The Effect of Active and Passive Household Cigarette Smoke Exposure on Pregnant Women With Asthma

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Background: The article was designed to estimate the effect of active and passive household cigarette smoke exposure on asthma severity and obstetric and neonatal outcomes in pregnant women with asthma.

Methods: We used a secondary observational analysis of pregnant women with mild and moderate-severe asthma enrolled in a prospective observational cohort study of asthma in pregnancy and a randomized clinical trial (RCT) comparing inhaled beclomethasone and oral theophylline. A baseline questionnaire detailing smoking history and passive household smoke exposure was given to each patient. Smoking status was confirmed in the RCT using cotinine levels. Data on asthma severity and obstetric and neonatal outcomes were collected and analyzed with respect to self-reported tobacco smoke exposure. Kruskal-Wallis and Pearson χ^2 statistics were used to test for significance.

Results: A total of 2,210 women were enrolled: 1,812 in the observational study and 398 in the RCT. Four hundred and eight (18%) women reported current active smoking. Of the nonsmokers, 790 (36%) women reported passive household smoke exposure. Active smoking was associated with more total symptomatic days ($P < .001$) and nights of sleep disturbance ($P < .001$). Among the newborns of active smokers, there was a greater risk of small for gestational age < 10th percentile ($P < .001$), and a lower mean birth weight ($P < .001$). There were no differences in symptom exacerbation or outcome between nonsmokers with and without passive household cigarette smoke exposure.

Conclusions: Among pregnant women with asthma, active but not passive smoking is associated with increased asthma symptoms and fetal growth abnormalities. *CHEST 2010; 137(3):601–608*

Abbreviations: ETS = environmental tobacco smoke; LBW = low birth weight; MFMU = Maternal-Fetal Medicine Units Network; OR = odds ratio; PROM = premature rupture of membranes; RCT = randomized clinical trial; SGA = small for gestational age

Asthma is a common medical complication of pregnancy, affecting 6% to 8% of women.[1,2] Both the prevalence and morbidity of asthma are increasing in the general population.[3] The literature has been inconsistent regarding the relationship between asthma and adverse pregnancy outcomes. Increased risks of low birth weight (LBW), small for gestational age (SGA), and preterm delivery have been reported with asthma.[4-8] Larger studies, however, have identified fewer significant adverse obstetric outcomes.[1,9,10]

A multicenter prospective observational cohort study performed by the Maternal-Fetal Medicine Units Network evaluated the relationship between asthma severity and maternal and fetal morbidity among pregnant women with asthma and matched controls.[11] This study demonstrated a strong relationship between asthma severity and exacerbation during pregnancy, as well as associations with nonpulmonary pregnancy outcomes, including cesarean delivery, preeclampsia, gestational diabetes, and

preterm birth.[12] Oral corticosteroid use was also associated with an increased incidence of preterm birth and LBW, but not SGA.[13]

Cigarette smoking is known to aggravate asthma.[14] Smoking is independently associated with both prematurity and intrauterine growth restriction,[15,16] as well as fetal and neonatal mortality.[17,18] A review of US national linked birth and infant death data for the 1997 birth cohort reported a prevalence of maternal smoking of 13.2%. The incidence of neonatal death was 40% higher among smokers, even after adjusting for confounding demographic variables.[19] The effect of cigarette smoking on perinatal outcome is also dose dependent. Neonatal mortality associated with smoking increased from 22% to 68% between the lowest and highest exposure groups.[19] The impact of smoking on pregnancy is usually underestimated, as maternal history underreports this exposure.[12]

Much less is known regarding the effect of passive environmental tobacco smoke (ETS) exposure on obstetric outcomes. Studies of ETS have revealed relatively modest effects on birth weight and length.[20,21] There are few data available regarding the effects of ETS exposure on pregnant patients with a hyperresponsive respiratory disorder such as asthma. The

goal of this investigation was to determine the effect of active and passive household ETS exposure on asthma severity and obstetric and neonatal outcomes in women with asthma.

MATERIALS AND METHODS

This is a secondary analysis of pregnant women with mild, moderate, or severe asthma enrolled in two previously reported studies sponsored by the National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute.[11,12] The first was a multicenter prospective observational cohort study, and the second was a prospective randomized clinical trial (RCT) comparing inhaled beclomethasone and oral theophylline for the treatment of moderate asthma in pregnancy.[22] The studies were undertaken simultaneously by the participating centers of the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network, with recruitment occurring between December 1994 and February 2000. The severity was stratified based on the 1993 National Asthma Educational Program Working Group Report on Asthma and Pregnancy.[14] The observational cohort included 906 women with mild asthma and 906 with moderate-severe asthma. The proportion of women who smoked (any in the past week) was prospectively balanced with the cohorts in the observational study (19% in both groups). In the RCT, women with moderate asthma were assigned to treatment with inhaled beclomethasone (n = 199) or oral theophylline (n = 199). Women with moderate asthma were offered entry into the observational cohort only if they declined the RCT. Patients in both studies were recruited by the same study nurses, and the same clinicians were involved in the patient management of both cohorts. Exclusion criteria for both studies included fetal demise, multiple gestation, gestational hypertension, congenital anomalies, pulmonary disease other than asthma, gestational age ≥ 26 weeks, or planned delivery elsewhere. Written informed consent was obtained from all participants. Institutional review board approval was obtained at all institutions.

Each patient completed a questionnaire at baseline detailing personal smoking history and passive household ETS exposure. The questionnaire asked: "Number of cigarettes smoked, per day, in the last week." If the answer was "1 or more," the patient was classified as a smoker. If on follow-up assessments the patient answered the above question with "1 or more," the patient was recategorized as an active smoker. Information on the pack-year history was not collected. Passive ETS exposure was defined by a single yes/no question that read: "Does anyone else in the patient's household smoke?" Smoking status was confirmed in the RCT by measuring urinary cotinine levels at randomization. Obstetric outcomes obtained by chart review included the occurrence of preterm birth, preterm premature rupture of the membranes (PROM), preeclampsia, gestational diabetes, chorioamnionitis, placental abruption, oligohydramnios, and cesarean delivery. Neonatal outcomes included birth weight, SGA (defined as < 10th percentile),[23] fetal sepsis, neonatal intensive care unit admission, transient tachypnea of the newborn, necrotizing enterocolitis, and intraventricular hemorrhage. Infant deaths included both stillbirths and neonatal demises.

In both studies, maternal asthma status was regularly evaluated with spirometry. FEV_1 measurements (> 4 h after bronchodilator use) were performed at enrollment and monthly thereafter. Information regarding symptom frequency was collected at each study visit from a symptom log diary, including nights with asthma symptoms, nights that asthma interfered with sleep, days that asthma interfered with activity, and asthma medication use. Asthma exacerbations were defined as symptoms severe enough

to result in (1) hospitalization, (2) an unscheduled office visit, (3) an ED visit, or (4) treatment with oral corticosteroids. Study visits were scheduled monthly in the observational trial and biweekly in the RCT. Symptom frequency data were collected for the time period since the patient's last study visit.

Data on asthma severity and obstetric and neonatal outcomes were analyzed with respect to self-reported cigarette smoking and household ETS. The Biostatistics Center of George Washington University analyzed the data using SAS 8.2 statistical software (SAS Institute; Cary, NC). Differences between the groups were compared using odds ratios (ORs) with 95th percentile CIs. Kruskal-Wallis and Pearson χ^2 statistics were used for comparison of continuous and categorical variables, respectively, in Tables 1, 2, and 3. Each application of these tests was to assess the hypothesis that there is no difference between the three smoking categories. Nominal statistical significance was defined as a $P < .05$. The Spearman correlation coefficient was used for analysis of the relationship between cotinine and subjective measures of asthma severity for women in the RCT only. The Wilcoxon P test was used to assess the relationship of cotinine as a continuous variable with dichotomous obstetric and neonatal outcome variables in Table 4.

Results

A total of 2,210 women with asthma were enrolled: 1,812 in the prospective observational cohort and 398 in the RCT (Fig 1). Eighty-seven patients were lost to follow-up (3.9%). Four hundred eight (18%) women reported current active smoking. The active smokers reported a median number of six cigarettes smoked per day, with a maximum of 40. Of the nonsmokers, 790 (36%) reported passive household ETS exposure. The remaining 1,011 women (46%) reported that they were nonsmokers and had no household ETS exposure. Information on active or passive ETS exposure was missing on a single patient. There were significant demographic and social differences between the three groups (Table 1). Smokers were more likely to be white and to report marijuana or cocaine use and less likely to have private insurance. The nonsmokers with household ETS exposure were younger than the women in either of the other two groups. These demographic differences remained significant

when smoking exposure was stratified by asthma severity classification (data not shown).

Table 2 presents subjective and objective measures of asthma severity. Smokers had significantly more symptomatic days, nights of sleep disturbance, and days of restricted activity. Nonsmokers with passive household ETS exposure had fewer symptomatic days or nights and fewer days of restricted activity than did the nonsmokers without ETS exposure, but these differences were not statistically significant. There were no significant differences between the total number of asthma exacerbations or hospitalizations between the smoking and nonsmoking groups. Nor were there any significant differences in the spirometric measures during pregnancy. A model of asthma exacerbations was constructed with the following covariates: asthma severity class, passive smoking, active smoking, passive smoking/asthma class interaction, and active smoking/ asthma class interaction. The only significant term in the model was the asthma severity class, indicating that passive and active smoking or their interactions with asthma status did not make a difference.

A comparison of obstetric and neonatal outcomes is presented in Table 3. Women with asthma who were also current smokers had significantly more frequent SGA < 10th percentile and higher perinatal mortality. There were 10 (2.6%) perinatal deaths among the active smokers (eight stillbirths and two neonatal deaths). Among nonsmokers with passive household ETS exposure, there were six (0.8%) perinatal deaths (five stillbirths and one neonatal death), whereas the nonexposed nonsmokers had 12 (1.2%) perinatal deaths (six stillbirths and six neonatal deaths). When the perinatal mortality data are divided by asthma severity, the sample sizes are too small for meaningful analysis; however, the mortality rates remain about the same for each smoking exposure group between the women with mild (4 [1.0%], 3 [1.0%], and 4 [2.4%]) and moderate/severe asthma (8 [1.4%], 3 [0.7%], and 6 [2.6%]). Birth weight was

Table 1—Demographic and Social Characteristics

Characteristic	Nonsmokers/No Household ETS Exposure[a] (n = 1,011)	Nonsmokers/Household ETS Exposure (n = 790)	Smokers (n = 408)	P Value[b]
Age, mean ± SD	24.4 ± 5.9	21.5 ± 5.0	23.7 ± 5.6	< .001
Race				< .001
African-American	579 (57)	514 (65)	162 (40)	
White	293 (29)	196 (25)	234 (57)	
Hispanic	120 (12)	67 (8)	6 (1)	
Other	19 (2)	13 (2)	6 (1)	
Private insurance	196 (19)	62 (8)	25 (6)	< .001
Marijuana use	13 (1)	24 (3)	41 (10)	< .001
Cocaine use	3 (0.3)	4 (1)	17 (4)	< .001
BMI (mean ± SD)	27.8 ± 7.9	27.7 ± 7.8	27.4 ± 7.7	.806

Data reported as No. (%) unless otherwise stated. ETS = environmental tobacco smoke.
[a]Data unavailable for one patient.
[b]Kruskal-Wallis and Pearson χ^2 tests used to assess the hypothesis that there is no difference between the three smoking categories.

Table 2—Objective and Subjective Symptoms of Asthma

	Nonsmokers/No Household ETS Exposure[a] (n = 1,011)	Nonsmokers/Household ETS Exposure (n = 790)	Smokers (n = 408)	P Value[b]
Total symptomatic days, mean ± SD	69.3 ± 63.0	63.5 ± 59.5	78.8 ± 66.9	< .001
Total nights sleep disturbance, mean ± SD	39.2 ± 50.5	36.5 ± 50.8	48.4 ± 59.0	< .001
Total days restricted activity, mean ± SD	23.4 ± 40.1	21.8 ± 39.0	26.8 ± 41.8	.006
Asthma exacerbation during study, n (%)	219 (23)	146 (19)	68 (17)	.062
Hospitalization, n (%)	54 (6)	43 (6)	16 (4)	.485
Percentage predicted FEV_1 at baseline, mean ± SD	93.4 ± 14.1	94.0 ± 14.7	92.6 ± 13.9	.296
Percentage predicted FEV_1 < 80% across pregnancy, n (%)	174 (17)	128 (16)	70 (17)	.836

See Table 1 for expansion of the abbreviation.
[a]Data unavailable for one patient.
[b]Kruskal-Wallis and Pearson χ^2 tests used to assess the hypothesis that there is no difference between the three smoking categories.

significantly less ($P < .001$) for current smokers of one to nine cigarettes per day (2,994 ± 733 g) or ≥ 10 cigarettes per day (2,955 ± 684 g) compared with nonsmokers with (3,107 ± 665 g) or without (3,191 ± 692 g) passive household ETS exposure. Current smokers with asthma had lower rates of preeclampsia (7%) than either nonsmokers with (13%) or without (12%) passive household ETS exposure. The Spearman correlation coefficient for the relationship between birth weight and the number of cigarettes reportedly smoked per day was significant (-0.11; $P = .03$). Both preeclampsia (OR, 0.61; 95% CI, 0.40-0.94) and SGA (OR, 2.44; 95% CI, 1.61-3.72) remained significantly related to active maternal smoking, even after controlling for asthma severity at enrollment and race.

Cotinine levels were available for 387 of the 398 patients in the RCT. Cotinine levels were highest among the 62 active smokers (1,109 ± 652 ng/mL; mean ± SD). Women who reported smoking one to nine cigarettes per day had cotinine levels of 1,107 ± 630 ng/mL (n = 32), while those who reported smoking 10 or more cigarettes per day had levels of 1,110 ± 686 (n = 30). The Spearman correlation between the number of cigarettes reported smoked and the cotinine levels was 0.24; $P = .05$. The mean cotinine level for the nonsmokers who reported passive household ETS exposure (n = 144) was more than twice as high (99 ± 315 ng/mL) as the non-smokers (n = 181) without household exposures (40 ± 188 ng/mL).

The serum cotinine levels were significantly higher ($P < .001$; Kruskal-Wallis) among the smokers compared with the nonsmokers with or without passive ETS exposure. The Spearman correlation coefficient demonstrated a significant association between cotinine levels and days of restricted activity (r = 0.11; $P = .03$), but no significant association with symptomatic days (r = 0.03; $P = .55$) or nights with sleep disturbances (r = 0.04; $P = .43$). There was a negative correlation between an increasing cotinine level and birth weight (r = -0.11; $P = .03$). There were significant differences in cotinine levels between women with and without an SGA infant and in those with oligohydramnios (Table 4). The relationship between

Table 3—Obstetric and Neonatal Outcomes

Characteristic	Nonsmokers/No Household ETS Exposure (n = 972)	Nonsmokers/Household ETS Exposure (n = 760)	Smokers (n = 391)	P Value[a]
Delivery < 37 wk	153 (16)	119 (16)	74 (19)	NS
Delivery < 32 wk	29 (3)	25 (3)	17 (4)	NS
Oligohydramnios	62 (6)	56 (7)	18 (5)	NS
Abruption	8 (0.8)	12 (2)	5 (1.3)	NS
Preeclampsia	113 (12)	102 (13)	29 (7)	.01
Perinatal death	12 (1)	6 (0.8)	10 (3)	.04
PROM	110 (11)	97 (13)	59 (15)	NS
SGA < 10th percentile	50 (5)	54 (7)	46 (12)	< .001
Birthweight, mean ± SD	3191 ± 692	3107 ± 665	2977 ± 712	< .001

Data reported as n (%) unless otherwise stated. Obstetric and neonatal outcome data unavailable for 87 patients. NS = not significant; PROM = premature rupture of membranes; SGA = small for gestational age. See Table 1 for expansion of the other abbreviation.
[a]Kruskal-Wallis and Pearson χ^2 tests used to assess the hypothesis that there is no difference between the three smoking categories.

Original Research

Table 4—Relationship Between Cotinine (ng/mL) as a Continuous Variable and Obstetric and Neonatal Outcomes in the Randomized Clinical Trial[22]

Characteristic	Outcome Present, N; Cotinine Means (SD)	Outcome Absent, N; Cotinine Means (SD)	Wilcoxon P Test for Significant Differences in Cotinine Levels, ng/mL
Asthma exacerbations on study	85; 203 (459)	290; 251 (542)	0.293
Asthma-related hospitalizations on study	24; 173 (386)	351; 245 (532)	0.338
Delivery < 37 wk	66; 294 (590)	309; 229 (509)	0.547
Delivery < 32 wk	15; 119 (298)	360; 245 (531)	0.557
Oligohydramnios	21; 36 (153)	354; 252 (536)	0.025
Preeclampsia	31; 187 (452)	344; 245 (531)	0.540
PROM	51; 285 (604)	324; 233 (511)	0.688
Perinatal death			Only six cases of perinatal death in RCT
SGA < 10th percentile	27; 527 (719)	345; 220 (502)	0.035
Abruption			Only two cases of abruption in RCT

Cotinine levels not available for 23 patients. RCT = randomized clinical trial. See Tables 1 and 3 for expansion of the other abbreviations.

cotinine levels and perinatal death was not significant, but there were only six perinatal deaths in the RCT.

Discussion

Active smoking among women with asthma is associated with increased asthma symptoms, lower birth weights, an increased risk of SGA, perinatal death, and a decreased rate of preeclampsia compared with nonsmokers with or without passive household ETS exposure. The two studies on which this analysis is based represent the largest multicenter prospective studies of asthma during pregnancy. While active maternal smoking was associated with significant increases in all the subjectively reported measures of asthma severity, it was not associated with increased asthma exacerbations or hospitalizations compared with the nonsmokers with or without household ETS exposure. Nor were there differences in FEV_1 values; however, these women may be too young, with too few pack-years of smoking to show significant group differences.

The association between active maternal smoking and impaired fetal growth has been well described[15,16] and is also found in this cohort. There is also a lower risk of preeclampsia among active smokers, a phenomenon previously reported in obstetric populations without asthma. We did not find any increased adverse obstetric or neonatal outcomes among nonsmokers with passive household ETS exposure compared with unexposed nonsmokers. Studies of ETS exposure on birth outcomes revealed significant heterogeneity between studies, and their synthesized findings are not robust.[20] A more recent retrospective study using interview data from the parents of 18,297 children born in the United Kingdom in 2000 and 2001 revealed that household ETS exposure reduced adjusted birth weight by 36 g (95% CI − 5 to − 67 g) compared with infants with no maternal ETS exposure.[21] Eskenazi et al[24] measured cotinine levels in maternal serum in 3,529 pregnant women at 27 weeks gestation. Based on the cotinine levels, nonsmokers were divided into those exposed (2-10 ng/mL) and unexposed (< 2 ng/mL), while smokers were divided into tertiles based on cotinine levels. The infants of ETS exposed nonsmokers averaged 45 g less (P = .28) in birth weight compared with those of unexposed nonsmokers, while the infants of the active smokers averaged 78, 191, and 233 g less for the first, second, and third tertiles, respectively, which shows a significant inverse correlation between birth weight and serum cotinine levels (P < .001).[24] As in Eskenazi and coworker's investigation, even this current large cohort lacks adequate power to identify the 84-g-reduction in birth weight among the nonsmokers with ETS exposure as being statistically significant.
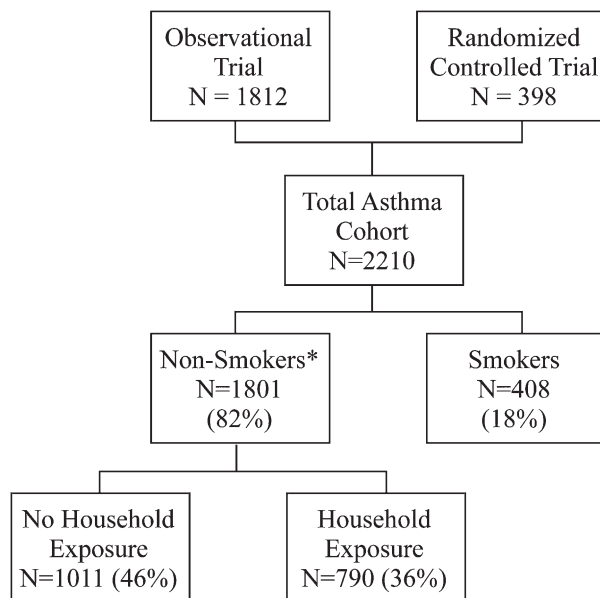
FIGURE 1. Enrollment of pregnant women with asthma from the observational cohort trial and the prospective RCT and their respective exposures to cigarette smoke. Data regarding ETS exposure were unavailable for one patient (*). ETS = environmental tobacco smoke; RCT = randomized clinical trial.

A weakness of this study is that the patients enrolled in the observational cohort study completed a questionnaire on household ETS exposure, but did not have cotinine levels measured. In obstetric patients, self-reported tobacco use is significantly underacknowledged. Only 66 women in the RCT (16.6%) reported active smoking; however, 116 women (29.1%) had simultaneously positive urinary cotinine levels.[22] Acknowledging the probability of underreporting, it is unlikely that results would be significantly altered. Since active smoking among women with asthma is associated with both increased asthma symptoms and reduced birth weight, the misclassification of active smokers into the nonsmoking cohorts would only serve to increase the number of maternal complications in those groups, making them more similar to the active smoking cohort.

Another limitation may be that the ETS exposure questionnaire focused only on the home. Among 4,687 prenatal patients in Sweden, 267 were nonsmokers passively exposed only at work. Passive exposure in the home did not affect pregnancy outcome; however, workplace exposure was weakly associated with preterm birth, although not LBW.[25] If occupational exposure of the nonsmoking/no-household-exposure group was significant, then that could have resulted in an overestimation of risk in the "nonexposed" nonsmokers. The restrictions against smoking in the workplace and public areas now prevalent in the United States should minimize the impact of nonhousehold exposure.

A final limitation is that all of the outcomes evaluated in this study were short term in nature. Five-year follow-up studies showed reductions in height but no differences in neurobehavior among children of ETS-exposed women.[26,27] More recently, researchers performed detailed neurodevelopmental assessments on children delivered of nonsmoking, nonexposed mothers (n = 96); nonsmoking but ETS-exposed mothers (n = 16); and mothers who smoked during the final 6 months of pregnancy (n = 21).[28] Both the smoking and ETS-exposed mothers had children with more severe psychologic problems, including attention deficit/hyperactivity disorder, aggressive behavior, defiance, and conduct disorders.

Because of the nature of the participating network centers, the patient population was heavily weighted toward single mothers, African-Americans, and those with subsidized insurance. This may limit the generalizability of the results, since African-American women have lower rates of smoking than most other racial and ethnic groups. However, this may also be a strength, as asthma is both more common and more severe among African-Americans and among patients of lower socio-economic status.[29,30]

The current study is reassuring in that passive household ETS exposure did not appear to have a significant impact on either subjective or objective measures of asthma severity during pregnancy. Further, passive ETS exposure did not appear to be associated with any increase in adverse obstetric or short-term neonatal outcomes. However, the strong evidence of an adverse effect of active cigarette smoking on maternal symptoms, fetal growth, and infant mortality among women with asthma as well as in the general obstetric population underscores the importance of this public health question. The lack of association between passive household ETS exposure and adverse outcomes may reflect an inadequate sample size to detect small differences between the exposed and unexposed nonsmokers, poor or inconsistent reporting of household ETS exposure, or the effect of noncaptured occupational ETS exposure. However, it may also reflect no actual biologic effect as the result of the household ETS exposure being below the threshold necessary to impact maternal or newborn outcomes. In the absence of a definitive answer to the above question, discouraging active smoking among women with asthma and emphasizing the National Asthma Educational Program recommendations to reduce or eliminate ETS exposure in both the home and workplace would seem to be the most appropriate clinical management approach.

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