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PREDICTORS OF ADVERSE EVENTS AMONG PREGNANT SMOKERS EXPOSED IN A NICOTINE REPLACEMENT THERAPY TRIAL

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Abstract

OBJECTIVE—To determine the contribution of randomization to nicotine replacement therapy (NRT), socio-demographic and psychosocial factors, and pregnancy and medical history to serious perinatal adverse events among pregnant smokers.

STUDY DESIGN—Retrospective review of all medical records for participants in the *Baby Steps Trial*. Data abstracted from 157 records was combined with baseline characteristics for logistic regression modeling of serious adverse events, adjusting for covariates.

RESULTS—Serious adverse events occurred in 17% (9/52) and 31% (33/105) of participants in the control and NRT arms, respectively. Black race, adverse pregnancy history, and use of analgesic medication during pregnancy were significant predictors (p-values =0.02, 0.04, and 0.01, respectively). Remaining covariates, including randomization to NRT, were not statistically significant.

CONCLUSION—While race, poor pregnancy history, and use of analgesics were associated with serious adverse events, randomization to NRT during pregnancy was not a significant factor. Further research is needed to examine the safety of analgesic medications during pregnancy.

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Keywords

Nicotine replacement therapy in pregnancy; smoking and preterm birth; smoking in pregnancy

INTRODUCTION

Smoking during pregnancy, one of the most important modifiable causes of adverse pregnancy outcomes in the United States, has been associated with spontaneous abortion, fetal demise, premature rupture of membranes, preterm birth, low birthweight, and perinatal mortality.[1–3] It is estimated that eliminating smoking during pregnancy would reduce infant mortality by 5% [4] and singleton low birthweight by 10%. [5] Despite awareness of the health consequences of smoking during pregnancy, at least half of women who smoke will continue to do so throughout pregnancy.[6] Based on data from the general population, the most successful smoking cessation programs combine both behavioral and pharmacological methods, with the addition of nicotine replacement therapy (NRT) nearly doubling long-term success rates.[7] Given that 60% of women will attempt to quit smoking during their pregnancy, but only a quarter of these women will be successful [8], the use of NRT to assist pregnant women with smoking cessation is an attractive option. Although existing evidence suggests that NRT use during pregnancy is not more harmful to the fetus than smoking itself [9–12], theoretical concerns are supported by animal models of nicotine's neurotoxicant effects. [13] Further, while several smoking cessation studies have evaluated NRT use during pregnancy, the results have been affected by poor participant compliance with NRT and multi-modal intervention strategies. [14–16]

We recently conducted a randomized, open label study (The *Baby Steps Trial*) of cognitive behavioral therapy (CBT) alone versus CBT + NRT among pregnant smokers. [17] *Baby Steps* demonstrated that the addition of NRT to CBT increased the rate of smoking cessation during pregnancy nearly three-fold, from 8% to 24%. However, recruitment was suspended early when an interim analysis found a higher rate of adverse perinatal outcomes in the NRT + CBT arm than in the CBT-only arm. Although the initial intent was to enroll 300 women in a 2:1 randomization scheme favoring the intervention group, only 181 women were enrolled. There were differences in the baseline characteristics between the two arms involving factors that could be related to adverse perinatal events. Final analysis showed no statistically significant difference in adverse events between the two arms after controlling for prior preterm birth. Furthermore, women with an adverse event had a mean cotinine value of 189.3 versus 140.8 for those who did not have an adverse event ($p = 0.85$).

We propose that the increased incidence of adverse events in the NRT group was due to differences in predisposing baseline factors and not to the pharmacological intervention. Cigarette smoking is often clustered with several social stressors and unhealthy behaviors which in turn, are also associated with poor pregnancy outcomes. Women who smoke are more likely to be of lower socioeconomic status, have lower educational attainment and suffer from low self-esteem. [18] Data from the National Health Interview Survey indicates that cigarette smoking aggregates with alcohol use, marijuana use, and other illicit substance use. [19] Furthermore, several studies have demonstrated a significant association between smoking and psychosocial distress (stress, depression, and anxiety) among women.[20–22] Given the well-known associations of smoking with adverse perinatal outcomes like preterm birth and low birthweight, we sought to determine the relative contribution of randomization to nicotine replacement therapy, socio-demographic characteristics, health status and medication use, and psychosocial stressors to adverse perinatal events among pregnant smokers.

MATERIALS & METHODS

The *Baby Steps Trial*, approved and monitored by the institutional review boards of all participating institutions, enrolled pregnant smokers between 13 – 25 weeks gestation from 14 clinical sites in Durham, Raleigh, and Fayetteville NC, between May 2003 through August 2005. One hundred eighty-one women were enrolled in the study, with 59 in the CBT-only arm and 122 in the NRT + CBT arm. Serious adverse events included preterm birth < 37 weeks, term low birthweight < 2500 g, preeclampsia, placental abruption, placental previa, neonatal intensive care unit (NICU) admission, fetal demise, and neonatal/infant death. Ten women in the CBT-only arm had at least one serious adverse event compared to 34 women in the NRT + CBT arm.

We performed a retrospective review of all prenatal and hospital records for study participants. Data collected through medical record abstraction included insurance status, detailed obstetric and medical history, detailed antenatal history including sexually transmitted infections, illicit substance use, medication use, and compliance with prenatal care. For those women who had had a prior pregnancy, poor pregnancy history was defined as at least one pregnancy affected by preterm birth, low birthweight or growth restriction, fetal death, preeclampsia, or placental abruption. Medication usage during pregnancy – prescription and over-the-counter drugs – included the following categories: antibiotics, anticoagulants, anti-hypertensive agents, respiratory agents, anti-convulsants, hyperglycemic agents, thyroid medications, gastrointestinal medications, psychiatric medications, and analgesia or pain management. Attendance to prenatal care was assessed using the Adequacy of Prenatal Care Utilization (APNCU) Index [23], a 4-level Likert variable that considers both the timing of initiation of prenatal care and the ratio of observed to expected number of prenatal visits with regards to gestational length.

Psychosocial stressors including perceived stress and coping skills, self-esteem, and depression were measured at baseline entry into the *Baby Steps Trial*. The Rhode Island Stress and Coping Inventory (*RISCI*) is a validated 10-item, 5-point Likert measure of perceived stress and coping items. [24] Using a 7-point Likert scale to assess pregnancy-related self esteem, participants were asked to rate the extent to which the pregnancy had made her feel 1) good about herself as a person, and 2) bad about herself as a person. Depressive symptoms were measured by the Center for Epidemiologic Studies Depression Scale (*CES-D*) which is a 10-item, 3-point Likert measure of frequency of depressive symptoms in the past week.[25]

Our primary objective was to examine the randomization-arm effect on incidence of adverse event, controlling for a number of clinically meaningful baseline covariates. Because the total number of women with adverse events was small (42 women), it is only as a secondary objective that we describe the set of baseline covariates that were predictive of adverse event incidence. Nineteen candidate predictors were considered. Baseline socio-demographic characteristics included maternal age, race (African American/non-African American), education (less than high school/high school or greater), partner status (presence or absence of a romantic partner), and employment (any employment /no employment). Other baseline characteristics included average number of cigarettes smoked per day, psychosocial stress (continuous), coping skills (continuous), self-esteem (7-item Likert), and depression (continuous). Medical and psychosocial history included history of depression (yes/no), history of anxiety (yes/no), history of drug or alcohol use (yes/no), history of sexually transmitted infections (yes/no), and adverse obstetric history. Adverse obstetric history was analyzed as a 2 degree of freedom categorical variable with the following 3 levels: no prior pregnancy, adverse history, no adverse history. Candidate predictors from the current pregnancy included study randomization arm, prenatal care adequacy (4-level Likert scale), use of analgesic medications during pregnancy (yes/no), and use of psychiatric medications (yes/no) during pregnancy.

The predictors of incidence of adverse events were analyzed both univariately and multivariately. Logistic regression modeling was used to calculate the p-value for the effect of each candidate predictor variable separately. Building on the model further, multivariate modeling was performed in a stepwise backwards elimination process. That is, all 19 candidate variables were included in the preliminary model and stepwise backwards elimination was used to remove variables with p-values greater than 0.50. The traditional removal from the model of all variables with p-values > 0.05 “violates every principle of statistical estimation and hypothesis testing,” as described by renowned biostatistician Frank Harrell. [26]

RESULTS

Although 181 women were enrolled in the original study, 10 had missing birth outcome data due to participant withdrawal or loss to follow-up. Of the remaining 171 women, 157 had complete records available for abstraction: 52 in the CBT-only arm and 105 in the NRT + CBT arm. Forty-two participants had at least 1 serious adverse perinatal event (9 in the CBT-only arm and 33 in the NRT + CBT arm). Preterm birth was the most common adverse event (32 of 42 participants) and was attributable to 13 of the 16 NICU admissions. There were 5 cases of clinically diagnosed preeclampsia (2 in the CBT-only arm and 3 in the NRT+CBT arm) and 4 cases of term low birthweight (all in NRT+CBT arm). There were 4 cases of placental abnormalities in the NRT + CBT arm. There were 5 perinatal losses, which included 1 first trimester miscarriage or embryonic demise, 2 perinatal deaths due to extreme prematurity at 23 and 25 weeks gestation, and 2 unexplained near-term perinatal deaths.

Table 1 describes the univariate effects of the 19 candidate predictors by incidence of adverse events, with dichotomization of continuous variables for purposes of presentation only. Serious adverse events occurred more frequently among African American women as compared to non-African American women (44% vs. 21%, $p = 0.004$). Also, women with a history of poor pregnancy outcome were more likely to have an adverse event as compared to those without such a history or those for whom this was their first pregnancy (52% vs. 20% vs. 16%, $p < 0.001$). There were no differences in the remaining covariates.

Table 2 describes the results of the final logistic regression model with odds ratios and corresponding 95% confidence intervals and p-values. A two-sided of 0.05 was used to assess the covariate-adjusted arm effect; p-values for the other predictors are provided for completeness only and not for delineation of statistical significance. Using the backward stepwise regression approach for multivariate modeling as previously described, 9 covariates were eliminated from the final logistic regression analysis: baseline coping, psychiatric medication usage, baseline cigarettes usage, baseline self esteem, employment status, partner status, history of sexually transmitted infections, history of illicit substance use, and history of anxiety. Study randomization arm (CBT alone vs. CBT + NRT) was not a statistically significant risk factor for adverse perinatal events with an odds ratio of 2.38, 95% confidence interval (CI) [0.91, 6.25] and p-value of 0.08. The odds of an African American woman having an adverse event were 3.15 times higher than the odds for a non-African American woman, with 95% CI [1.18, 8.40] and p-value 0.02. Use of analgesic or pain medications during pregnancy was also associated with adverse events, with an odds ratio of 2.63 [1.02, 6.81] and p-value of 0.04. Adverse pregnancy history was the strongest predictor of adverse events, with a p-value of 0.01; specifically, women with no prior history of adverse event and women for whom this was the first pregnancy both had a predicted incidence of adverse events of 17%, while the women with a prior history of adverse event had a predicted incidence of 44%.

In an attempt to determine whether concomitant smoking and NRT use contributed to adverse perinatal events, a subgroup analysis of participants in the CBT + NRT arm was performed. Adherence data, or actual use of NRT, was available for 93 of the 105 participants in the CBT

+ NRT arm. Among the women who had a serious adverse event, 16 of 28 (57.1%) reported using NRT and smoking for at least 1 day as compared to 31 of 65 women (47.7%) who did not have a serious adverse event.

COMMENT

Although there was an increased incidence of adverse perinatal events among women randomized to the intervention arm than among those in the control arm, randomization to nicotine replacement therapy for smoking cessation does not appear to be the attributable risk factor. In univariate and multivariate analysis, poor obstetric history and African American race were the strongest predictors of adverse perinatal events. Both traits are well-known risk factors for adverse pregnancy outcomes [27,28] and were more prevalent among participants in the intervention arm than in the control arm. The imbalance in baseline characteristics of our study population was possibly due to the 2:1 randomization scheme combined with early study closure. An unanticipated finding was the association between analgesic medications and adverse perinatal events. Although opioid narcotics are known to cause respiratory and neurologic depression in the fetus or neonate, such medications when used appropriately during pregnancy, are not a recognized risk factor for adverse perinatal events such as preterm birth and low birthweight. Among the 38 women who used any analgesic medication during their pregnancy, 22 used narcotics such as percocet, vicodin, and fioricet and 2 were on chronic methadone maintenance therapy. The remaining 14 women used over-the-counter agents such as non-steroidal anti-inflammatory drugs and acetaminophen or prescribed agents such as muscle relaxants. While such agents do cross the placenta and could plausibly be contributors to adverse perinatal events, it is possible that the use of analgesic medications is a confounder or proxy for some other high-risk behavior that was not identified in this analysis.

A recent review article, focusing more on the long-term developmental neurotoxicant effects of nicotine in animal studies, staunchly opposes the use of NRT during pregnancy. [13] The author claims that no studies have conclusively documented that NRT during pregnancy is successful for smoking cessation, has a better success rate than non-pharmacologic approaches, and is safe. Short-term data has shown that NRT use during pregnancy is no more harmful than nicotine from smoking. [10,12] While previous trials of NRT in pregnancy have not been powered for testing safety outcomes, no significant patterns or trends have raised concerns. [16,29] Wisborg's and Oncken's trials of NRT vs. placebo both demonstrated a statistically significant *increase* in mean birthweight among those in the NRT arm relative to the placebo arm (186 gm and 337 gm, respectively) but unfortunately neither showed efficacy for smoking cessation. Alternatively, the *Baby Steps Trial*, which combined NRT with behavioral therapy, clearly demonstrated the effectiveness of NRT for smoking cessation during pregnancy and showed that the addition of NRT was better than a non-pharmacologic approach alone for cessation. [17] However, *Baby Steps* did not show any improvement in birthweight and actually raised questions regarding the risk of adverse perinatal events associated with NRT, as previously described. Although all were randomized controlled trials, it is important to note the significant differences among the three studies that could impact the interpretation of the results. Wisborg's study, which randomized women to nicotine or placebo patch, was conducted in Denmark where the population is quite homogeneous and the incidence of adverse perinatal events is much lower than in the US. For example, the incidence of preterm birth in 2004 in Denmark was 6.3% compared to 12.5% in the US. [30,31] Wisborg et al. did not report their prior preterm birth rates while Oncken's study population had a prior preterm birth rate of 18% compared to that in *Baby Steps* of 26%. Furthermore, in Oncken's study of nicotine or placebo gum, more than 50% of study participants were Hispanic and 7% were non-Hispanic Black as compared to *Baby Steps* where 24% of participants were African American and less than 10% were Hispanic. Finally, the mean number of cigarettes smoked prior to pregnancy was 13 in Wisborg's study compared to 18 and 19 in Oncken's study and *Baby Steps*,

respectively. Given the well-documented racial disparity in adverse perinatal events with non-Hispanic Black women having higher rates of adverse outcomes as compared to non-Hispanic White and Hispanic women, the potential differences in exposure from nicotine gum vs. patch, and the differences in “nicotine addiction” as measured by cigarettes smoked at baseline, comparisons of these trials on both efficacy and safety is challenging.

Our trial was not powered to study the safety of NRT during pregnancy; however, we were interested in examining whether inappropriate use of NRT, i.e. concomitant smoking and NRT use, contributed to adverse perinatal events, as this is one hypothesized causal pathway. [13] While our limited subgroup analysis cannot be used to confirm or refute the concern for risk of adverse perinatal events associated with concomitant smoking and NRT use, it does support the importance of aggressive counseling on appropriate NRT use and possibly biologic measurement of nicotine levels in pregnant women using NRT.

We performed a rigorous review of all available clinical documentation, which provided a comprehensive list of potential covariates for examining the role of NRT in adverse perinatal outcomes. Previous similar studies have primarily described their adverse events in the context of a clinical trial but have not delved further into possible causal relationships. Retrospective chart review for data collection relies on the accuracy of documentation by physicians, nurses, and clerical staff as well as the truthfulness in disclosure by pregnant women. While patient self-report is generally accurate for conditions such as diabetes or hypertension, there may be under-reporting of conditions such as depression, substance use, and sexually transmitted infections which we included in this analysis. Finally, while our overall sample size was relatively small due to lack of complete records or unavailability, our sample population represents an ethnically diverse group of women with varied education and income, allowing for generalization to other diverse populations of pregnant smokers.

Although we were concerned by the interim analysis results which led the Data & Safety Monitoring Board to recommend suspension of participant recruitment, we were reassured by the combination of results from the final outcomes of the *BabySteps Trial* [17] and this secondary analysis. While randomization to the NRT-containing study arm was not a statistically significant contributor to adverse events, the odds ratio point estimate and wide confidence interval suggest a possible effect. Evaluating the safety of NRT with regards to short-term perinatal outcomes as well as long-term neurotoxicant effects on human development requires a large sample population and measurement of cognitive functioning of children exposed to NRT *in utero*. Although reassuring, our results should serve as a guide to assist investigators designing and implementing additional studies to clarify further the potential risks and benefits of NRT use during pregnancy. The SNAP trial, which is a large-scale randomized trial of NRT during pregnancy being conducted in the UK, will provide useful insight into this potential safety concern as it will follow the offspring up to 2 years of age. [32]

Women who smoke tobacco represent a high-risk population with significant socioeconomic, psychosocial, and environmental stressors and often have concomitant “unhealthy” lifestyles such as co-morbid illnesses or illicit substance use. These same factors are known contributors to the multi-factorial etiology of adverse perinatal outcomes. While it is unlikely that either smoking or NRT use alone functions as an isolated cause of adverse perinatal outcomes, further research is needed to determine the safety and benefit of NRT use during pregnancy.

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Table 1
Probability of Adverse Events by Candidate Predictors Among Pregnant Smokers

Characteristic	N	% Adverse Events	p-value ^a
Randomization			
CBT	52	17%	0.06
NRT+CBT	105	31%	
Age			
Less than or equal to 25	78	23%	0.07
Greater than 25	79	30%	
Race			
African American	38	44%	0.004
Non-African American	119	21%	
Education			
Less than High School	45	22%	0.05
High School or greater	112	37%	
Employment			
Employed	74	25%	0.78
Unemployed	83	27%	
Partnered			
No Partner	50	30%	0.53
Partner	107	25%	
Obstetric History			
1 st pregnancy	24	16%	<0.001
Healthy pregnancy history	99	20%	
Adverse pregnancy history	34	52%	
History of Depression			
Yes	43	30%	0.55
No	114	25%	
History of Anxiety Disorder			
Yes	19	42%	0.11
No	138	24%	
History of Drug or Alcohol Use			
Yes	35	31%	0.48
No	122	25%	

Characteristic	N	% Adverse Events	p-value ^a
History of Sexually Transmitted Infection			
Yes	38	25%	0.44
No	119	31%	
Adequate prenatal care index			
Index of 1 or 2	38	18%	0.06
Index of 3 or 4	119	29%	
Baseline # cigs/day			
Less than or equal to 9	67	28%	0.82
Greater than 9	90	26%	
Baseline CESD/depression score (median)			
Less than or equal to 13	75	27%	0.68
Greater than 13	82	27%	
Baseline self-esteem			
Less than or equal to 5	88	27%	0.58
Greater than 5	69	26%	
Baseline stress			
<=15	76	24%	0.42
>15	81	30%	
Baseline Coping			
<=20	75	27%	0.83
>20	82	27%	
Analgesic medication use during pregnancy			
Yes	38	36%	0.11
No	119	23%	
Psychiatric medication use during pregnancy			
Yes	32	31%	0.52
No	125	25%	

CBT = cognitive– behavioral therapy, NRT = nicotine replacement therapy, CESD = Center for Epidemiologic Studies Depression Scale

^aP-values are from Wald tests in logistic regression models containing only one predictor. Continuous predictors were analyzed as continuous variables but are dichotomized in this Table for the purposes of presentation.

Table 2

Covariate-adjusted Odds Ratios for Association of Candidate Predictors with the Serious Adverse Events

Predictor	Denominator: Numerator of Odds Ratio	Odds Ratio	95% Confidence Interval	p-value ^a
Randomization arm	NRT : CBT	2.38	0.91 – 6.25	0.08
Maternal age	5-unit increase ^b	1.18	0.80 – 1.75	0.41
Education	Did not complete HS: completed at least HS	2.05	0.75 – 5.60	0.16
Race	African-American : Non-African American	3.15	1.18 – 8.4	0.02
Baseline stress	5-unit increase ^b	1.83	0.92 – 3.67	0.08
Baseline CESD	5-unit increase ^b	0.68	0.44 – 1.05	0.08
Adequate prenatal care index (1=inadequate, ... , 4=adequate plus)	1-unit increase ^c	1.42	0.91 – 2.22	0.12
History of depression	Yes : No	1.78	0.69 – 4.61	0.23
Analgesic medication use during pregnancy	Yes : No	2.63	1.02 – 6.81	0.04
Adverse pregnancy history	Prior history : first pregnancy	3.84	0.90 – 16.35	0.02 ^d
	No prior history : first pregnancy	1.01	0.27 – 3.81	

CBT = cognitive– behavioral therapy, NRT = nicotine replacement therapy, HS = high school

^a P-values and odds ratios are from a multivariate logistic regression model.^b Odds ratios are for a 5-unit increase in this predictor^c Odds ratios are for a 1-unit increase in this predictor^d 2 degree of freedom test of difference among the 3 levels of “adverse pregnancy history”