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Associations of Maternal Obesity and Smoking Status with Perinatal Outcomes

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Introduction

Modifiable conditions can impact overall health, including pregnancy health. Behaviors contributing to obesity and smoking, for example, are particularly important due to their prevalence. Rates of maternal obesity have significantly increased over the past 20 years, with approximately 30% of reproductive aged women having a body mass index (BMI) ≥ 30 kg/m².¹ Although overall rates of maternal smoking have declined, in the United States up to 15% of pregnant women continue to smoke.² With an overrepresentation of obesity and smoking among women of lower socioeconomic status, these factors contribute to health disparities amongst disadvantaged women.^{3,4}

Maternal smoking has long been recognized as a modifiable and dose-dependent risk factor for pregnancy complications, including ectopic pregnancy, placental abruption, placenta previa, intrauterine growth restriction, preterm delivery, and stillbirth.⁵⁻⁷ In contrast to non-smokers, women who smoke during pregnancy have up to a 2-fold increased risk of preterm delivery and a 30% increase in stillbirth rates.^{7,8} Maternal smoking also confers a risk of small-for-gestational age neonates (<2500g) that is up to 2.5 times greater than in non-smoking women.⁸

Likewise, pre-pregnancy overweight and obesity is associated with multiple adverse perinatal outcomes, including increased risks for cesarean delivery, stillbirth, and fetal macrosomia. Compared to normal weight women, overweight and obese women have an estimated 1.2 to 3.0-fold increased risk of cesarean delivery and a 60% increase in stillbirth rates.^{7,9,10} There is a linear increase in birth weight as maternal BMI increases with a 2-fold

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increase in the rate of macrosomia in obese compared to normal weight gravidas.^{9,11} The impact of maternal pre-pregnancy BMI on preterm delivery has been mixed, most likely due to studies combining spontaneous and indicated preterm deliveries, sub-type of preterm delivery and how preterm delivery is defined (< 32 vs < 37 weeks).

Whether there exists a differential effect of maternal weight and smoking status on important fetal outcomes has been studied much less frequently than their individual influences despite the high prevalence of each of these risk factors. In a Chinese population, passive smoke exposure was additive to maternal obesity on risk of developing gestational diabetes.¹² Another study found no interaction of smoking and obesity on risk of venous thromboembolism in pregnancy.¹³ We have recently characterized the co-occurrence of smoking and obesity among disadvantaged women and their significant association with adverse health biomarkers in a nationally representative sample.¹⁴ We have also shown that among women who quit smoking during pregnancy, breastfeeding rates are lower in obese compared to normal weight women, suggesting that maternal BMI moderates the effects of smoking cessation on breastfeeding.¹⁵ In this study, we sought to examine possible moderating effects of maternal BMI on associations of smoking cessation on short-term perinatal outcomes. We hypothesized that abstainers would have better outcomes than smokers but those would be greater among underweight/normal weight than overweight/obese women.

Materials and Methods

Participants

This is a secondary analysis of outcomes assessed as part of several prospective randomized clinical trials. Participant recruitment and data collection have been previously described.^{15,16} These trials examined the efficacy of financial incentives to promote smoking cessation and/or relapse prevention during pregnancy in women reporting smoking at the time of conception. Four trials of smoking cessation (n = 271) and 3 trials of relapse prevention (n = 117) were included in the analysis. These trials were completed at one academic institution between 2001 and 2012 and all were approved by the Institutional Review Board.¹⁶⁻¹⁹ Eligible participants were less than 25 weeks gestation at enrollment and reported current smoking (cessation trials) or quitting smoking after conception (relapse prevention trials), were English speaking, and residing within the county in which the clinic is located. Participants were excluded if they were currently in an opioid maintenance program, were using psychotropic medications other than antidepressants, or were either incarcerated or living in a group residence.

Assessment of smoking, body mass index, and pregnancy outcomes

All participants completed questionnaires regarding sociodemographic characteristics and smoking history at intake and repeatedly throughout the study. Smoking status was biochemically verified with exhaled breath carbon monoxide and urine cotinine levels. Body mass index was calculated from the self-reported pre-pregnancy weight and height obtained from the medical record (BMI = (weight, kg/height, m²)).

Outcomes including gestational age at delivery, birth weight, mode of delivery, admission to the neonatal intensive care unit (NICU), and NICU length of stay were abstracted from the medical record. Preterm birth was defined as birth at a gestational age less than 37 weeks. Low birth weight was defined as birth weight less than 2500 grams; macrosomia was defined as birth weight greater than 4000 grams. Due to small numbers, pre-pregnancy BMI categories were grouped as underweight/normal weight (BMI < 25 kg/m²) and overweight/obese (BMI ≥ 25 kg/m²).

Treatment

The treatment condition has been previously described.¹⁹ Briefly, participants were randomized to an abstinence-contingent incentive or control condition. In the treatment condition, participants received vouchers exchangeable for retail items contingent on biochemically verified smoking abstinence. Participants in the control condition received vouchers of comparable value independent of smoking status. In addition, all participants received care for smoking cessation at the discretion of their obstetrical providers. This commonly involves discussion of the benefits of quitting smoking during pregnancy and referral materials for the Vermont quit line, a phone helpline for smoking cessation.

Both incentivized and control participants were included in this analysis. Smokers were considered any woman who was smoking at the beginning of pregnancy and continued smoking throughout the pregnancy or women who quit smoking at the beginning of pregnancy but resumed smoking prior to delivery. Abstainers included those who spontaneously quit smoking at the beginning of pregnancy and did not relapse back to smoking during the trial and those who quit smoking during participation in the trial. We compared smokers to abstainers among underweight/normal weight and overweight/obese women.

Statistical analysis

Late pregnancy smoking status (smoking vs abstinent) was compared on participant characteristics using chi square tests for categorical measures and t-tests for continuous measures. The effects of smoking status, pre-pregnancy BMI (underweight/normal weight vs overweight/obese) and their interaction on perinatal outcomes were assessed using analysis of covariance models with smoking status and BMI as fixed effects for continuous outcomes and multiple logistic regression models for dichotomous outcomes. All models included baseline smoking status as a covariate. Demographic and baseline smoking characteristics that were significantly correlated with an outcome were included in the model for that outcome. If the interaction was significant in the ANCOVA, Bonferroni adjusted pairwise comparisons were used to examine the simple effects of smoking status within each BMI category. In the logistic regression, if the interaction was not significant it was removed from the model. If the interaction was significant then simple effects of smoking status within each BMI category were examined using odds ratios. All analyses were performed using SAS Version 9 statistical software (SAS Institute, Cary NC). Statistical significance was based on $\alpha = .05$.

Results

Among the 388 participants, 56% were under- or normal weight (BMI ≤ 24.9 kg/m²) and 44% were overweight or obese (BMI ≥ 25.0 kg/m²). 50% of the underweight/normal weight and 58% in the overweight/obese groups continued smoking during pregnancy. The comparison of demographic and baseline smoking characteristics between continued smokers versus abstainers are shown in Table 1. Women who continued smoking during pregnancy were younger, less educated, more likely to be multiparous, single, and not have private insurance. Compared to those who abstained from smoking during pregnancy, those who continued smoking had started smoking at a younger age, smoked more cigarettes, and were less likely to have made a quit attempt prior to pregnancy.

Table 2 examines birth outcomes among smokers and abstainers by maternal BMI category. Late-pregnancy smoking was associated with significantly lower birth weights (3203 ± 36 g vs. 3457 ± 40 g $p < .001$), an 80% decrease in the odds of macrosomia, and a 50% reduction in the odds of primary cesarean delivery, independent of BMI. Compared to underweight/normal weight women, infants born to overweight/obese women had significantly greater mean birthweight (3410 ± 35 g vs 3250 ± 30 g; $p < .001$) and a 3.6 fold increase in the odds of macrosomia. Underweight/normal weight and overweight/obese women did not differ on rates of preterm birth or primary cesarean delivery.

Two significant interactions of smoking status and maternal BMI category were noted. There was a significant interaction of maternal pre-pregnancy BMI and smoking status on gestational age at delivery ($p = .03$). Among underweight/normal weight gravidas, maternal smoking resulted in delivery at an earlier gestational age than in those who abstained (38.4 ± 0.2 vs 39.5 ± 0.2 weeks, respectively, $p = .002$); however among overweight/obese gravidas there was no difference in gestational age at delivery between abstainers and smokers (39.1 ± 0.2 vs 39.4 ± 0.2 weeks, respectively, $p = .99$). Additionally, there was a significant interaction of maternal BMI and smoking status on admission to the NICU ($p = .04$). Among underweight/normal weight women, neonates of smokers were more likely than neonates of abstainers to be admitted to the NICU (OR=1.7; 95% CI 0.6 - 5.1) while among overweight/obese women neonates of smokers were less likely than neonates of abstainers to be admitted to the NICU (OR=0.3; 95% CI 0.1 - 1.3). Although neither odds ratio was significantly different from 1.0, the opposing direction contributed to a significant moderating effect of maternal BMI. The most common indication for NICU admission was prematurity and/or respiratory distress in all groups (Table 3). We next examined the NICU length of stay among the four groups. Although the overall numbers are too small for a statistical analysis, the neonates born to those women continuing to smoke throughout pregnancy, appeared to have longer median lengths of stay in the NICU and wider ranges of length of stay regardless of maternal BMI.

Discussion

Maternal overweight/obesity appears to moderate the effect of smoking on gestational age at delivery and admission to the NICU, but not other perinatal outcomes. Gestational age at delivery is differentially affected where underweight/normal weight smokers are more likely

to have earlier deliveries than abstainers while among overweight/obese women there was no difference by smoking status. Additionally, BMI and smoking status interact differentially on rates of NICU admission; with infants born to underweight/normal weight smokers having significantly increased risk of NICU admissions than those born to abstainers while among infants born to overweight/obese women the direction was reversed with infants born to smokers realizing lower rates of NICU admissions than abstainers. These results are consistent with our hypothesis that maternal BMI would have a moderating effect but discordant in the direction of that effect. That is, we anticipated that overweight/obese status would exacerbate adverse effects associated with continuing to smoke during pregnancy while the results suggest an attenuation where overweight/obese smokers did not have earlier deliveries and greater NICU admissions, compared to overweight/obesity abstainers as was observed among the underweight/normal weight women.

Despite both groups delivering at “term”, there is an increased emphasis on differentiating “early” versus “full” term deliveries with early term deliveries defined as those occurring between 37 0/7 through 38 6/7 weeks and full term deliveries occurring between 39 0/7 through 40 6/7 weeks gestation.²⁰ This differentiation has evolved with the growing recognition that neonatal outcomes, especially those related to respiratory morbidity, vary within term deliveries. For example, neonatal mortality decreases from 3.9 per 1,000 live births at 37 weeks gestation to 2.5 per 1,000 live births at 38 weeks gestation compared to 1.9 per 1,000 live births at 40 weeks.²¹ Additionally, respiratory distress syndrome or transient tachypnea of the newborn was much more likely to occur in those neonates born by elective cesarean delivery at 37 compared to 39 weeks gestation (8.2% vs 3.4%, $p < 0.001$).²² Thus, there may be clinical significance to the moderating effect of maternal BMI on earlier deliveries in smokers.

To our knowledge, this is the only study reported evaluating the co-occurrence of maternal smoking and obesity on cesarean delivery and NICU admission rates. Although we found no moderating effect of BMI on cesarean delivery rates among smokers and abstainers, NICU admission rates were affected by BMI and smoking status. Whereas neonates born to underweight/normal weight smokers were more likely to require NICU admission, those born to overweight/obese smokers were less likely to be admitted to the NICU. The reason behind this is unclear but may be related to gestational age at delivery and/or birthweight. Both maternal underweight status and maternal smoking are risk factors for intrauterine growth restriction, increasing the likelihood of needing NICU care at birth. Although the numbers are small, of those neonates who were admitted to the NICU, there was a trend for those born to underweight/normal weight smokers to have longer lengths of stay than those born to overweight/obese smokers and all abstainers.

Our results from the main effects model are consistent with the published literature. Maternal smoking during pregnancy is a risk factor for lower birthweights and preterm delivery.^{6,23,24} On the other hand, obesity in pregnancy is associated with higher rates of macrosomia and cesarean delivery.^{10,11} We have previously shown, in a smaller cohort that compared to women who quit smoking during pregnancy the neonates of those who continue smoking have lower birth weights and are more likely to be small for gestational

age. In that analysis, there was also a trend towards earlier gestational ages at delivery, an increased risk of preterm birth, and higher rates of admission to the NICU.¹⁶

Obesity and smoking, as adverse health behaviors, often coincide, and are commonly overrepresented among disadvantaged populations. Data from the National Health and Nutrition Examination Survey (NHANES) between 2005-2008 indicates that 42% of women with less than a high school degree are obese (compared to 23% who hold a college degree).²⁵ Likewise, women with low levels of educational attainment are at particularly high risk of smoking and are less likely to quit once they initiate smoking.²⁶ Approximately 20% of obese individuals are current smokers.²⁷ In non-pregnant adults, the co-occurrence of obesity and tobacco use is associated with an up to 5-fold increased risk of all-cause and circulatory or cardiovascular disease mortality over either condition alone.^{27,28} Similarly, among pregnant women, those who are morbidly obese (BMI ≥ 40 kg/m²) are more likely to smoke and to continue smoking during pregnancy compared to women with a BMI < 25 kg/m².^{29,30} Limited data from prior studies supports the conclusion that the interaction of obesity and smoking modifies perinatal outcomes. Rates of smoking-associated small-for-gestational age neonates were higher in women with a prepregnancy BMI < 25 compared to ≥ 25 kg/m².³¹ In another study, smoking was protective against the development of preeclampsia among underweight, but not overweight and obese gravidas.³² We are aware of only a single study also evaluating the co-occurrence of obesity and smoking on preterm delivery. Voigt et al showed higher rates of preterm birth in underweight and obese non-smokers compared to normal weight smokers. Across all BMI groups, smokers had an increased rate of preterm birth compared to abstainers.²⁹ Finally, breastfeeding rates among women who quit smoking during pregnancy are lower in overweight/obese compared to underweight/normal weight postpartum women.¹⁵

These results should be interpreted with caution pending replication. Rather than being seen as beneficial for smokers to also be overweight or obese, these results need to be viewed in the context of the growing obesity epidemic. Although increasing BMI resulted in longer gestations in smokers, the longer term consequences are not explored here. With larger numbers, differences in cesarean delivery and macrosomia may be seen. Increasing rates of cesarean delivery are associated with rising rates of abnormal placentation in subsequent pregnancies including cesarean scar pregnancy and morbidly adherent placenta which are associated with significant maternal morbidity and mortality.³³ Additionally, macrosomic fetuses are at increased risks of childhood obesity and metabolic syndrome, further perpetuating the obesity epidemic.^{11,34,35} Unfortunately, obesity and maternal smoking are overrepresented among disadvantaged women of childbearing age. Long term adverse consequences may further exacerbate the growing health disparities of disadvantaged women. Just as maternal smoking has a protective effect against preeclampsia,⁵ the possible beneficial effect of maternal overweight/obesity and/or smoking does not outweigh the multiple medical and obstetrical risks associated with these risk factors during pregnancy.

Although this study provides useful information on the interaction of two common pregnancy comorbidities, there are limitations that should be addressed. This is a secondary analysis of previously collected information. The study sample was modest; therefore, the absence of some interactions may be the result of inadequate statistical power. It is also

important to note the heterogeneity in the study groups. The women in this study were prospectively enrolled over a time period of 11 years in multiple primary studies. Due to the nature of the previous studies, all women were smoking at the time of conception. The smoking group consists of women that were smoking at their last prenatal visit and included women who continued smoking throughout pregnancy as well as those who were in relapse prevention studies and resumed smoking; therefore, the duration and volume of exposure varied between women.

In conclusion, these results further expand our previous work on perinatal outcomes and maternal smoking status during pregnancy. Maternal smoking interacts with prepregnancy BMI to effect gestational age at delivery and rates of NICU admission. This data provides useful information as we counsel patients about their modifiable risk factors and pregnancy outcome. Addressing the over-representation of these risk factors in disadvantaged populations could help to improve health disparities.

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Table 1

Baseline demographics and smoking characteristics

	<u>Late Pregnancy Smoking Status</u>			<i>P</i> value
	Overall	Abstainer (n=180)	Smoker (n=208)	
<i>Demographics</i>				
Age, years	24.5 ± 5.2	25.5 ± 5.2	23.6 ± 4.9	<.001
Caucasian, %	95	97	94	.26
Education, %				<.001
> 12 years	29	42	18	
12 years	47	47	47	
< 12 years	24	11	34	
Primigravida, %	60	67	55	.01
Married, %	25	31	20	.02
Private insurance, %	30	41	20	<.001
BMI, kg/m ²	26.0 ± 6.6	25.6 ± 6.5	26.3 ± 6.7	.35
Overweight or obese, %	44	39	47	.13
<i>Smoking Characteristics</i>				
Age first started smoking cigarettes	15.2 ± 3.1	16.1 ± 3.0	14.4 ± 3.0	<.001
Cigarettes per day pre-pregnancy	16.6 ± 9.3	12.5 ± 7.4	20.2 ± 9.3	<.001
% Attempted to quit pre-pregnancy	70	79	62	<.001

BMI = body mass index

Results are reported as mean ± standard deviation unless otherwise noted.

p-values derived from t-tests for continuous measures and chi-square test for categorical measures.

Birth outcomes of continued smokers versus abstainers in a cohort of women smoking at the time of conception

	Underweight + normal weight (n = 219)			Overweight + obese (n = 169)		P value				
	Abstainer (n = 109)		Smoker (n = 110)	Abstainer (n = 71)		Smoker (n = 98)	smoking status*	BMI*	interaction	Odds ratio ^f
Gestational age at delivery, weeks²	39.5±0.2 ^a	38.4±0.2 ^b	39.4±0.2 ^a	39.1±0.2 ^{ab}	.11	.03				
Preterm birth, % ³	2.8±1.7	12.6±3.8	5.6±3.0	8.3±3.1	.68	.19				
Birthweight², grams⁴	3348±47	3152±46	3566±57	3254±48	<.001	.20				
Low birth weight, % ⁴	1.5±1.2	2.0±1.3	1.6±1.4	1.2±1.0	.71	.84				
Macrosomia, % ⁵	7.1±2.5	1.5±1.1	20.4±5.5	6.4±2.5	.001	.76				
Smoking status										
BMI										0.2 (0.1–0.6)
NICU admission, %⁶	6.9±2.7	11.2±3.3	10.9±4.1	3.9±2.0	.36	.04				3.6 (1.7–7.7)
Smoking status among under/normal weight										1.7 (0.6 - 5.1)
Smoking status among overweight/obese										0.3 (0.1 - 1.3)
Primary cesarean delivery, %³	19.9±4.2	12.9±3.4	29.8±6.0	14.0±3.7	.20	.41				0.5 (0.3 – 0.9)
Smoking status										

Tabled values are least square means and standard errors for continuous outcomes and estimated predicted probabilities and standard errors for dichotomous outcomes.

For gestational age, means sharing a common letter do not differ significantly from one another.

* From the main effects model.

^f Reported odds ratios are for smokers vs abstainers and overweight/obese vs underweight/normal weight.

² Covariates include smoking status at intake, parity and quit attempts prior to pregnancy.

³ Covariates include smoking status at intake and parity.

⁴ Covariates include smoking status at intake, gestational age at delivery and education.

⁵ Covariates include smoking status at intake and gestational age at delivery.

⁶ Covariates include smoking status at intake.

Table 3
Percent of NICU admissions due to prematurity and/or respiratory distress and length of stay among NICU admissions in smokers and abstainers by maternal BMI category

BMI Category	Smoking status	N	% Premature/respiratory distress	Median, days	Interquartile range
Underweight/normal weight	Abstainer	7	86	2	1-5
	Smoker	13	76	6	2-35
Overweight/obese	Abstainer	7	71	4	1-6
	Smoker	4	100	4.5	2-11