

The relationship of asthma medication use to perinatal outcomes

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Background: Maternal asthma has been reported to increase the risk of preeclampsia, preterm deliveries, and lower-birth-weight infants, but the mechanisms of this effect are not defined.

Objective: We sought to evaluate the relationship between the

use of contemporary asthma medications and adverse perinatal outcomes.

Methods: Asthmatic patients were recruited from the 16 centers of the National Institute of Child Health and Human Development Maternal Fetal Medicine Units Network from December 1994 through February 2000. Gestational medication use was determined on the basis of patient history at enrollment and at monthly visits during pregnancy. Perinatal data were obtained at postpartum chart reviews. Perinatal outcome variables included gestational hypertension, preterm births, low-birth-weight infants, small-for-gestational-age infants, and major malformations.

Results: The final cohort included 2123 asthmatic participants. No significant relationships were found between the use of inhaled β -agonists ($n = 1828$), inhaled corticosteroids ($n = 722$), or theophylline ($n = 273$) and adverse perinatal outcomes. After adjusting for demographic and asthma severity covariates, oral corticosteroid use was significantly associated with both preterm birth at less than 37 weeks' gestation (odds ratio, 1.54; 95% CI, 1.02-2.33) and low birth weight of less than 2500 g (odds ratio, 1.80; 95% CI, 1.13-2.88).

Conclusions: Use of inhaled β -agonists, inhaled steroids, and theophylline do not appear to increase perinatal risks in pregnant asthmatic women. The mechanism of the association between maternal oral corticosteroid use and prematurity remains to be determined. (*J Allergy Clin Immunol* 2004;113:1040-5.)

Key words: Asthma, asthma medications, pregnancy, perinatal outcomes, prematurity, inhaled β -agonists, inhaled corticosteroids, theophylline, oral corticosteroids

Asthma might be the most common potentially serious medical problem to complicate pregnancy.¹ Several studies have reported increased incidences of preeclampsia, preterm birth, or lower birth weight in infants of asthmatic compared with nonasthmatic mothers.²⁻⁵ Two main potentially remedial mechanisms have been hypothesized to explain these observations⁶: (1) poor asthma control

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Abbreviations used

MFMU: Maternal Fetal Medicine Units
NICHD: National Institute of Child Health and
Human Development

leading to fetal hypoxia and (2) asthma medication. There are some data to support a relationship between poor asthma control, as defined by hospitalization^{7,8} or lower FEV₁ values⁹ and either lower birth weight^{7,8} or low ponderal indices.⁹

Most of the data regarding the safety of contemporary asthma medications during pregnancy have focused on congenital malformations,¹⁰ which have not generally been reported to be increased in infants of asthmatic mothers.^{2,4} Perlow et al⁵ reported increased incidences of low birth weight and preterm births among asthmatic gravidas treated with oral corticosteroids compared with noncorticosteroid-treated asthmatic participants. Stenius-Aarniala et al¹¹ reported an increased incidence of preeclampsia in oral corticosteroid-treated versus non-oral corticosteroid-treated patients. However, the effects of more severe or uncontrolled asthma could not be differentiated from the corticosteroid exposure in these studies.

Only 2 studies have evaluated these outcomes in pregnant patients receiving asthma medications while attempting to adjust for asthma severity or control. Schatz et al¹² reported perinatal outcomes in patients exposed between 1978 and 1990 to β -agonists (n = 667), inhaled corticosteroids (n = 149), theophylline (n = 429), and oral corticosteroids (n = 130). In this study only an independent association between oral prednisone use and preeclampsia was found. More recently, Bracken et al¹³ reported an increased risk of preterm birth in pregnant asthmatic patients treated with oral steroids (n = 52) or theophylline (n = 15) after controlling for demographic factors and asthma symptom frequency.

The National Institute of Child Health and Human Development (NICHD) Maternal Fetal Medicine Units (MFMU) Network Asthma Studies were designed to evaluate the relationships among asthma severity, control, and treatment during pregnancy and maternal and fetal morbidity in a large cohort of pregnant asthmatic patients and matched control subjects. Prior reports from this study have described the relationship of asthma severity to gestational asthma morbidity¹⁴ and perinatal outcome¹⁵ and the effects of inhaled beclomethasone compared with theophylline on asthma morbidity in pregnant patients with moderate asthma.¹⁶ The purpose of this report is to evaluate the relationships between contemporary asthma medication use and important perinatal outcomes while adjusting for other important risk factors and parameters of asthma severity-control.

METHODS

Patients in this report were asthmatic participants who completed either the NICHD MFMU Network asthma observational cohort

study^{14,15} or the NICHD MFMU Network randomized controlled trial of beclomethasone versus theophylline for moderate asthma during pregnancy.¹⁶ These studies were conducted at 16 centers of the MFMU Network of the NICHD, with recruitment from December 1994 through February 2000. Participants from both studies were drawn from the same network center populations, and both studies ran simultaneously from December 1995 through March 1999. During this time, patients with moderate asthma were first offered entry into the randomized controlled trial, and if they refused, then they were offered entry into the observational cohort study. Combining the populations to increase study power was thus believed to be appropriate, but analyses using only the observational cohort participants were performed as well.

In the observational cohort study, asthmatic patients with all levels of severity were enrolled and monitored, but management was determined by the patient's individual physician. The observational cohort study included 873 delivered participants with mild asthma, 814 with moderate asthma, and 52 with severe asthma. The proportion of participants who smoked was balanced between the mild and moderate-severe cohorts. In the randomized controlled trial only patients with moderate asthma were enrolled, patients were randomly assigned to treatment with inhaled beclomethasone or theophylline, and management was by study protocol.

The following methods were used in both studies. Case finding was performed by questioning all obstetric patients about having physician-diagnosed asthma. Informed written consent was obtained from all participants, and the study was approved by each institution's local institutional review board. Participants were excluded for known multiple gestations, intrauterine fetal demise, major congenital abnormalities, active pulmonary disease other than asthma, inability to schedule an ultrasound for gestational age confirmation, or gestational age of greater than 25 weeks and 6 days at intake.

Spirometry (>4 hours after the bronchodilator) was performed on all participants at enrollment. On each monthly study visit, an FEV₁ measurement and information regarding symptom frequency, asthma medication use, and the occurrence of asthma hospitalizations or unscheduled visits (physician office or emergency department) were obtained.

Medication exposure was defined as any use during pregnancy. The gestational age at the time of randomization was determined from the last menstrual period if it correlated with the first ultrasound. Dating was based on the first ultrasound if the last menstrual period estimate varied by greater than 7 days from the ultrasound gestational age estimate if the first ultrasound was performed at less than 20 weeks' gestation or greater than 14 days if the initial ultrasound was performed at or after 20 weeks' gestation. Perinatal data were obtained at postpartum chart reviews. Perinatal outcome variables included the following: (1) gestational hypertension; (2) preterm birth at less than 32 weeks' gestation; (3) preterm birth at less than 37 weeks' gestation; (4) low birth weight (<2500 g); (5) small for gestational age, defined as less than the 10th percentile birth weight for gestational age¹⁷; and (6) major malformations (including multiple malformation syndromes) defined at birth, as classified by an independent dysmorphology specialist (Kenneth Lyons Jones, MD, University of California, San Diego, School of Medicine) on the basis of descriptions by the attending pediatricians-neonatologists and blinded to medication treatment. Gestational hypertension was defined as 2 blood pressure measurements of 140/90 mm Hg or greater on at least 2 occasions (≥ 4 hours apart) at or beyond a gestational age of 20 weeks; a clinical diagnosis of preeclampsia, eclampsia, or HELLP (hemolysis, elevated liver, low platelets) syndrome; or both. Preterm births at less than 37 weeks' gestation were further classified as (1) associated with premature rupture of membranes, (2) indicated if induced or Cesarean section birth was the

result of fetal or maternal conditions other than premature rupture of membranes, (3) stillbirths, and (4) preterm labor if none of the above. Potentially relevant covariates included maternal parity, age, smoking, African American race, insurance status (private vs other), mean gestational FEV₁, and unscheduled asthma care (hospital, emergency department, or office) during pregnancy.

The Biostatistics Center of George Washington University maintained the data and performed the statistical analysis using SAS version 8.2 (SAS Institute, Cary, NC) statistical software. Univariate data were analyzed by means of χ^2 or Fisher analysis for dichotomous variables and by means of the Wilcoxon rank sum test for continuous variables. Multivariable analyses were performed by using logistic regression techniques. Two-tailed statistical tests were used for univariate analyses. Nominal statistical significance was set at a *P* value of less than .05 without adjustment for multiple comparisons, but outcomes with associations of borderline significance in univariate analyses (.05 < *P* < .10) were evaluated in multivariable analyses. Comparisons with less than 70% power to detect a doubling of the outcome compared with the nonexposed group are identified.

RESULTS

The final delivered cohort included 2123 asthmatic participants, 1739 from the observational cohort study and 384 from the randomized control trial (Table I). The participants ranged in age from 13 to 44 years (mean, 23.3 years), and more than 18% were smokers. Slightly more than half of the participants were primiparas, slightly more than half were African American, and almost one third experienced unscheduled asthma care during pregnancy.

No significant relationships were found between adverse perinatal outcomes and the use of inhaled β -agonists, inhaled corticosteroids, theophylline, or cromolyn-nedocromil, although power was inadequate for several outcomes in participants exposed to cromolyn-nedocromil (Table II). In addition, only inhaled corticosteroid and theophylline exposure provided adequate power to be evaluated for preterm birth at less than 32 weeks' gestation, and only inhaled corticosteroid exposure provided adequate power to be evaluated for major malformations. Oral corticosteroid use was associated with a significantly increased incidence of preterm birth at less than 37 weeks' gestation (*P* = .007) and an increased incidence of low birth weight of borderline significance (*P* = .082). Oral corticosteroid exposure (vs nonexposure) was associated with a significantly lower mean ($\pm$ SD) gestational age (37.4 $\pm$ 4.1 vs 38.0 $\pm$ 3.4 weeks, *P* = .010) and lower mean ($\pm$ SD) birth weight (3030 $\pm$ 698 vs 3158 $\pm$ 637 g, *P* = .008). After adjusting for relevant covariates (maternal parity, age, smoking, African American race, insurance status, previous preterm delivery, mean gestational FEV₁, unscheduled asthma care during pregnancy, and use of β -agonists, inhaled steroids, theophylline, and cromolyn-nedocromil), oral corticosteroid use was significantly associated with both preterm birth at less than 37 weeks' gestation (odds ratio, 1.54; 95% CI, 1.02-2.33) and low birth weight (odds ratio, 1.80; 95% CI, 1.13-2.88). Data analysis for the observational cohort

TABLE I. Characteristics of the observational, randomized controlled trial, and total asthma cohorts

Parameter	Observational	RCT	Total
N	1739	384	2123
Age range, y	13-44	14-42	13-44
(mean $\pm$ SD)	(23 $\pm$ 6)	(23 $\pm$ 6)	(23 $\pm$ 6)
Primipara, %	45.1	38.5	44.0
Smokers, %	18.8	16.9	18.4
African American race, %	55.5	62.5	56.8
Mean ($\pm$ SD) FEV ₁	94 $\pm$ 14	92 $\pm$ 14	93 $\pm$ 14
Patients with unscheduled asthma visits (hospital, ER, office), %	31.9	38.8	33.2

RCT, Randomized controlled trial.

participants only revealed findings similar to those above (data not shown).

Types of preterm births were compared in patients receiving and not receiving oral corticosteroids (Table III). No preterm stillbirths occurred in women exposed to oral corticosteroids. All other categories of preterm births were increased in women treated with oral corticosteroids compared with mothers not receiving these medications; the biggest difference was seen in the category of indicated preterm births. In the 16 exposed patients with indicated preterm deliveries, 7 were for fetal stress, 4 were for intrauterine growth restriction, 4 were for preeclampsia, and 12 were for one or more of those indications.

DISCUSSION

Asthma has been reported to complicate 7% of pregnancies,¹ making it probably the most common potentially serious medical problem to complicate pregnancy. Data regarding the effect of maternal asthma on pregnancy outcomes have been conflicting,⁶ but the largest retrospective study has shown that pregnancies in women with asthma are significantly more likely to be complicated by preeclampsia, preterm birth, or low birth weight, but not congenital malformations, compared with pregnancies in nonasthmatic women.⁴ The 2 main potentially remedial mechanisms of this effect, poor asthma control and asthma medication use, could require diametrically opposite interventions. If poor control is the mechanism, increased medication might be required, whereas if medications themselves are responsible, decreased or different medications might be required. The best data on this subject would come from a study addressing both possibilities simultaneously.

Schatz et al¹² performed a prospective study of 824 asthmatic patients followed between 1978 and 1990. In this study, in which asthma control was assessed on the basis of gestational spirometry and the occurrence of acute exacerbations, no independent relationships to adverse perinatal outcomes were found for inhaled β -agonists, inhaled corticosteroids, or theophylline. However,

TABLE II. Perinatal outcomes in asthmatic participants exposed and unexposed to asthma medications

Exposure	Percent incidence stratified by drug exposure										Total
	β-Agonists		Inhaled steroids		Oral steroids		Theophylline		Cromolyn-nedocromil		
	Yes*	No	Yes†	No	Yes	No	Yes	No	Yes	No	
N	1828	295	722	1401	185	1938	273	1850	60	2063	2123
Gestational hypertension	11.8	9.9	11.2	11.7	9.7	11.7	10.6	11.7	13.3	11.5	11.5
Preterm <32 wk	(3.3)	(3.4)	3.2	3.4	(3.8)	(3.3)	2.6	3.5	(3.3)	(3.3)	3.3
Preterm <37 wk	15.8	19.3	16.2	16.4	23.2‡	15.6	16.1	16.3	21.7	16.1	16.3
Low birth weight	13.5	15.2	13.0	14.1	17.9§	13.3	14.4	13.6	20.0	13.5	13.7
SGA	7.1	7.2	7.1	7.1	6.5	7.2	7.8	7.0	(16.7)	(6.8)	7.1
Major malformation	(2.0)	(2.0)	1.9	2.0	(2.2)	(2.0)	(1.5)	(2.1)	(3.3)	(1.9)	2.0

Values in parentheses have low power (<70% power to detect a doubling of risk) on the basis of the sample size of the smaller of the yes/no groups.

SGA, Small for gestational age

*Albuterol = 1753, salmeterol = 77, other = 66 (some patients used more than one specific β -agonist).

†Beclomethasone = 485, triamcinolone = 206, other = 78 (some patients used more than one specific inhaled glucocorticosteroid).

‡ $P = .007$.

§ $P = .082$.

TABLE III. Delivery status and exposure to oral corticosteroids*

Delivery status†	Not exposed (n = 1938)		Used oral corticosteroids (n = 185)	
	N	%	N	%
Term delivery	1635	84.4	142	76.8
Preterm (<37 wk)	303	15.6	43	23.2
PROM	92	4.8	12	6.5
Indicated	81	4.2	16	8.7
Preterm labor	113	5.8	15	8.1
Stillbirths	17	0.9	0	0.0

PROM, Premature rupture of the membranes.

* $P = .013$ for difference in distributions.

†See the Methods section for definitions of categories.

albuterol is the most commonly used short-acting β -agonist today (used by 96% of our patients who used short-acting β -agonists), but less than 25% of the participants in the prior study used albuterol. In addition, only 149 participants in that study used inhaled corticosteroids (mostly beclomethasone). The current study extends the observations to inhaled albuterol and to a larger number of patients using contemporary inhaled corticosteroids. Similar to the previous study, the current study was able to adjust for asthma severity-control and other potentially relevant covariates.

Schatz et al¹² did report an independent relationship between oral corticosteroid use and preeclampsia but not low birth weight or preterm birth. The current study found the opposite result: no increased risk of gestational hypertension but an increased risk of preterm and low-birth-weight infants associated with oral corticosteroid use.

Perlow et al⁵ reported similar findings, although their results were not adjusted for asthma severity-control. The current finding of both an increase in preterm and low-birth-weight infants, but not small-for-gestational-age

infants, suggests that the effect is on prematurity rather than intrauterine growth restriction. The reasons for the different results between the current study and those of the prior observational cohort study are unclear but could include differences between the 2 study populations in the clinical criteria used to diagnose gestational hypertension-preeclampsia, techniques for gestational age dating, asthma severity, or concomitant treatment (eg, theophylline), which has been reported¹⁸ to decrease the occurrence of preeclampsia, although it was insignificantly lower in the current theophylline-treated cohort.

Another large prospective cohort study of asthma and asthma medications in 873 pregnant women with a history of asthma and 449 additional pregnant patients with symptoms but no diagnosis has recently been published.¹³ Several of the findings in that study agreed with ours, including no increased risk of preterm or small-for-gestational-age infants with maternal use of short-acting bronchodilators (n = 529) or inhaled corticosteroids (n = 176). In addition, similar to our findings, maternal oral corticosteroid use was associated with an increased risk of preterm birth but not small-for-gestational-age infants. Although this relationship persisted after adjustment for asthma symptom frequency, residual confounding by factors associated with increased asthma severity could not be excluded. That study also found a significant independent relationship between theophylline use and preterm birth, although only 15 patients in the study used theophylline.

The mechanisms whereby oral corticosteroid use is independently associated with prematurity are not clear. Subclinical intra-amniotic infection has been associated with fetal inflammatory response syndrome and preterm delivery,¹⁹ and corticosteroids could potentially exacerbate such an intra-amniotic infection because of immunosuppression. Corticosteroid exposure appeared to increase the occurrence of indicated preterm deliveries to a greater degree than other preterm deliveries. Most of these involved fetal stress, intrauterine growth restriction, and/or preeclampsia. Fetal stress could plausibly be due to

acute or chronic maternal hypoxia associated with severe asthma. Intrauterine growth restriction could also be due to chronic hypoxia associated with uncontrolled asthma⁹ or be a direct effect of corticosteroids.²⁰ Preeclampsia has been previously reported to be increased in patients with asthma in general²¹ and asthma treated with oral corticosteroids in particular.^{11,12} Although this study tried to account for some aspects of asthma severity and control (monthly FEV₁ and acute episodes), these would be unlikely to fully account for disease severity or control in individual patients. It is therefore still not clear whether oral corticosteroids are the cause of the prematurity or rather serve as a marker for asthma severe or uncontrolled enough to be associated with prematurity through other mechanisms.

Although this is the largest prospective cohort study addressing a relationship between asthma medication use, severity-control, and perinatal outcomes, it did not have sufficient power to address specific congenital malformations. However, data for major malformations were reassuring for inhaled corticosteroids. This confirms other previously published data. First, as noted above, congenital malformations were not increased in asthmatic patients treated during the past 2 decades compared with the general Swedish population.⁴ Second, reassuring data for first-trimester exposures to beclomethasone (n = 395)²² and budesonide (n = 2534)²³ have been published.

This study has some important clinical implications. First, it suggests that contemporary inhaled β -agonists and inhaled corticosteroids can be safely used in the management of asthma during pregnancy, which conforms to current guidelines for asthmatic patients in general.²⁴ Second, it suggests that, if possible, asthma should be controlled without oral corticosteroids, which appropriate use of inhaled β -agonists and inhaled corticosteroids usually allows. However, for severe exacerbations, such as those that might be associated with viral infections, or if chronic asthma is severe in spite of other therapy, benefit-risk considerations still suggest that oral corticosteroids should be used. Severe asthma during pregnancy has been associated with maternal mortality, fetal mortality, or both.⁶ These risks would outweigh the increased risk of prematurity demonstrated in this study. The current study also suggests that patients who require oral corticosteroids during pregnancy should be counseled regarding the signs and symptoms of threatened preterm delivery.

In summary, although inhaled β -agonists and inhaled steroids were not associated with adverse perinatal outcomes, oral corticosteroid use was independently associated with prematurity in this study. It is not clear, however, whether oral corticosteroids directly cause the prematurity or whether they serve as a marker for asthma severe or uncontrolled enough to cause the prematurity. Further studies will be necessary to clarify the mechanism or mechanisms of the relationship between oral corticosteroids and prematurity in asthmatic women.

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APPENDIX

Institutions and staff members participating in the NICHD Network of Maternal-Fetal Medicine Units were

as follows: University of Pittsburgh Magee Women's Hospital—P. Heine, M. Cotroneo, E. Daugherty; University of Tennessee—B. Sibai, R. Ramsey; University of Southern California—Y. Rabello; University of Alabama at Birmingham—W. Andrews, R. Copper S. Tate, A. Northen; Wayne State University—Y. Sorokin, G. S. Norman, A. Millinder; University of Cincinnati—T. A. Siddiqi, N. Elder, V. Pemberton; University of Oklahoma—J. C. Carey, A. Meyer; Wake Forest University—M. Harper, M. Swain, A. Luper; University of

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Correction

With regard to “A historical review of bone marrow transplantation for immunodeficiencies,” the April issue's The Allergy Archives feature (2004;113:793-800), the legend to Figure 2 should have appeared as follows: “An infant with SCID who had lethal GVHD from a nonirradiated packed RBC transfusion. Copyright 2001. From *Case Studies in Immunology, A Clinical Companion*, 3rd Ed, by Fred Rosen & Raif Geha. Reproduced by permission of Garland Science/Taylor & Francis Books, Inc.”