 1 cigarette per day.

Preterm birth rates related to each smoking behavior were stratified by maternal race (non-Hispanic black race and non-Hispanic white race). The rate of PTB to non-Hispanic black mothers was increased in all categories over those of non-Hispanic white mothers. In fact, the rate of PTB in non-Hispanic black mothers was nearly double (15.3% vs 8.7%) compared to that of non-Hispanic white mothers. The relative influence of smoking cessation in pregnancy was similar in black compared to white mothers, respectively: for cessation after the 1st trimester: adj OR 1.10 (0.99, 1.21) vs adj OR 1.06 (1.01, 1.12); cessation after 2nd trimester: adj OR 1.59 (1.40, 1.82) vs adj OR 1.81 (1.70, 1.94); and smoked throughout pregnancy: adj OR 1.15 (1.10, 1.21) vs adj OR 1.28 (1.26, 1.32) - data not shown in table.

When stratified by preterm birth subtype, smoking had a similar influence on risk of both indicated and spontaneous preterm births. Quitting smoking early in pregnancy after the 1st trimester did not increase the overall risk of spontaneous or indicated preterm birth <37 weeks significantly, table 3. However, quitting after the 1st trimester was associated with a significant increase in risk of extreme spontaneous PTB <28 weeks, an effect not seen with indicated PTB <28 weeks. Delaying cessation until late in pregnancy – after the 2nd trimester - was associated with the highest risk increases, 65% increased odds of spontaneous and 78% increase in odds of indicated preterm birth.

Comment

Smoking in pregnancy has been widely accepted as a significant risk factor for preterm birth.[14] As such, smoking cessation reduces the risk of preterm birth.[15] Our large population based study includes nearly a million women who live in a state that has a rate of smoking in pregnancy twice as high as the national average, an area that needs urgent attention to smoking cessation interventions. We found that women who quit smoking early in pregnancy, either in the 1st or 2nd trimester, had similar risks of PTB compared to non-smokers. However, delayed smoking cessation until late in pregnancy, after the 2nd trimester, or continued smoking throughout pregnancy were associated with significant increases in the risk of PTB. We also observed a notable further increased risk of preterm birth in women

with concomitant PTB factors: 23.9% in Non-Hispanic black women, 29.5% in women of advanced maternal age (>35), and 21.8% in women with low educational attainment if cessation did not occur until after the 2nd trimester.

Similar to Hodyl et al's study, we too found that early smoking cessation reduces a woman's risk of preterm birth to levels comparable with a non-smoker and with continuation of smoking throughout pregnancy the rates of preterm and very preterm births are increased.[16] However, this previously published study did not distinguish between cessation in the 2nd or 3rd trimester with smoking throughout pregnancy. Additionally, our study is unique in that it is a very large (n=927,424) population-based study in the United States, which allows for better generalizability. Numerous other studies have shown analogous results related to early smoking cessation and preterm risk relative to that of a non-smoker.[17–19] Polakowski et al similarly used birth certificate data, however their study only evaluated preterm births >28 weeks.[18] Our results show a 20% increase in extreme preterm births (20–27 weeks) if cessation occurred after the 1st trimester.

Delayed smoking cessation until late in pregnancy is associated with increased risk of both preterm subtypes, both indicated and spontaneous preterm births. Smoking in pregnancy is known to increase the risk of IUGR, which is a significant contributor to indicated preterm births. IUGR risk is increased even if smoking cessation occurs in pregnancy, with risk highest for those who quit later in pregnancy.[13] This study demonstrates that smoking also negatively influences the risk of spontaneous preterm births overall. Even quitting in the 2nd trimester may be too late to protect from the influence of smoking on extreme spontaneous preterm birth <28 weeks, as evidenced by a 20% increased PTB odds even after adjustment for other preterm birth risk factors.

One strength of our study is that it analyzes a large population base by use of birth certificate data. The newest version (2003 revision) of the birth certificate was used which allowed us to perform a detailed evaluation of each woman's smoking status for each trimester.[20] Furthermore, the population-based contemporary basis allows for generalizability to most pregnancies cared for in the United States. To our knowledge, this study is the largest looking at preterm births and its association with trimester specific smoking patterns. Specifically, our study analyzes the risk of extreme preterm births which is not reported in previous studies. We recognize that our study does have limitations, however. Birth certificate data is not designed for this particular research purpose. Concomitant data regarding alcohol use, drug use, and second hand smoke exposure was not available from our data source and therefore could not be accounted for in our adjusted analyses. Data on the etiology of preterm birth, i.e. spontaneous versus indicated, is not directly collected on the birth certificate. However, our method of defining these categories from associated delivery characteristics resulted in distributions consistent with that known from prospectively collected data.[21] Since smoking status on the birth records are self-reported there may be an element of under-reporting or misclassification resulting in an underestimate of our effect size estimates, however, studies have shown that self-reporting of reproductive smoking behaviors have been quite reliable.[22,23] Lastly, we received data on live births only. Stillbirths occurring before 37 weeks account for approximately 5% of preterm births. Including only live births may underestimate the true burden of smoking on

preterm birth, especially if smoking has a differential effect on periviable preterm birth or stillbirth.[24]

This study reinforces the findings of prior studies regarding smoking in pregnancy and preterm birth, and adds depth to our overall understanding of those populations most strongly affected. Our study provides novel information about smoking behavior in each trimester specifically, and its relationship to the rate of preterm birth. Public health initiatives and interventions should focus on early smoking cessation as smoking beyond the 2nd trimester significantly increases the overall risk of preterm birth and smoking beyond the 1st trimester has a significant risk on early preterm births <28 weeks. Since preterm births have serious short and long term impacts (physically, mentally, emotionally, and financially) on these infants, their families, and those caring for them, incorporating a no smoking in pregnancy campaign or at least early smoking cessation programs focused on reproductive age women are imperative.

Acknowledgments

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Maternal Characteristics

	Non-Smokers N=697,266	Smoked Preconception Only N=53,355	Smoked Through 1st Trimester N=21,803	Smoked Through 2nd Trimester N=8,797	Smoked throughout pregnancy N=132,536
Demographic Factors					
Maternal Race					
Non-Hispanic White	517,166 (8.7%)	44,435 (8.8%)	17,728 (10.4%)	7,130 (17.0%)	114,230 (13.0%)
Non-Hispanic Black	120,430 (15.3%)	6,534 (14.9%)	3,123 (16.9%)	1,355 (23.9%)	14,920 (18.6%)
Hispanic	36,657 (11.7%)	1,858 (9.0%)	753 (10.5%)	249 (18.1%)	2,564 (13.8%)
Other	21,805 (9.1%)	471 (10.6%)	169 (9.5%)	48 (12.5%)	651 (12.4%)
Age Group					
<20	63,110 (14.1%)	6,163 (10.3%)	3,580 (11.4%)	1,524 (17.7%)	16,883 (12.9%)
20-34	538,815 (9.4%)	43,783 (9.2%)	17,068 (11.0%)	6,777 (17.3%)	106,755 (13.3%)
35	95,341 (10.7%)	3,409 (12.5%)	1,155 (17.1%)	496 (29.4%)	8,898 (18.3%)
Socioeconomic Factors					
Less than High School Diploma	94,378 (13.2%)	7,171 (11.3%)	4,243 (12.6%)	2,192 (21.8%)	42,280 (15.3%)
Unmarried	238,063 (13.4%)	29,475 (10.3%)	15,005 (11.9%)	6,533 (18.2%)	94,084 (14.1%)
Medicaid	239,827 (10.8%)	26,265 (9.1%)	13,141 (11.1%)	5,709 (18.1%)	90,035 (13.8%)

Data listed as N (rate of preterm birth in each group)

All comparisons are statistically significant at p-value 0.001 for the X2 statistic corresponding to the 5 smoking group comparison for each maternal characteristic in this table.

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

Table 2

Preterm birth risk associated with smoking in pregnancy

Preterm Birth	Never Smokers	Smoked Preconception Only	Adj OR* (95%CI)	Quit after 1st Trimester	Adj OR* (95%CI)	Quit after 2nd Trimester	Adj OR* (95%CI)	Smoked throughout pregnancy	Adj OR* (95%CI)
Overall PTB <37 weeks									
<37 weeks, n(%)	69,794 (10.01)	5,096 (9.55)	0.91 (0.88, 0.94)	2,477 (11.36)	1.02 (0.98, 1.07)	1,590 (18.07)	1.70 (1.60, 1.80)	18,053 (13.62)	1.21 (1.19, 1.24)
Subcategories of PTB									
20–27 weeks, n(%)	4,230 (0.61)	312 (0.58)	0.87 (0.77, 0.98)	202 (0.93)	1.20 (1.03, 1.40)	n/a		870 (0.66)	0.90 (0.83, 0.97)
28–36 weeks, n(%)	65, 564 (9.40)	4,784 (8.97)	0.91 (0.88, 0.94)	2,275 (10.43)	1.01 (0.96, 1.05)	1,268 (14.41)	1.46 (1.37, 1.55)	17,183 (12.96)	1.24 (1.21, 1.26)

*
Adjusted for mother's race, mother's education, mother's age, medicaid, marital status, and parity. Anomalies and multiples excluded

All comparisons are statistically significant at p-value 0.001 for the X2 statistic corresponding to the 5 smoking group comparison for each maternal characteristic in this table.

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

Table 3

Influence of smoking cessation in pregnancy on spontaneous and indicated preterm births

Preterm Birth	Never Smokers	Smoked Preconception Only	Adj OR* (95% CI)	Quit after 1st Trimester	Adj OR* (95% CI)	Quit after 2nd Trimester	Adj OR* (95% CI)	Smoked Throughout Pregnancy	Adj OR* (95% CI)
Spontaneous Preterm Birth									
Overall <37 weeks, n (%)	48,779 (7.00)	3,476 (6.52)	0.90 (0.87, 0.93)	1,700 (7.81)	1.03 (0.97, 1.08)	1,058 (12.06)	1.65 (1.54, 1.77)	12,299 (9.31)	1.20 (1.17, 1.22)
28–36 weeks, n (%)	43,116 (6.43)	3,077 (5.99)	0.90 (0.87 0.94)	1,472 (7.08)	1.02 (0.96, 1.08)	767 (9.62)	1.37 (1.26, 1.48)	11,245 (8.94)	1.25 (1.22, 1.28)
20–27 weeks, n (%)	2,994 (0.47)	223 (0.46)	0.88 (0.77, 1.02)	146 (0.75)	1.20 (1.00, 1.43)	n/a		650 (0.56)	0.93 (0.84, 1.02)
Indicated Preterm Births									
Overall <37 weeks, n (%)	20,183 (2.90)	1,546 (2.90)	0.92 (0.87, 0.97)	744 (3.42)	1.01 (0.94, 1.09)	505 (5.76)	1.78 (1.62, 1.96)	5,319 (4.03)	1.22 (1.18, 1.26)
28–36 weeks, n (%)	22,230 (3.42)	1,675 (3.35)	0.91 (0.87, 0.96)	792 (3.94)	0.99 (0.92, 1.07)	508 (6.58)	1.66 (1.51, 1.83)	5,592 (4.66)	1.18 (1.14, 1.22)
20–27 weeks, n (%)	8,757 (1.38)	620 (1.27)	0.85 (0.78, 0.93)	283 (1.44)	0.93 (0.82, 1.05)	n/a		1,279 (1.10)	0.73 (0.69, 0.78)

*
Adjusted for mother's race, mother's education, mother's age, medicaid, marital status, and parity. Anomalies and multiples excluded

All comparisons are statistically significant at p-value 0.001 for the X2 statistic corresponding to the 5 smoking group comparison for each maternal characteristic in this table.

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