

Association of Asthma Diagnosis, Severity, Symptoms, and Treatment With Risk of Preeclampsia

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OBJECTIVE: Existing studies relating asthma and preeclampsia provide conflicting results, perhaps due to differences in study populations, varying definitions of asthma, and inadequate control for confounding, particularly asthma medication use. This prospective study examines associations between aspects of asthma (diagnosis, severity, symptoms, and medication use) and risk of preeclampsia.

METHODS: A total of 1,708 pregnant women, of whom 656 had asthma diagnosis and 1,052 had no asthma diagnosis, were included in this analysis. Asthma symptoms, treatment, and severity were classified according to Global Initiative for Asthma guidelines. Hospital records were abstracted, and strict criteria were applied to classify women as preeclamptic based on National Heart, Lung, and Blood Institute guidelines.

RESULTS: There were 568 of 656 women with diagnosed asthma and 353 of 1,052 women without asthma diagnosis who had symptoms or took asthma medication during pregnancy. Separate adjusted logistic regression models were run for different measures of asthma status: 1) asthma diagnosis; 2) overall Global Initiative for Asthma severity; 3) Global Initiative for Asthma symptom and treatment steps; and 4) Global Initiative for Asthma symptom step and medication type. Women at increased risk of preeclampsia were those classified as Global Initiative for Asthma symptom step 3/4 compared with no symptoms (odds ratio 3.36, 95% confidence interval 1.24–9.14) and theophylline users (odds ratio 1.16 for every dose/month increase in use, 95% confidence interval 1.02–1.33). In con-

trast, neither a history of physician-diagnosed asthma nor Global Initiative for Asthma treatment step was associated with preeclampsia status.

CONCLUSION: Our findings suggest that women with moderate to severe asthma symptoms, regardless of asthma diagnosis or treatment, are at increased risk of preeclampsia compared with women with no symptoms. (Obstet Gynecol 2004;104:585–93. © 2004 by The American College of Obstetricians and Gynecologists.)

LEVEL OF EVIDENCE: II-2

Asthma is one of the most common chronic conditions affecting pregnancy and has been implicated as a risk factor for preeclampsia.^{1–7} From national surveys, it is estimated that between 4.0% and 8.0% of pregnant women have a history of asthma, and this proportion is expected to increase, because the prevalence of asthma has been rising dramatically among younger age groups.⁸

Existing studies examining the association between asthma and preeclampsia provide conflicting results. Some indicate that well-treated asthmatics are no more likely than nonasthmatics to develop preeclampsia,^{9–13} while others demonstrate an increased risk of preeclampsia among women diagnosed with asthma.^{1–7} Contradictory findings may be explained in part by different study populations, varying definitions of asthma, inconsistent criteria for preeclampsia classification, and inadequate control for confounding factors, particularly asthma medication use. Most previous studies simply considered “diagnosed” compared with “nondiagnosed” women. The difficulty with this is that, because of the episodic nature of the disease, some diagnosed women may not be symptomatic during pregnancy. In addition, because there are no definitive diagnostic criteria for asthma, there may be women who are undiagnosed but who have symptoms during pregnancy. Thus, distinctions made solely on the basis of asthma diagnosis can lead to considerable misclassification. In the few studies examining effects of asthma severity on preeclampsia, women were classified into an overall severity category

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based on both symptom frequency and medication use, making it difficult to disentangle underlying disease effects from treatment effects. Yet to date, no study has considered the effects of the components of severity (ie, symptoms and treatment) on preeclampsia, irrespective of asthma diagnosis. In this study, we examine the association of various aspects of asthma status, including diagnosis, overall severity, symptom severity, and treatment, on risk of preeclampsia. Differentiation of these various aspects of asthma may shed light on some of the discrepancies among findings of previous studies.

MATERIALS AND METHODS

Detailed study methods have been described previously in a report of the effects of asthma on intrauterine growth restriction (IUGR) and preterm delivery.¹⁴ Pregnant women receiving prenatal care from one of 56 private obstetric practices or 15 hospital or community clinics associated with 6 hospitals in Connecticut and south central Massachusetts were informed of the study in their providers' offices. Study personnel visited each office at least weekly to identify women who were interested in the study. These women were contacted and screened for eligibility. Women who intended to terminate their pregnancy, did not speak English or Spanish, were more than 24 weeks gestation at the time of enrollment, or had insulin-dependent diabetes mellitus were ineligible.

A total of 11,484 women were screened between April 1997 and June 2000. All women with a self-reported history of physician-diagnosed asthma ($n = 1,343$) and a simple random sample of approximately 1.5 nonasthmatic women for every asthmatic woman ($n = 2,070$) were invited to participate. Of these, 2,379 (69.7%) enrolled, 15.6% declined, 11.4% were not eligible at enrollment, 2.1% miscarried before enrollment, and 1.2% did not participate for other reasons. Stillborn fetuses, molar pregnancies, abortions, and multiple births were excluded from analysis ($n = 172$). Asthma status was not available for 2 additional subjects. This analysis is limited to 1,708 women for whom adequate information to determine preeclampsia status was available; of these, 1,052 had an asthma diagnosis, and 656 had no asthma diagnosis.

An initial interview conducted before 24 weeks of gestation collected information on self-reported maternal characteristics. All women with a history of physician-diagnosed asthma ($n = 656$) and a 10% random sample of nonasthmatics were followed up prospectively by telephone interview at 20, 28, and 36 weeks of gestation. A final interview was conducted, usually in the hospital, shortly after delivery. Informed consent was obtained

from all women before enrollment, and the human investigation committee at each participating hospital approved the study protocol.

A subject was considered to have asthma if she reported, at initial interview, physician-diagnosed asthma at any time in her life. Data on respiratory symptoms and medication use during the early part of pregnancy (less than 24 weeks) were collected at initial interview for all women. These women were provided with a calendar and asked to record symptoms and medication use throughout pregnancy. For women with a history of asthma and the 10% random sample of nonasthmatics, information was prospectively collected on symptoms and medication use at 20, 28, and 36 weeks of gestation. For the remaining women, data on symptoms and medication use for the latter part of pregnancy were collected at postpartum interview. Women were asked to report number of days of chest tightness, wheeze ("wheezing or whistling sounds when you breathe"), or persistent cough ("where you feel like you can't stop coughing for long periods of time") during each month of pregnancy, as well as night symptoms.

Because some women without a diagnosis of asthma had symptoms, and some women with a diagnosis did not have symptoms or take medications, all women who reported any symptom at least once during pregnancy were further classified into overall severity, symptom frequency, and treatment intensity using modified¹⁴ 2002 Global Initiative for Asthma guidelines.¹⁵ Symptom steps were defined as Step 1, Intermittent, symptoms 1–7 days per month or night symptoms less than 2 nights per month; Step 2, Mild Persistent, symptoms more than 7 days per month but less than every day per month, or night symptoms 2–7 nights per month; Step 3/4, Moderate/Severe Persistent, daily symptoms with frequent exacerbations and night symptoms more than 7 nights per month.

At each interview, women were asked to report all medications taken for respiratory symptoms or breathing problems, including the number of days in each month medication was taken and number of doses or tablets taken daily. Asthma medications were gleaned from these data and categorized according to drug class: 1) short-acting bronchodilators (short-acting β_2 -agonists or anticholinergics), 2) long-acting β_2 -agonists, 3) inhaled steroids, 4) leukotriene inhibitors, 5) theophylline, 6) chromones, or 7) oral steroids. Total doses of each class were calculated by multiplying the number of days by the doses per day for each month of pregnancy.

Medication use data were used to classify women into Global Initiative for Asthma treatment steps: Step 1, Intermittent, no daily controller medications, inhaled short-acting bronchodilators as needed to relieve symp-



toms; Step 2, Mild Persistent, 1 controller medication—inhaled glucocorticosteroid or theophylline or leukotriene modifier or chromone; Step 3, Moderate/Severe Persistent, 2 or more controller medications—inhaled glucocorticosteroid plus 1 or more of long acting inhaled β_2 -agonist, theophylline, leukotriene modifier, chromone, or oral glucocorticosteroid. Women were cross-classified by symptom step and treatment step to derive overall severity as described in the Global Initiative for Asthma guidelines.¹⁵

Monthly symptom, treatment, and overall severity steps were averaged over the number of months of pregnancy, rounding up to the next highest integer, to obtain an average score (“step”) for the entire pregnancy for each factor.

Hospital records for all index pregnancies were abstracted using a structured form by abstractors who were masked to exposure information. Antenatal blood pressure ranges, International Classification of Diseases, 9th Revision, diagnoses, and all maternal and infant medical problems were recorded. If the abstractor noted any indication of 1) at least 1 blood pressure reading 140 mm Hg or greater systolic or 90 mm Hg or greater diastolic; 2) a urine dipstick value of 1+ or higher; or 3) an International Classification of Diseases, 9th Revision, diagnosis indicating pregnancy-induced hypertension or preeclampsia, a more detailed supplemental abstraction was conducted in which all available blood pressure and urine protein readings from the prenatal care period, prior hospitalizations during pregnancy, and the delivery hospitalization (before or during labor and delivery and postpartum before discharge) were recorded. Strict criteria were applied to classify women as having preeclampsia based on guidelines from the National Heart, Lung, and Blood Institute Working Group on High Blood Pressure in Pregnancy:¹⁶ de novo hypertension (blood pressure of 140 mm Hg or greater systolic or 90 mm Hg or greater diastolic on 2 or more occasions at least 6 hours apart) beginning after 20 weeks of gestation, accompanied by proteinuria, defined as urine protein concentrations of 30 mg/dl or greater (dipstick value of 1+ or higher) from 2 or more specimens collected at least 4 hours apart or one or more urine dipstick values of 2+ or higher near the end of pregnancy or 1 or more catheterized dipstick values of 1+ or higher during delivery hospitalization or 24-hour protein of 300 mg or higher. Because of uncertain diagnosis, 498 women were excluded from the analyses for the following reasons: 1) preexisting hypertension determined by self-reported history of high blood pressure at home interview or one or more high blood pressure readings (140 mm Hg or greater systolic or 90 mm Hg or greater diastolic) recorded in the prenatal care chart before 20 weeks gestation or 2) some indication of hypertension but a defini-

tive diagnosis of preeclampsia could not be made (eg, urine protein values unavailable, prenatal blood pressure readings unavailable but antenatal range includes high values so we could not exclude preexisting hypertension). This analysis is limited to the 1,708 women for whom adequate information on preeclampsia was available. The overall study population (N = 2,206) and women included in these analyses (n = 1,708) had similar distributions of maternal characteristics.

Analyses focused on the relationships between preeclampsia and various aspects of asthma status or asthma diagnosis, overall severity, symptoms, and treatment. Unadjusted analyses examined the association between each asthma variable and preeclampsia. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for these associations were calculated from logistic regression models using PC-Statistical Analysis System 8.02 (SAS Institute Inc., Cary, NC). Models were built for each of the following exposures: 1) history of asthma diagnosis; 2) history of asthma diagnosis plus symptoms in the past 2 years; 3) overall Global Initiative for Asthma severity step; 4) Global Initiative for Asthma symptom step and Global Initiative for Asthma treatment step; and 5) Global Initiative for Asthma symptom step and medication use (by class of medication). Final models were chosen using a backward elimination strategy. Exposure variable(s) of interest were retained in all models. Other variables were retained if they were independent risk factors ($P < .10$) or if their removal resulted in an increase or decrease in the parameter estimates of the exposure variables of 10% or more. Covariates considered in the models included maternal race, age, prepregnancy body mass index (BMI), education, parity, and first trimester cigarette smoking. Additional analyses of the association among symptoms, treatment, and overall severity were stratified by asthma diagnosis.

RESULTS

Table 1 describes the study population. Only 11% of the women were less than 20 years of age, and 17% were 35 or older. The majority of women in this study were white (68%), whereas 18% were Hispanic, and 9% were African American. More than 85% of participants had at least a high school diploma. More than half of the women had a normal prepregnancy BMI; however, 33% were overweight or obese. Nearly 30% were nulliparous with no prior pregnancy, whereas 15% were nulliparous with a prior pregnancy. Approximately 17% reported smoking cigarettes in the first trimester of pregnancy.

Having a diagnosis of asthma was related to having symptoms or taking medication during pregnancy (data not shown). Of the 656 women with a history of physi-



Table 1. Unadjusted Associations Between Selected Characteristics of Study Population and Preeclampsia, Connecticut and South-Central Massachusetts, 1996–2001

	n*	Percent of total N	With preeclampsia (%)	Odds ratio	95% confidence interval
Total	1,708	100.0	3.5		
Maternal age					
Less than 20	182	10.7	6.0	Reference	
20–24	241	14.1	3.7	0.60	0.24–1.49
25–29	441	25.8	3.4	0.55	0.25–1.22
30–34	543	31.8	2.6	0.41 [†]	0.18–0.92
35 or older	301	17.6	3.3	0.53	0.22–1.28
Race					
White	1,175	69.0	2.8	Reference	
African American	139	8.2	8.6	3.25 [†]	1.64–6.44
Hispanic	316	18.6	4.1	1.49	0.77–2.86
Other	73	4.3	1.4	0.48	0.06–3.57
Education					
<High school	244	14.3	4.9	Reference	
High school graduate	288	16.9	3.5	0.70	0.30–1.64
Some college	406	23.8	3.7	0.74	0.34–1.61
College graduate	394	23.1	3.3	0.66	0.30–1.47
>College	375	22.0	2.4	0.48	0.20–1.15
Body mass index					
Underweight (<19.8)	234	13.8	1.7	0.46	0.16–1.32
Normal (19.8–26.0)	965	57.0	3.6	Reference	
Overweight (>26.0–29.0)	220	13.0	4.1	1.14	0.54–2.40
Obese (>29.0)	274	16.2	4.0	1.11	0.56–2.22
Parity					
Nulliparous, no prior pregnancy	464	27.2	7.8	Reference	
Nulliparous, with prior pregnancy	251	14.7	4.0	0.49 [‡]	0.24–1.01
Parous	991	58.1	1.3	0.16 [†]	0.08–0.30
Smoking during 1st trimester					
None	1,435	84.1	3.3	Reference	
≤10 cigarettes/day	217	12.7	4.2	1.25	0.61–2.59
>10 cigarettes/day	55	3.2	3.6	1.09	0.26–4.61

* Includes only women (n = 1,708) for whom diagnosis of preeclampsia was possible (definite yes or no); numbers may not sum to total due to missing data.

[†] $P < .05$

[‡] $.05 < P \leq .10$.

cian-diagnosed asthma, 568 (87%) had some symptoms during pregnancy. However, of the 1,052 women without a history of diagnosed asthma, 353 (33.6%) had symptoms during pregnancy.

Several maternal characteristics were associated with preeclampsia in unadjusted analyses (Table 1). Women over 20 years of age were less likely to have preeclampsia than those under 20; however, only those between 30 and 34 years of age were significantly less likely to be affected than those under 20 (OR 0.41, 95% CI 0.18–0.92). African-American women were more than 3 times as likely as white women to have preeclampsia (OR 3.25, 95% CI 1.64–6.44). Parous women were only 0.16 times as likely as nulliparous women with no prior pregnancy to have preeclampsia (95% CI 0.08–0.30); nulliparous women with at least one prior pregnancy were only half as likely as women with no prior pregnancy to have preeclampsia (OR 0.49, 95% CI 0.24–1.01). First trimes-

ter smoking, maternal education, and BMI were not associated with preeclampsia.

In unadjusted associations between asthma status and preeclampsia, neither a diagnostic history of asthma nor a diagnosis plus symptoms in the past 2 years was associated with preeclampsia (Table 2). Women classified as having an average overall Global Initiative for Asthma severity of Moderate Persistent, regardless of asthma diagnosis, were 2.38 times more likely than women with no symptoms or medication use to have preeclampsia (95% CI 1.00–5.71). Those classified as Severe Persistent were not at increased risk of preeclampsia. Women who had asthma symptoms every day (Global Initiative for Asthma symptom step 3/4) were 2.75 times more likely to have preeclampsia than women with no symptoms during pregnancy (95% CI 1.24–6.08). None of the Global Initiative for Asthma treatment steps were associated with preeclampsia. The-



Table 2. Unadjusted Associations Between Asthma Status, Symptoms, Medication Use, Severity, and Preeclampsia, Connecticut and South-Central Massachusetts, 1996–2001*

	n*	Percent preeclampsia	Odds ratio	95% confidence interval
History of physician-diagnosed asthma				
No	1,052	3.2	Reference	
Yes	656	3.8	1.19	0.70–2.01
Diagnosis of asthma with symptoms in past 2 years				
No	1,128	3.3	Reference	
Yes	485	3.1	0.94	0.51–1.73
GINA severity step (mean across pregnancy)				
No symptoms or medication use	775	3.0	Reference	
Step 1: Intermittent	549	3.1	1.04	0.55–1.98
Step 2: Mild Persistent	227	4.4	1.51	0.71–3.21
Step 3: Moderate Persistent	103	6.8	2.38 [†]	1.00–5.71
Step 4: Severe Persistent	54	3.7	1.26	0.29–5.48
GINA Symptom step				
No symptoms	787	3.0	Reference	
Step 1: 1–7 days of symptoms, or night symptoms < 2 nights	577	3.1	1.02	0.55–1.90
Step 2: Symptoms > 7 but < every day, or night symptoms 2–7 nights	231	3.5	1.14	0.51–2.57
Steps 3 and 4: Symptoms every day	113	8.0	2.75 [‡]	1.24–6.08
GINA treatment step				
No treatment	1,303	3.3	Reference	
Step 1: Intermittent use of short-acting bronchodilator only	306	3.9	1.19	0.62–2.29
Step 2: One controller medication	77	3.9	1.19	0.36–3.91
Steps 3 and 4: Two or more controller medications	24	4.2	1.27	0.17–9.64
Asthma medication use				
Short-acting bronchodilator use				
No	1,314	3.4	Reference	
Yes	394	3.6	1.04	0.56–1.91
Long-acting bronchodilator use				
No	1,666	3.5	Reference	
Yes	42	2.4	0.68	0.09–5.00
Leukotriene inhibitor use				
No	1,702	3.5	Reference	
Yes	6	0.0	N/A	...
Chromone use				
No	1,691	3.5	Reference	
Yes	17	0.0	N/A	...
Theophylline use				
No	1,700	3.4	Reference	
Yes	8	25.0	9.61 [‡]	1.90–48.65
Oral steroid use				
No	1,671	3.5	Reference	
Yes	37	2.7	0.77	0.10–5.73
Inhaled steroid use				
No	1,585	3.5	Reference	
Yes	123	2.4	0.68	0.21–2.21

GINA, Global Initiative for Asthma.

* Includes only women (n = 1,708) for whom diagnosis of preeclampsia was possible (definite yes or no); numbers may not sum to total because of missing data.

[†] .05 < P ≤ .10.[‡] P < .05.

ophylline, although only used by 8 women, was associated with a large increase in the likelihood of preeclampsia (OR 9.61, 95% CI 1.90–48.65). Use of other asthma medications was not associated with preeclampsia.

In adjusted logistic regression models (Table 3) Global Initiative for Asthma symptom step and theophylline use remained associated with preeclampsia status. Neither history of physician-diagnosed asthma nor Global Initia-



Table 3. Adjusted Associations Between Asthma Status, Symptoms, Medication Use, Severity, and Preeclampsia, Connecticut and South-Central Massachusetts, 1996–2001*

	Odds Ratio	95% confidence interval
Model 1[†]		
History of physician-diagnosed asthma—ever		
No	Reference	
Yes	1.05	0.61–1.84
Model 2[†]		
Diagnosis of asthma with symptoms in past 2 years		
No	Reference	
Yes	0.83	0.44–1.56
Model 3[‡]		
GINA severity step (mean across pregnancy)		
No symptoms or medication use	Reference	
Step 1: Intermittent	1.00	0.51–1.91
Step 2: Mild Persistent	1.19	0.54–2.62
Step 3: Moderate Persistent	2.32 [§]	0.93–5.78
Step 4: Severe Persistent	1.56	0.34–7.12
Model 4[†]		
GINA symptom step		
No symptoms	Reference	
Step 1: 1–7 days of symptoms, or night symptoms < 2 nights	1.00	0.50–1.98
Step 2: Symptoms > 7 but < every day, or night symptoms 2–7 nights	0.98	0.40–2.41
Steps 3 and 4: Symptoms every day	3.36	1.24–9.14
GINA treatment step		
No treatment	Reference	
Step 1: Intermittent use of short-acting bronchodilator only	0.93	0.43–1.99
Step 2: One controller medication	0.86	0.22–3.29
Steps 3 and 4: Two or more controller medications	0.81	0.09–7.46
Model 5		
Medication type (mean doses per mo)		
Short-acting bronchodilator use	1.00	0.99–1.02
Long-acting bronchodilator use	0.99	0.94–1.04
Leukotriene inhibitor use	N/A	–
Chromone use	N/A	–
Theophylline use	1.16	1.02–1.33
Oral steroid use	0.14	0.01–1.55
Inhaled steroid use	0.98	0.95–1.01

GINA, Global Initiative for Asthma.

* Includes only women for whom diagnosis of preeclampsia was possible (definite yes or no) (n = 1,708); adjusted model n = 1,684 due to missing data.

[†] Controlling for race/ethnicity, parity, body mass index, age, and education.

[‡] Controlling for race/ethnicity, parity, body mass index, and education. Model 5 also contains symptom step variables; effect sizes similar to those shown in Model 4.

[§] 0.05 < P ≤ 0.10.

^{||} P < 0.05.

[¶] Controlling for race/ethnicity, parity, body mass index, age, and first trimester cigarette smoking.

tive for Asthma treatment step was associated, and Global Initiative for Asthma severity step 3 was essentially unchanged but no longer statistically significant. In Model 4, controlling for Global Initiative for Asthma treatment step, women in symptom steps 3/4 were more than 3 times as likely as women without asthma symptoms to have preeclampsia (OR 3.36, 95% CI 1.24–9.14). In Model 5, controlling for Global Initiative for Asthma symptom step and other confounders, theophylline use remained associated with preeclampsia (OR 1.16 for every dose per month increase in use, 95% CI 1.02–1.33).

Additional analyses (Table 4) examined the influence of asthma diagnosis on the relationships between asthma symptoms, treatment, and preeclampsia. Among women with a diagnosis and among women without a diagnosis of asthma, symptoms were associated with preeclampsia (respectively, OR 3.06, 95% CI 0.56–16.74; OR 4.51, 95% CI 0.83–24.54). Neither association reached statistical significance due to the reduced sample sizes in each subgroup. We also observed evidence of increased risk of preeclampsia in women with no asthma diagnosis, but with a Global Initiative for Asthma severity classification of Moderate Persistent (OR 5.11, 95%CI 0.91–28.88),



Table 4. Adjusted* Associations Between Symptoms, Medication Use, Severity and Preeclampsia, Stratified by History of Physician-Diagnosed Asthma, Connecticut and south-central Massachusetts, 1996–2001†

	No diagnosis (n = 1,035)		Asthma diagnosis (n = 649)	
	Odds ratio	95% confidence interval	Odds Ratio	95% confidence interval
Model 1				
GINA severity step (mean across pregnancy)				
No symptoms or medication use	Reference		Reference	
Step 1: Intermittent	0.91	0.37–2.24	1.64	0.31–8.61
Step 2: Mild Persistent	1.57	0.48–5.10	1.40	0.25–7.70
Step 3: Moderate Persistent	5.11 [‡]	0.91–28.88	2.70	0.44–16.65
Step 4: Severe Persistent	...	...	2.40	0.28–20.92
Model 2				
GINA symptom step				
No symptoms	Reference		Reference	
Step 1: 1–7 days of symptoms, or night symptoms < 2 nights	0.91	0.37–2.27	1.22	0.29–5.17
Step 2: Symptoms > 7 but < every day, or night symptoms 2–7 nights	1.55	0.47–5.05	0.67	0.12–3.57
Steps 3 and 4: Symptoms every day	4.51 [‡]	0.83–24.54	3.06	0.56–16.74
GINA treatment step				
No treatment	Reference		Reference	
Step 1: Intermittent use of short-acting bronchodilator only	1.28	0.15–10.92 [§]	1.10	0.40–3.04
Step 2: One controller medication			1.36	0.29–6.33
Steps 3 and 4: Two or more controller medications			1.60	0.14–18.60

GINA, Global Initiative for Asthma.

* Adjusted for race/ethnicity, parity, body mass index, age, first trimester cigarette smoking, and education.

† Includes only women for whom diagnosis of preeclampsia was possible (definite yes or no) (n = 1,708); adjusted model n = 1,684 due to missing data.

[‡] .05 < P ≤ .10.

[§] No treatment compared with Steps 1–4 combined.

although here too the stratified sample decreased precision in the estimate.

DISCUSSION

This study examined associations between preeclampsia and asthma diagnosis, overall severity, symptoms, and medication use in a large cohort of women followed up through pregnancy. Neither overall asthma severity nor having a diagnosis of asthma was associated with an increased risk of preeclampsia in these women. However, frequency of asthma symptoms (wheeze, persistent cough, and chest tightness) across pregnancy was associated with preeclampsia as defined following strict guidelines, controlling for treatment and medication use and other confounding variables. We also found that women taking theophylline were at increased risk of preeclampsia, controlling for symptoms, other medication use, and confounding factors.

This is one of the largest cohorts on which detailed respiratory symptom and medication information was prospectively collected throughout pregnancy. The study design enabled us to examine various aspects of asthma, including diagnosis, overall severity, symptoms,

and treatment, all defined according to Global Initiative for Asthma guidelines. A potential limitation of the study is the self-reported nature of symptom and treatment data. It is possible that some symptoms reported by women were actually normal physiologic changes of pregnancy rather than asthma symptoms, leading to misclassification of these unexposed women as exposed. This misclassification should be nondifferential with respect to the outcome and would result in a bias of effects toward then null, making it more difficult, rather than more likely, to detect an association. Although we did not obtain clinical confirmation of asthma diagnosis, we were able to examine the effects of asthma symptoms and medication use simultaneously, rather than classifying women simply as asthmatic or nonasthmatic based on a history of diagnosis. Because asthma severity is reported to change during pregnancy,¹⁷ it was classified based on symptom frequencies and medication use throughout pregnancy, rather than at a single point in time.

Fetal hypoxia has been suggested as a mechanism for the association between asthma and preeclampsia as well as between asthma and IUGR.^{18,19} Our findings suggest an association between preeclampsia and asthma that is



similar in magnitude to our previously observed association between IUGR and asthma in this same population.¹⁴ To determine whether the association between symptoms and preeclampsia was independent of IUGR status, we ran the adjusted models with preeclampsia as the outcome, controlling for IUGR (data not shown). In fact, IUGR was independently associated with preeclampsia (OR 3.35, 95% CI 1.67–6.72), but the addition of IUGR to the models did not appreciably change the observed association between asthma symptom step 3/4 and preeclampsia with and without IUGR, (respectively, OR 3.83, 95% CI 1.41–10.42 compared with OR 3.36, 95% CI 1.24–9.14).

Our findings indicate that having a self-reported diagnosis of asthma does not increase risk of preeclampsia; rather, it is having active asthma symptoms through pregnancy that increases risk. Results from prior studies examining the association between asthma diagnosis and preeclampsia have been conflicting. Seven of 12 studies showed an approximately 2-fold increased risk of preeclampsia for asthmatic women,^{1–7} whereas 5 of 12 showed no significantly increased risk^{9–13}; however, three of these^{9,12,13} had elevated point estimates similar to the significant studies. Two additional studies, including a recent large cohort study by the Maternal-Fetal Medicine Unit Network, showed no increased risk of preeclampsia for asthmatic patients whose severity was assessed early in pregnancy.^{10,11}

One explanation for discrepant findings may be differences in asthma “control” or symptom severity of enrolled patients. Studies with significant findings tended to enroll women with more severe, active asthma. For example, in 4 studies, patients with a diagnosis code for asthma were identified from hospital databases or medical registries;^{1,2,6,7} the other 3 studies identified active asthmatics seen in emergency rooms or pulmonary medicine.^{3–5} Among studies finding no association between asthma and preeclampsia, most enrolled less severe patients or actively managed them to avoid exacerbations during pregnancy. Dombrowski et al¹⁰ gave no indication of how asthma status was ascertained, and Mihrshahi et al⁹ enrolled self-reported asthmatics and compared them to nonasthmatics who had a partner or child with asthma. Schatz et al¹³ and Dombrowski et al¹¹ confirmed asthma status by clinical evaluation including spirometry, but prospectively controlled patients’ asthma to avoid exacerbations using a step therapy approach. Perlow et al¹² identified patients who had an asthma visit (active asthma) from a computerized database; although not statistically significant, they found increased odds of preeclampsia of greater than 4.0 in asthmatic compared with nonasthmatic patients.

Three studies^{4,11,12} attempted to determine whether asthma severity increased risk of preeclampsia, but only Dombrowski et al¹¹ used a classification based on clinical guidelines. These guidelines use symptom frequency and treatment intensity during the prior 4 weeks to group women into an overall severity category. We classified asthma severity based on the entire pregnancy. Despite these differences, our findings are consistent with those of Dombrowski: overall severity was not significantly associated with preeclampsia. This is likely due to aggressively managed asthmatics being placed in a higher severity category, even if they have few symptoms.

None of the prior studies was able to delineate symptom from treatment effects. Because we collected information on symptoms and medication use for each month of pregnancy and our study subjects had varying symptom and treatment combinations (eg, of 97 asthmatic women with daily symptoms, 14 used no medication, 43 took only bronchodilators, 26 used 1 controller medication, and 14 used 2 or more controller medications; of 16 nonasthmatic women with daily symptoms, 15 took no medication and 1 used only bronchodilators), we determined that frequent symptoms increased the risk of preeclampsia, independent of medication use. This effect was found among symptomatic women receiving treatment, but was even stronger among symptomatic women not receiving treatment.

Averaging symptom frequency over pregnancy might overlook some associations at a particular point in pregnancy, so we reanalyzed the data for each trimester. Third trimester analyses were similar to those averaged over the entire pregnancy. Theophylline use in the second and third but not first trimester was also associated with increased risk of preeclampsia. Finally, we considered whether maximal (as compared with average occurring in pregnancy) severity, symptom, or treatment step was associated with risk of preeclampsia, but found no evidence to support this. Thus, it seems that women who have only 1 month with near-daily symptoms are not at increased risk of preeclampsia compared with women with intermittent symptoms throughout pregnancy.

The finding that theophylline use increased risk of preeclampsia was somewhat unexpected. Three studies have previously examined this association: one found a decreased risk of preeclampsia among asthmatic women who took theophylline compared with asthmatic women who took sympathomimetic drugs¹; another found an increased risk of preeclampsia among asthmatic women taking theophylline compared with asthmatic women not taking theophylline or nonasthmatic controls⁵; and a third found no association between theophylline use and preeclampsia among actively controlled asthmatics.²⁰



Because of the small number of women using theophylline ($n = 8$), this finding could be a chance result.

Our findings suggest that women with moderate to severe asthma symptoms, regardless of asthma diagnosis or treatment, have an increased risk of preeclampsia compared with women with no symptoms. Taken together with previous findings that actively managed asthmatics have better outcomes than untreated asthmatics, our findings suggest that patients with asthma symptoms, with or without an asthma diagnosis, should be closely monitored during their pregnancies. Future research should attempt to confirm the finding of increased preeclampsia risk in women with asthma symptoms regardless of asthma diagnosis and investigate further the association between theophylline and risk of preeclampsia in a larger population of theophylline users.

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