

The safety of asthma and allergy medications during pregnancy

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Background: Although no asthma or allergy medications can be considered proven safe for use during pregnancy, these medications are often used to prevent the potential direct and indirect consequences of uncontrolled asthma or allergy. **Objective:** The safety of asthma medications, antihistamines, and decongestants was assessed in a prospectively monitored cohort of 824 pregnant women with and 678 pregnant women without asthma.

Methods: Medications used since conception were recorded on each subject's initial visit (< 28 weeks' gestation). Thereafter, diary cards for medications were completed by the patient through the time of delivery. Perinatal outcomes were compared in exposed versus unexposed individuals. A multivariate analysis accounted for the potential effects of age, parity, smoking, race, weight gain during pregnancy, maternal pulmonary function, acute asthmatic episodes, and multiple medication exposure.

Results: No significant relationships were identified between major congenital malformations and first trimester or any exposure to β -agonists, theophylline, cromolyn, corticosteroids, antihistamines, or decongestants. In the multivariate analyses, oral corticosteroids were independently associated with preeclampsia (odds ratio = 2.0, $p = 0.027$), but no other independent associations were observed between asthma or allergy medications and adverse perinatal outcomes.

Conclusion: Use of most common asthma and allergy medications during pregnancy was not associated with increased perinatal risks. Maternal use of oral corticosteroids was independently associated with the occurrence of preeclampsia in this study, although the mechanism of this association is not clear. However, because prior observations suggest that severe asthma may be associated with maternal and/or fetal mortality, risk-benefit considerations still favor the use of oral corticosteroids when indicated for the treatment of asthma during pregnancy. (*J Allergy Clin Immunol* 1997;100:301-6.)

Key words: pregnancy, medications, corticosteroids, preeclampsia, asthma, allergy

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Asthma and allergy are among the most common medical problems to complicate pregnancy.¹ Although few asthma and allergy medications have been proved harmful, no asthma and allergy medications can be considered proven safe for use during pregnancy.² However, because of the potential direct and indirect consequences of uncontrolled asthma and allergy during pregnancy, benefit-risk considerations often favor the use of these medications during pregnancy.³

The Collaborative Perinatal Project⁴ assessed the safety of many asthma and allergy medications during pregnancy, but a number of newer, commonly used medications, such as cromolyn and inhaled corticosteroids, were not included; and only congenital malformations were evaluated. The Group Health Cooperative Study⁵ included many antihistamines and decongestants, but this study equated drug exposure with prescriptions filled as early as 3 months before conception. Thus it is difficult to interpret the data generated by this study, and the Group Health Cooperative Study also only assessed congenital malformations. Isolated reports have evaluated perinatal outcomes in pregnant patients by using inhaled bronchodilators,⁶ theophylline,⁷ cromolyn,⁸ inhaled beclomethasone,⁹ and oral prednisone¹⁰; but the sample sizes in these studies were frequently relatively small, simultaneous controls were often not included, and confounding effects of other medications and severe disease were rarely evaluated.

In this study we assessed the safety of asthma medications, antihistamines, and decongestants in a prospectively followed cohort of 824 pregnant women with and 678 pregnant women without asthma. The effects of multiple medications, asthma severity, and associated risk factors were also evaluated in these subjects.

METHODS

Subjects and medications

Subjects were participants in the Kaiser-Permanente Prospective Study of Asthma During Pregnancy, the methodology of which has been previously described.¹¹ Briefly, subjects registering for prenatal care at San Diego Kaiser-Permanente Health Care Plan between June 1978 and December 1989 were asked to complete a questionnaire regarding their history of asthma or symptoms of asthma. All subjects with asthma were recruited to enter the study, and control subjects without asthma who matched a previously entered subject with asthma on the basis of age, parity, and smoking (> 10 cigarettes/day for > 1 month of pregnancy) were also recruited. All medications used since conception (based on last menstrual period if the

TABLE I. Subjects from the Kaiser-Permanente Prospective Study of Asthma During Pregnancy included in this analysis

	Subjects with asthma	Control subjects
Total entering study	1044	860
Subjects excluded from analysis		
Multiple gestation	14	6
Patient withdrawal	149	135
Spontaneous abortion (< 20 wk)	57	30
Inadequate medication information	0	11
TOTAL	220	182
Subjects included in analysis	824	678

date of conception was not known) and smoking history were recorded on the subject's initial visit (< 28 weeks). Thereafter, daily diary cards for all medications (name, strength, and amount taken) and smoking (number of cigarettes/day) were completed by the patient through the time of delivery. Subjects with asthma also maintained asthma symptom diaries and were evaluated in the allergy clinic at least monthly, at which time diary cards were reviewed and an FEV₁ was obtained. Control subjects were contacted by phone at least every 3 months to remind them of study procedures. Diary cards for control subjects were mailed in after the women gave birth.

Subjects with asthma were treated in the allergy clinic by the principal investigator (MS) or, in his absence, by other allergy clinic physicians. The goals of asthma therapy were the prevention of acute asthmatic episodes and the prevention of symptoms that interfered with sleep or normal activity. When medications were required to achieve these goals, they were generally administered sequentially in the following order: (1) inhaled β -agonist bronchodilators as required or on a regular basis, (2) regular theophylline and/or inhaled cromolyn, (3) inhaled beclomethasone, and (4) oral prednisone to control increased symptoms unresponsive to the previously mentioned medications. Acute asthmatic episodes were defined as respiratory distress caused by asthma requiring treatment with inhaled bronchodilators in the clinic or emergency department.

The current evaluation includes the 824 women with and the 678 women without asthma (total $n = 1502$) who delivered a singleton birth later than 20 weeks' gestation and for whom complete information regarding medications taken during pregnancy was available (Table I). Medications were considered used during the first trimester if taken before 14 weeks' gestation on the basis of gestational age at delivery. Corticosteroid use was categorized as follows: intranasal (for rhinitis), inhaled (for asthma), oral, inhaled total (with or without oral), inhaled only (without oral), and any (intranasal, inhaled, or oral).

Perinatal outcome variables

Length of gestation was based on clinical obstetric criteria (menstrual history, quickening, first recorded unamplified fetal heart tones, and progression of fundal height) supplemented when clinically indicated by ultrasonography performed before 24 weeks of gestation. The outcome variables were: (1) major congenital malformations¹²; (2) maternal preeclampsia defined as elevated blood pressure (systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg) noted after the twentieth week of gestation and associated with proteinuria (> 30 mg/dl), edema, or both; (3) preterm birth (< 37 weeks'

gestation); (4) low birth-weight infants (< 2500 gm); and (5) small for gestational age infants, defined as an infant whose birth weight is below the tenth percentile for gestational age, on the basis of California normative data.¹³

Data analysis

Perinatal outcome variables were compared in exposed and unexposed individuals by using chi square analysis. In addition, a dose-response relationship between degree of corticosteroid exposure and perinatal outcome was evaluated by linear trend analysis and by Student's *t* test.

Relationships between perinatal outcome variables and (1) age greater than 35 years, (2) parity (primipara vs multipara), (3) smoking, (4) African-American race, (5) weight gain during pregnancy, (6) acute asthmatic episodes, and (7) mean gestational FEV₁ were also evaluated in subjects with asthma. Dichotomous variables were analyzed by means of chi square analysis or by Fisher's exact test when minimum expected cell frequencies were less than 5, and continuous variables were evaluated by Student's *t* test. In addition, the relationship of the occurrence of preeclampsia to the delivery of preterm or low-birth-weight infants was evaluated by chi square analysis.

A multivariate (stepwise logistic regression) analysis was performed in subjects with asthma when significant univariate associations were identified between drug exposure and perinatal outcome variables. All medication and other variables found to be significantly associated with a given outcome were considered as potential predictors. Variables were selected for entry into the regression model in a stepwise fashion, with improvement in chi square value as the criterion. Two-tailed statistical tests were used for all analyses. An α less than 0.05 was considered significant.

RESULTS

The incidence of spontaneous abortion was higher in subjects with asthma than in control subjects (Table I). However, the significance of this observation is uncertain because subjects with asthma generally entered the study earlier in their pregnancies, according to the study protocol. The incidence of oral corticosteroid use in subjects with asthma experiencing spontaneous abortions (10.5%) was less than that in subjects with asthma not experiencing a spontaneous abortion (15.7%).

No significant relationships (all *p* values > 0.05) were identified between major congenital malformations and exposure during the first trimester or at any time to β -agonists (inhaled or oral), theophylline, cromolyn (inhaled, intranasal, or ophthalmic), corticosteroids (oral, inhaled, or intranasal), antihistamines, or decongestants (Table II). There were also no significant relationships (all *p* values > 0.05) identified between β -agonist, cromolyn, antihistamine, or decongestant use and increased incidences of any of the other adverse perinatal outcomes evaluated (data not shown). In addition, no significant relationships (all *p* values > 0.05) were identified between specific medication use and an increased incidence of small for gestational age infants (data not shown).

Significant relationships were identified in the total cohort between theophylline use and preterm birth (6.0% exposed, 3.6% unexposed, *p* = 0.034). Significant relationships were also demonstrated between any cor-

TABLE II. Relationships between major congenital malformations and drug exposure in all subjects

Drug	% Incidence of major congenital malformations (total number)*			
	First trimester†		Anytime	
	Exposed	Unexposed	Exposed	Unexposed
β-agonists‡	4.3 (488)§	5.6 (1000)	3.7 (667)	6.2 (823)
Theophylline	4.5 (292)	5.3 (1208)	4.7 (429)	5.3 (1061)
Cromolyn	6.0 (151)	5.0 (1348)	6.2 (243)	4.9 (1247)
Corticosteroids¶	6.9 (204)	4.9 (1295)	6.1 (297)	4.9 (1190)
Antihistamines#	3.7 (321)	5.5 (1175)	3.9 (493)	5.7 (996)
Decongestants**	5.5 (453)	4.8 (1032)	5.2 (790)	4.9 (698)

* $p > 0.05$ for all comparisons.

†Less than 14 weeks, based on gestational age at delivery.

‡Number of patients exposed to inhaled (metaproterenol = 309, terbutaline = 316, albuterol = 129, isoetharine = 82, other = 69), oral (terbutaline = 60, ephedrine = 60, other = 10), or injectable (epinephrine = 31, susphrine = 20, terbutaline = 16) β-agonists.

§First-trimester exposure in 59 of 113 subjects with asthma who received oral β-agonists and 0 of 8 control subjects.

||Number of patients exposed to inhaled ($n = 158$), intranasal ($n = 113$), or ophthalmic ($n = 23$) cromolyn.

¶Number of patients exposed to inhaled (beclomethasone = 137, other = 12), intranasal (beclomethasone = 157, other = 21), or oral ($n = 130$) corticosteroids.

#Number of patients exposed to chlorpheniramine ($n = 269$), tripelemnamine ($n = 192$), or other ($n = 193$) antihistamines.

**Number of patients exposed to oral (pseudoephedrine = 714, phenylpropanolamine = 77, other or unknown = 119) or intranasal (oxymetazoline = 197, phenylephrine = 56) decongestants.

TABLE III. Relationships between specific routes of corticosteroid exposure and adverse perinatal outcomes in all subjects

Corticosteroid exposure	Perinatal outcome	Perinatal outcome occurrence/total (%)		<i>p</i> Value
		Exposed	Unexposed	
Any*	Preeclampsia	34/296 (11.5)	85/1197 (7.1)	0.013
	Preterm birth†	19/297 (6.4)	45/1195 (3.8)	0.045
	Low birth weight‡	18/297 (6.1)	40/1197 (3.3)	0.030
Inhaled-total§	Preeclampsia	17/137 (12.4)	102/1356 (7.5)	0.044
	Preterm birth	13/138 (9.4)	51/1354 (3.8)	0.002
	Low birth weight	11/138 (8.0)	47/1356 (3.5)	0.009
Inhaled-only	Preeclampsia	7/64 (10.9)	112/1429 (7.8)	NS
	Preterm birth	5/64 (7.8)	59/1428 (4.1)	NS
	Low birth weight	3/64 (4.7)	55/1430 (3.8)	NS
Oral	Preeclampsia	17/129 (13.2)	102/1364 (7.5)	0.022
	Preterm birth	10/130 (7.7)	54/1362 (4.0)	NS
	Low birth weight	11/130 (8.5)	47/1364 (3.4)	0.005

NS, Nonsignificant ($p > 0.05$).

*Intranasal, inhaled, or oral.

†Birth <37 weeks' gestation.

‡Birthweight <2500 gm.

§Patients receiving inhaled corticosteroids with or without oral corticosteroids.

||Patients receiving inhaled corticosteroids but not oral corticosteroids.

ticosteroid use and preeclampsia (11.4% exposed, 7.1% unexposed, $p = 0.014$), preterm birth (6.4% exposed, 3.8% unexposed, $p = 0.048$), and low birthweight (6.0% exposed, 3.3% unexposed, $p = 0.032$). The mean ($\pm$ SD) gestational age was 33.08 ± 2.84 weeks in the preterm infants of theophylline-treated mothers and 32.74 ± 3.75 weeks in the preterm infants of mothers treated with any corticosteroid.

Relationships between perinatal outcomes and specific routes of corticosteroid exposure were evaluated (Table III). Total exposure to inhaled corticosteroids (with or without exposure to oral corticosteroids) was associated significantly with preeclampsia, preterm birth,

and low-birth-weight infants; whereas exposure to inhaled but not oral corticosteroids was not significantly associated with these outcomes. Exposure to oral corticosteroids was associated significantly with preeclampsia and low-birth-weight infants but not with preterm birth.

A dose-response relationship between corticosteroid exposure and adverse perinatal outcome was sought. A relationship between degree of exposure (none, inhaled or intranasal, or systemic) and the incidence of adverse outcomes was demonstrated for preeclampsia, preterm births, and low-birth-weight infants (Table IV). However, no significant relationships were demonstrated between these adverse outcomes and the total amount

TABLE IV. Relationship between degree of corticosteroid exposure and adverse perinatal outcomes for all subjects

Corticosteroid exposure	% Perinatal outcome incidence in exposed subjects			
	Major congenital malformation	Preeclampsia	Preterm birth*	Low birth weight†
None	4.9	7.1	3.8	3.3
Inhaled or intranasal only	5.4	10.2	5.4	4.2
Oral	7.0	13.2	7.7	8.5
Linear trend <i>p</i> value	NS	0.008	0.027	0.007

NS, Nonsignificant ($p > 0.05$).

*Birth <37 weeks' gestation.

†Birthweight <2500 gm.

TABLE V. Multivariate analysis of medication exposure and other factors related to adverse perinatal outcomes in asthmatic subjects

Outcome	Incidence	Potential predictors	Odds ratio (95% confidence interval)	<i>p</i> Value
Preeclampsia	65/817	Oral steroids	2.00 (1.11-3.61)	0.027
		Inhaled steroids*	—	NS
		Acute asthma episodes	—	NS
Preterm births	43/812	African-American race	4.02 (1.64-9.86)	0.007
		Lower weight gain	2.22 (1.15-4.29)	0.001
		Inhaled steroids*	—	NS
		Smoking	—	NS
		Theophylline	—	NS
Low birthweight	38/810	African-American race	5.25 (2.05-13.40)	0.002
		Lower weight gain	3.38 (1.55-7.36)	< 0.001
		Oral steroids	—	NS
		Inhaled steroids*	—	NS
		Mean FEV ₁	—	NS

Denominators other than 824 represent missing information in some subjects.

NS, Not significant (predictor did not enter model).

*With or without oral corticosteroids.

TABLE VI. Reports of the safety of asthma medications during pregnancy

Drug	Reference No.	Number exposed	Congenital malformations	Other adverse outcomes
Inhaled bronchodilators	6	259	Not increased (C)	Not increased (C)
Theophylline	4	193	Not increased (C)	Not reported
	7	212	Not increased (C)	Increased preeclampsia (C)
Inhaled beclomethasone	9	45	Not increased (G)	Possible increased LBW (G)
Cromolyn	8	296	Not increased (G)	Prematurity not increased (G)
Oral steroids	20	261	Not increased (G)	Not increased (G)
	17	58	Not reported	Increased preeclampsia (C)
	10	31	Not increased (C)	Increased LBW and preterm* (C)

C, Compared with an unexposed control group; G, compared with general population; LBW, low birth weight (< 2500 gm).

*Preterm = < 37 weeks' gestation

(in milligrams) of oral prednisone equivalent received during pregnancy in subjects receiving systemic corticosteroids (data not shown).

The previously mentioned results may be confounded by the presence and severity of asthma. Only three subjects without asthma were exposed to any corticosteroid (one oral corticosteroid for ulcerative colitis and two intranasal corticosteroids). In addition, subjects with asthma who were treated with any, inhaled, or oral

corticosteroids demonstrated a lower mean FEV₁ and were more likely to have experienced an acute episode of asthma than were subjects with asthma not treated with corticosteroids (data not shown, $p < 0.001$ for all analyses).

The following relationships were identified between perinatal outcomes and demographic and asthma severity variables: (1) Preterm birth was related to smoking ($p = 0.049$), African-American race ($p = 0.005$), and

lower weight gain during pregnancy ($p < 0.001$); (2) low birthweight was related to African American race ($p < 0.001$), lower weight gain during pregnancy ($p < 0.01$), and lower mean FEV₁ ($p = 0.04$); (3) preeclampsia was related to acute asthmatic episodes ($p = 0.033$); and (4) small for gestational age was related to smoking ($p = 0.011$) and lower weight gain during pregnancy ($p = 0.026$). In addition, asthmatic subjects with preeclampsia were more likely (10.8%) than subjects without preeclampsia (3.9%) to deliver low-birth-weight infants ($p = 0.019$).

The results of the multivariate analyses are shown in Table V. Oral corticosteroids were independently associated with preeclampsia (odds ratio = 2.00, $p = 0.027$). When preeclampsia was included in the model for low birth weight, it was independently related (odds ratio = 3.13, $p = 0.025$), but it did not substantially change the demonstrated independent relationships with African American race (odds ratio = 5.25, $p = 0.002$) and lower weight gain during pregnancy (odds ratio = 3.38, $p < 0.001$) and the lack of independent relationships with oral or inhaled corticosteroids or mean FEV₁.

DISCUSSION

No prior studies of asthma or allergy medications or asthma during pregnancy have reported an increased incidence of congenital malformations.^{4-11, 14-19} This study adds additional reassuring data regarding antihistamines (especially chlorpheniramine and triphenylamine), decongestants (especially pseudoephedrine), inhaled β -agonists (especially terbutaline and metaproterenol), theophylline, inhaled or intranasal cromolyn, inhaled or intranasal corticosteroids (especially beclomethasone), and oral corticosteroids. In this study we considered classes of drugs that have generally similar chemical structures and exerting relatively similar tissue effects. However, although these results may be generalizable to members of those groups not well represented herein, the results are most relevant to the above-mentioned specific drugs, which were most commonly used in this study.

The statistical power of this study (80% power, $\alpha = 0.05$) ranges from the ability to detect an odds ratio of 1.83 for any exposure to any decongestant to the ability to detect an odds ratio of 2.37 for first-trimester exposure to cromolyn. Data from prior peer-reviewed reports of the safety of asthma medications during pregnancy are summarized in Table VI. Although none of these studies reported an increase in the incidence of congenital malformations, the prior controlled study with the largest number of exposed individuals (inhaled bronchodilators = 259) only had 50% power to detect an odds ratio of 2.0. Taken together, the existing data suggest that asthma and allergy medications are not teratogenic, but the sample sizes of the studies do not allow exclusion of some increased risk. For example, two recent case-control studies^{21, 22} have suggested that oral decongestant use during the first trimester of pregnancy may increase the risk of gastroschisis from 1 to 2 per

10,000 births to 4 to 6 per 10,000 births, an increased risk clearly undetectable in this series.

Prior studies of asthma medications used during pregnancy (Table VI) have reported increased incidences of preeclampsia associated with theophylline⁷ and oral corticosteroids¹⁷ and increased incidences of low-birth-weight and preterm infants associated with oral corticosteroids.¹⁰ In addition, a small study of inhaled beclomethasone during pregnancy did suggest a possible association with an increase in the incidence of low-birth-weight infants.⁹ However, the designs of these studies did not allow for the exclusion of the potential confounding effects of concomitant medication use or asthma severity.

In this study, after we attempted to account for confounding factors, oral corticosteroids were associated with preeclampsia (Table IV), but no other independent associations were observed between gestational medication use and adverse perinatal outcomes. This association between oral corticosteroids and preeclampsia could represent a drug effect. Alternatively, this association could represent common pathogenetic factors shared by patients with more severe asthma (requiring oral corticosteroids) and patients experiencing preeclampsia. Indeed, recent epidemiologic studies have suggested that subjects with asthma may be at increased risk of experiencing pregnancy-induced hypertension.²³ It has been hypothesized that common factors may lead to bronchial muscle hyperreactivity and vascular hyperreactivity.^{1, 23} Vascular hyperreactivity, in the form of β -adrenergic hyporeactivity²⁴ and α -adrenergic hyperreactivity,²⁵ has been reported in subjects with asthma. In addition, mediators such as endothelin²⁶ and angiotensin²⁷ may cause contraction of both vascular and bronchial smooth muscle. Further studies will be necessary to sort out the etiology of this association. However, because severe asthma may be associated with maternal and/or fetal mortality,^{1, 3, 20} risk-benefit considerations still favor the use of oral corticosteroids when indicated in the treatment of asthma during pregnancy.

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