

Safety of Asthma and Allergy Medications in Pregnancy

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Up until the second half of the 20th century, the fetus was believed to occupy a privileged spot, where it was protected from insults that originated from the external environment. Birth defects were assumed to have a genetic etiology. That changed in 1961 when Lenz [1] in West Germany and McBride [2] in Australia independently reported that thalidomide, a fairly commonly prescribed sedative, caused serious problems for the developing embryo when taken between the 20th and 36th day after conception. Over the ensuing 50 years, the pendulum swung precipitously in the opposite direction to a situation today in which women and their health care providers must consider safety issues for any medications that are used during pregnancy. Surprisingly, for most drugs that are taken by women during their pregnancy, inadequate human data are available to support those decisions.

Typically, the safety of new medications cannot be evaluated ethically in pregnant women during premarketing clinical trials. Thus, when a new medication is approved for use, premarketing animal reproductive toxicity studies generally are the only source of safety information regarding pregnancy. Owing to species specificity and sensitivity to reproductive toxins, it is difficult to extrapolate with confidence from animal studies to human pregnancy. Nevertheless, this usually is the only information that the clinician has available to rely on for evaluating the safety of most medications. Despite its limited relevance, these data often are the only information that is available to consider in assigning the pregnancy label category for drug safety [3].

In the postmarketing arena, information on drug safety in pregnancy can be obtained through case reports that appear in the literature; adverse event reporting

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systems, such as the program managed by the U.S. Food and Drug Administration; pregnancy registries; birth defects surveillance programs; observational cohort studies; case-control studies; and large database linkage studies. Each of these approaches has strengths and limitations. Even for medications that are used commonly by pregnant women, the sample sizes that are required to rule out risks for rare events (eg, specific major birth defects) are difficult to achieve, even when resources are devoted to these efforts. Moreover, no single type of study or source of data usually is sufficient to address adequately the risks for the spectrum of pregnancy outcomes that might be associated with a given medication used in pregnancy [4].

Therefore, clinical decision-making regarding drug safety in pregnancy is a challenge at best. Medications that are used for the treatment of asthma and rhinitis are not exceptions. Because asthma is one of the most common, potentially serious chronic diseases in women of reproductive age—occurring in 3.7% to 8.4% of all pregnancies [5]—and allergy occurs in greater than 20% of women of child-bearing age [6], the clinician frequently is required to interpret available data in the context of almost universal lack of comprehensive safety information on the medications that are used to treat these conditions.

This article summarizes available human data regarding pregnancy outcome in women who take various medications for the treatment of asthma and rhinitis during pregnancy. Where possible, the potential contribution of the maternal underlying disease is taken into consideration, and the strengths and limitations of existing data are emphasized, including methodologic issues in published studies. Finally, a list of resources for further information that is continually updated is provided.

Medications used for the treatment of asthma in pregnancy

Published studies of pregnancy outcome in asthmatic women who were treated with a variety of medications have produced inconsistent results, with increased risks for birth defects overall, and specifically, oral clefts, spontaneous abortion or stillbirth, preterm delivery or shortened gestational age, preeclampsia, low or reduced birth weight, neonatal hypoxia, cesarean section, and hemorrhage noted in some studies [7].

In the following text and accompanying tables, summaries of the available human data are provided for each medication category with respect to increased risks for major birth defects overall, specific birth defects, birth size, preterm delivery, and preeclampsia.

Although spontaneous abortion also is an adverse outcome of interest that could occur more frequently in asthmatic women, well-designed studies to examine rates of spontaneous abortion are infrequent. The greatest risk for this event typically occurs before clinical recognition of pregnancy, which makes it difficult to identify most women who have experienced a pregnancy loss. Nevertheless, one cohort study that was conducted by Schatz and colleagues [8] compared rates

of spontaneous abortion among 824 asthmatic women and 678 nonasthmatic women who were receiving care through a large health maintenance organization in San Diego, California. Although rates of spontaneous abortion were increased significantly among asthmatics relative to controls, there was no evidence that any specific asthma medication carried more risk than another. This suggested that if a risk exists, it may be related to the disease, rather than the treatment. Furthermore, because asthmatic women tended to enter the study earlier, the excess risk for spontaneous abortion may have been related to the timing of enrollment.

Theophylline

Selected studies of pregnancy outcomes associated with theophylline use are shown in Table 1. Using a retrospective cohort design in which 212 pregnant asthmatic women who were treated with theophylline were compared with 292 pregnant asthmatics without exposure to theophylline and 237 nonasthmatic

Table 1
Summary of selected studies on theophylline

Investigators or study [ref]	Design	Source of subjects	No. of subjects	End points	<i>P</i> value or Odds ratio (OR)
Stenius Aarniala et al [9]	Retrospective cohort	Clinic/hospital- based Finland	212 exposed asthmatics	Congenital anomalies	NS
			292 unexposed asthmatics	Low birth weight	NS
			237 nonasthmatic controls	Perinatal death	NS
				Preterm delivery	NS
Schatz et al [10]	Cohort	U.S. multicenter MFMU Network	2123 asthmatics	Preeclampsia	NS ^a
			273 exposed	Congenital anomalies	NS
				Low birth weight	NS
				Perinatal death	NS
Collaborative Perinatal Project [12]	Cohort	U.S. multicenter	55,000 women	Preterm delivery	NS
			117 exposed	Preeclampsia/PIH	NS
				Congenital anomalies	NS
Michigan Medicaid [11]	Database	U.S. medical claims Data	1240 "exposed"	Congenital anomalies	NS
Bracken et al [13]	Cohort	Practice/clinic- based U.S. northeast	2379 enrolled	Low birth weight	NS
			872 asthmatic	Preterm	Adjusted
			1333 controls 15 exposed	delivery	OR 1.1 (CI, 1.0, 1.1)

Abbreviations: CI, confidence interval; MFMU, U.S. National Institute of Child Health and Development Maternal Fetal Medicine Units; NS, not significant; PIH, pregnancy-induced hypertension.

^a Not significant compared with other asthmatics but increased relative to nonasthmatics.

pregnant control women, Stenius-Aarniala and colleagues [9] found no significantly increased risks for major congenital anomalies, reduced birth weight, perinatal death, or preterm delivery. An increased risk for preeclampsia was noted in theophylline-exposed women compared with nonasthmatic women (15.6% versus 6.4%, $P < .03$), but not compared with other asthmatic women. This suggested that theophylline-treated asthmatic patients may have had more severe underlying disease. Consistent with that conclusion, Stenius-Aarniala and colleagues noted that 19% of the women in their theophylline-treated group reported acute exacerbations of asthma as compared with 6% in the group of asthmatic women without exposure to theophylline ($P < .001$).

Using data from 16 centers involved in the U.S. National Institute of Child Health and Development Maternal Fetal Medicine Units Network (MFMU), Schatz and colleagues [10] reported on pregnancy outcome among 2123 asthmatic women who were enrolled between 1994 and 2000. These investigators found no increased risks for congenital anomalies, low birth weight, preterm delivery, or preeclampsia among 273 theophylline-exposed women compared with asthmatics who did not use the drug.

Similarly, in medical claims data from Michigan that were analyzed by Rosa [11], the rates of major congenital anomalies among 1240 pregnant women who received a prescription for theophylline were not substantially higher than expected rates in the general population [11]. The Michigan Medicaid data are not based on validated exposure information, there is no control group, and the data have not been peer-reviewed. Finally, in 117 first trimester theophylline-exposed pregnancies that were identified through the Collaborative Perinatal Project—a large prospective multisite cohort study that was conducted in the 1960s—no significant increased risk for all major congenital anomalies combined was seen, compared with unexposed women [12]. Although no significantly increased risk for major birth defects was noted with first trimester exposure to theophylline in any of the studies cited above, sample sizes in each study were insufficient to rule out anything but high relative risks for major birth defects overall or for any specific birth defect.

In one additional study that addressed only low birth weight and preterm delivery as outcomes, Bracken and colleagues [13] prospectively recruited 872 asthmatic and 1333 nonasthmatic women from clinics in Connecticut and Massachusetts. Although an increased risk for low birth weight was not seen among women who used theophylline, the odds of preterm delivery were elevated significantly compared with unexposed women. In multivariate analysis, there was an estimated 5% increase in risk for each additional dose per month (adjusted odds ratio [OR], 1.05; 95% confidence interval [CI], 1.01–1.09) in the 15 women who used theophylline at anytime in pregnancy.

Short-acting β_2 agonists

Selected studies that addressed the effects of short-acting bronchodilators on pregnancy outcome are shown in Table 2. Data on major congenital anomalies

Table 2

Summary of selected studies on short-acting β_2 agonist medications

Investigators or study [ref]	Design	Source of subjects	No. of subjects	End points	<i>P</i> value
Collaborative Perinatal Project [12]	Cohort	U.S. multicenter	55,000 women	Congenital anomalies	NS
Michigan Medicaid [11]	Database	U.S. medical claims data	373 ephedrine 189 epinephrine 1090 albuterol 361 metaproterenol 149 terbutaline	Congenital anomalies	NS
Schatz et al [8]	Cohort	U.S. hospital/clinic-based southwest	1000 unexposed 488 exposed	Congenital anomalies Low birth weight Preterm delivery Preeclampsia/PIH	NS NS NS NS
Schatz et al [10]	Cohort	U.S. multicenter MFMU Network	295 unexposed 1753 exposed	Congenital anomalies Low birth weight Preterm delivery Preeclampsia/PIH	NS NS NS NS
Bracken et al [13]	Cohort	Practice/clinic-based U.S. northeast	1800 unexposed 401 exposed 1676 unexposed 529 exposed	Low birth weight Preterm delivery	NS NS

Abbreviations: NS, not significant; PIH, pregnancy-induced hypertension.

from the Collaborative Perinatal Project showed no significant increased risk for defects overall in 373 women who were exposed to ephedrine in the first trimester; however, among 189 women who were exposed to epinephrine, a significantly elevated relative risk of 1.7, for all major birth defects combined ($P < .05$), was reported [12].

In the Michigan Medicaid claims dataset, 1090 women who received prescriptions for albuterol, 361 who were prescribed metaproterenol, and 149 who received terbutaline did not demonstrate any excess of major malformations over the number expected [11]. Similarly, in the 1997 Kaiser Study authored by Schatz and colleagues [8] as well as the 2004 MFMU study [10] described above, no increased risk for major birth defects was shown among 488 and 1753 β_2 agonists users, respectively, compared with nonasthmatic women in the earlier study and with unexposed asthmatic patients in the latter study. Metaproterenol, terbutaline, and albuterol were the most common agents in the 1997 study, whereas albuterol was the only short-acting bronchodilator reported in the MFMU study. Again, although there is reassuring consistency of the data regarding safety, numbers in

these cohort studies do not allow for any conclusions to be drawn about increased risks for specific major birth defects.

With respect to other perinatal outcomes, neither the 1997 Kaiser study [8] nor the MFMU study [10] showed any indication of increased risks for preterm delivery, low birth weight, gestational hypertension, or preeclampsia. These findings were corroborated by Bracken and colleagues [13], who noted no significant increased risk for preterm delivery (OR, 1.14; 95% CI, 0.79–1.66) among 529 women who were exposed to short-acting β_2 agonists, and no increased risk for low birth weight among 401 women with exposure in the third trimester (OR, 0.97; 95% CI 0.65–1.47).

Long-acting β_2 agonists

Only a few studies have examined pregnancy outcomes with prenatal exposure to long-acting β_2 agonists (Table 3). These include two studies by Wilton and colleagues [14,15], drawn from a prescription event monitoring program in Great Britain, which is designed to collect case reports of pregnancy outcomes for newly marketed medications. This system received reports of 91 pregnancy exposures to salmeterol, among which 65 infants who had first-trimester exposure were live born. Rates of congenital anomalies (2%), spontaneous abortion (8%), and preterm delivery (0%) were similar to, or less than, that expected in the general population. In the second publication from this data source, case reports from 31 women with first trimester exposure to formoterol were identified; 8% of infants had major congenital anomalies, 10% of pregnancies ended in spontaneous abortion, and 20% of infants were born preterm. Although some of these figures are greater than what would be expected, the number of exposed maternal–infant pairs is small, and there is no formal comparison group.

Table 3
Summary of selected studies on long-acting β_2 agonist medications

Investigators [ref]	Design	Source of subjects	No. of subjects	End points	Percent with event or <i>P</i> value
Wilton et al [14]	Cohort	UK Prescription event monitoring	91 salmeterol 65 exposed 1 st trimester liveborn	Congenital anomalies Spontaneous abortion Preterm delivery	2% 8% 0%
Wilton & Shakir [15]	Cohort	UK Prescription event monitoring	31 formoterol	Congenital anomalies Spontaneous abortion Preterm delivery	8% 10% 20%
Bracken et al [13]	Cohort	Practice/clinic based U.S. northeast	2141 unexposed 48 exposed 64 exposed	Low birth weight Preterm delivery	NS NS

Abbreviation: NS, not significant.

The MFMU study included 77 salmeterol-exposed subjects; outcomes were not reported separately from short-acting β_2 agonists, but as a group, no increased risks were associated with all β_2 agonists combined [10]. Similarly, Bracken and colleagues [13] reported no increased risk for preterm delivery in 64 pregnancies with exposure to long-acting bronchodilators (OR, 1.69; 95% CI, 0.76–3.77), and no increased risk for low birth weight among 48 exposed asthmatic women (OR, 1.10; 95% CI, 0.39–3.11), compared with unexposed asthmatic and non-asthmatic women combined.

Oral corticosteroids

In contrast to generally reassuring data about most older asthma medications, the data on oral corticosteroids (Table 4) have raised some concerns. In the 1997 cohort study by Schatz and colleagues [8], among 130 women who were exposed to oral, but not inhaled, steroids, rates of preeclampsia (13.2% versus 7.5%, $P=.022$) and low birth weight (8.5% versus 3.4%, $P=.005$) were increased compared with unexposed controls. In multivariate analysis, the association of oral steroids with preeclampsia persisted (adjusted OR, 2.0; 95% CI, 1.11–3.61).

In the MFMU cohort study [10], the rate of preterm delivery was significantly higher in 185 oral steroid users compared with 1938 unexposed asthmatic women, even after adjustment for demographic and disease severity confounders (OR, 1.54; 95% CI, 1.02–2.33); the prevalence of low birth weight also was increased (OR, 1.80; 95% CI, 1.13–2.88). Although rates of major malformations were similar between exposed and unexposed women (2.2% versus 2.0%), small cohort studies such as this have limited power to detect anything other than high relative risks for this particular outcome.

These findings were replicated in the study of northeastern U.S. clinics by Bracken and colleagues [13], in which the odds of preterm delivery were increased among 52 women who used oral steroids relative to all other pregnancies (OR, 3.37; 95% CI, 1.66–6.86). In multivariate analysis, with each additional dose per month, the odds of preterm delivery increased by 11% (adjusted OR, 1.11; 95% CI, 1.03–1.18). This translated to a reduction in gestational age of 2.2 weeks in women who used oral steroids daily across pregnancy. No increased risk was noted for low birth weight among 26 women who were exposed to oral steroids in the same study.

Four large case-control studies have implicated oral steroids with respect to risk for a specific major birth defect—oral clefts. The first, drawn from the Hungarian population-based birth defects surveillance study, reported a significantly elevated OR for oral steroid use in the first month of pregnancy (adjusted OR for cleft lip with or without cleft palate 5.9; 95% CI, 1.7–20.3) [16]. Maternal use of steroids was reported in this study for a variety of indications, only 25% of which were asthma. No adjustment was made for maternal smoking, which is an independent risk factor for clefts; and the OR estimate was based on three cases of affected and exposed infants.

Table 4
Summary of selected studies on oral corticosteroids

Investigators [ref]	Design	Source of subjects	No. of subjects	End points	<i>P</i> value or OR (95% CI)
Schatz et al [8]	Cohort	U.S. hospital/clinic- based Southwest	1364 unexposed 130 exposed	Low birth weight Preterm delivery Preeclampsia	NS NS Adj. OR 2.0 (1.1–3.6)
Schatz et al [10]	Cohort	U.S. multicenter MFMU Network	1938 unexposed 185 exposed	Congenital anomalies Low birth weight Preterm delivery	NS Adj OR 1.8 (1.1–2.9) Adj OR 1.5 (1.0–2.3)
Bracken et al [13]	Cohort	Practice/clinic- based U.S. northeast	2153–2175 unexposed 26 exposed 52 exposed	Low birth weight Preterm delivery	NS Adj. OR 1.1 (1.0–1.2)
Czeizel & Rockenbaver [16]	Case- control	Hungary	20,800 malformed 35,700 controls	Cleft lip ± cleft palate	Adj. OR 5.9 (1.7–20.3)
Rodriguez- Pinilla & Martinez- Frias [17]	Case- control	Spain	24,000 malformed 11,100 controls	Cleft lip ± cleft palate Cleft palate	Adj. OR 6.6 (1.4–29.8)
Carmichael & Shaw [18]	Case- control	California	662 cases 734 controls	Cleft lip ± cleft palate Cleft palate	OR 4.3 (1.1–17.2) OR 5.3 (1.1–26.5)
Pradat et al [19]	Case- control	International	645 cases ~11,000 mal- formed controls	Cleft lip ± cleft palate	OR 2.59 (1.18–5.67)
Park-Wyllie et al [20]	Cohort	Teratogen Information Service Canada	188 unexposed 187 exposed	Congenital anomalies Lower birth weight Preterm delivery	NS <i>P</i> < .001 <i>P</i> < .001

Abbreviations: Adj, adjusted; NS, not significant.

The second study, which was published in 1998 by Rodriguez-Pinilla and Martinez-Frias [17], reported data from a hospital-based case-control study in Spain. Significantly elevated ORs for oral clefts (cleft palate and cleft lip with or without cleft palate) were associated with any corticosteroid use in the first trimester compared with normal and malformed controls (adjusted OR, 6.6; 95% CI, 1.4–29.8). These estimates were based on five exposed cases, three of which were multiply malformed; no information was provided on the indication for treatment.

The third study was derived from data collected by the California Birth Defects Monitoring Program, in which significantly elevated ORs were noted for

isolated cleft lip with or without cleft palate (OR, 4.3; 95% CI 1.1–17.2) and isolated cleft palate (OR, 5.3; 95% CI, 1.1–26.5) in association with oral steroid use in the 3-month period around conception [18]. These estimates were based on nine exposed cases, one of which involved maternal asthma; no adjustment was made for confounders.

The fourth study, a recent update from nine malformation registries that contribute to the Malformation Drug Exposure Surveillance database [19], also reported a statistically significant increased risk for cleft lip with or without cleft palate with systemic corticosteroid use (OR, 2.59; 95% CI, 1.18–5.67). This estimate was based on seven exposed cases with no information about indication for use and no adjustment for confounders.

In contrast, cohort studies have not shown a statistically significant increased risk for overall malformations or oral clefts alone with systemic steroid use in pregnancy. A meta-analysis that was conducted recently by Park-Wyllie and colleagues [20] summarized six published cohort studies, and came to a similar conclusion regarding the risk for all malformations combined (OR, 1.45; 95% CI, 0.81–2.60). Even with aggregated data from these cohort studies, only 535 exposed pregnancies could be included; this sample size is far too limited to examine risk for oral clefts alone. In this same meta-analysis, the summary OR derived from case-control studies was statistically significant with an estimate of 3.35 (95% CI, 1.97–5.69) for oral clefts in association with systemic steroid use around the first trimester.

Thus, if the association between systemic steroid use and oral clefts is causal, and if the risk applies equally when oral steroids are used to treat asthma as well as any other condition, the best estimate of the risk is that for every 1000 women who take oral steroids during the critical period in embryonic development, the risk may be increased from a baseline of about one per 1000 to approximately three affected infants per 1000 exposed.

Inhaled corticosteroids

Several recent studies addressed the risks that are associated with prenatal exposure to inhaled steroids (Table 5). In a cohort study drawn from a perinatal database in Nova Scotia, Alexander and colleagues [21] reported on 139 steroid-exposed pregnancies. Users of inhaled steroids were not distinguished from oral steroid users; nevertheless, in comparison with 678 asthmatic women and 13,709 nonasthmatic controls, no increased risks were shown for major congenital anomalies overall (adjusted relative risk [RR], 0.8; 95% CI, 0.4–1.7), low birth weight (adjusted RR, 1.0; 95% CI, 0.4–2.5), or preterm delivery (adjusted RR, 1.4; 95% CI, 0.6–3.0). A relative risk of borderline significance was shown for pregnancy-induced hypertension (adjusted RR, 1.7; 95% CI, 1.0–2.9).

In the 1997 study by Schatz and colleagues [8], only a small number of women were exposed to inhaled steroids without concomitant exposure to oral steroids (n=64). Compared with approximately 1428 asthmatic and nonasthmatic unexposed women, no significant increased risks were noted for preeclampsia,

Table 5
Summary of selected studies on inhaled corticosteroids

Investigators	Design	Source of subjects	No. of subjects	End points	<i>P</i> value or OR (95% CI) or rate ratio
Alexander et al [21]	Cohort	Perinatal database Nova Scotia	13,709 controls	Congenital anomalies	Adj. OR 0.8 (0.4–1.7)
			678 asthmatic unexposed	Low birth weight	Adj. OR 1.0 (0.4–2.5)
			139 asthmatic steroid (any)	Preterm delivery	Adj. OR 1.4 (0.6–3.0)
			exposed	PIH	Adj. OR 1.7 (1.0–2.9)
Schatz et al [10]	Cohort	U.S. multicenter MFMU Network	2123 asthmatics	Congenital anomalies	NS
			722 exposed	Low birth weight	NS
				Preterm delivery	NS
				Preeclampsia/PIH	NS
Namazy et al [22]	Cohort	Allergists U.S. American College/AAAAI	474 exposed	Congenital malformations	Comparable to population rates
			No controls	Low birth weight	
				Preterm delivery	
Kallen et al [23]	Cohort	Swedish Medical birth register	Concurrent population comparison	Congenital anomalies	Rate ratio 1.1
			2014 exposed to budesonide		
Norjavaara & de Verdier [24]	Cohort	Swedish medical birth register	Concurrent population comparison	Mean birth weight	<i>P</i> < .05 ^a
			2968 exposed to budesonide	Stillbirth	NS
				Preterm delivery	<i>P</i> < .05 ^b
Bracken et al [13]	Cohort	Practice/clinic-based U.S. northeast	2029–2065 unexposed	Low birth weight	Adj. OR 1.0 (0.9–1.1)
			176 exposed	Preterm delivery	Adj. OR 1.0 (1.0–1.0)
			136 exposed		

Abbreviations: AAAAI, American Academy of Asthma, Allergy and Immunology; Adj, adjusted; PIH, pregnancy-induced hypertension.

^a Mean difference in birth weight for girls exposed to budesonide early in pregnancy relative to all girls –40 grams; mean difference in birth weight for boys with early pregnancy exposure to budesonide –20 grams.

^b Mean difference in gestational age for boys exposed to budesonide early in pregnancy relative to all boys is –0.2 weeks; no difference for girls.

preterm birth, or low birth weight. In the more recent MFMU study, 722 subjects were exposed to inhaled steroids, most commonly beclomethasone, followed by triamcinolone. Rates of major malformations, preterm delivery, low birth weight, and gestational hypertension were equal to or less than rates for these same outcomes in the unexposed asthmatic comparison group [10].

Similar findings were reported from another cohort study that was conducted by allergists across the United States through the American College of Allergy, Asthma and Immunology and the American Academy of Asthma, Allergy and Immunology [22]. Among 474 inhaled-steroid users who were enrolled in the study, no increased incidence of low birth weight, preterm birth, or congenital malformations was noted compared with expected rates in the general population; however, no control group was recruited as part of this study.

Exposure to the specific inhaled steroid, budesonide, in 2014 infants who were born to asthmatic women was evaluated by Kallen and colleagues [23] using data from the population-based Swedish Medical Birth Register cohort study. Compared with all other pregnancy outcomes, the risk ratio for all major congenital anomalies combined was 1.1 (3.8% versus 3.5%). Four infants were born with oral clefts (risk ratio, 1.2; 95% CI, 0.3–3.1), but this number not substantially in excess of expected numbers. Again, this larger cohort study lacks sufficient power to rule out risks for specific malformations, such as oral clefts. Therefore, this question remains unanswered.

The same Swedish population-based resource was used by Norjavaara and de Verdier [24] to examine risks for low birth weight, stillbirth, and preterm delivery. With 2968 budesonide-exposed pregnancies, no significant excess of stillbirths was noted compared with women who used other asthma drugs or nonasthmatics. Although slightly smaller adjusted mean birth weights were noted among girls (−40 g) and boys (−20 g) with early exposure to budesonide relative to all others, these differences were similar to those found among infants whose mothers used asthma drugs other than budesonide. Furthermore, infants who were born to women who continued to use budesonide throughout pregnancy had slightly higher mean birth weights compared with nonasthmatic controls. With respect to gestational age, the findings were similar, with an approximately 1 to 2 days average shortened gestational age among boys with early or late pregnancy exposure to budesonide. The investigators concluded that exposure to budesonide was not linked to any clinically relevant effect in this large study.

Cromolyn

Limited recent data are available on the safety of cromolyn in pregnancy. In the 1997 cohort study by Schatz and colleagues [8], 151 first-trimester users were enrolled (including inhaled, intranasal, and ophthalmic); no significant increased risk for birth defects overall was noted (6.0% versus 5.0%, $P>.05$). Similarly, in 191 women who were prescribed cromolyn in the Michigan Medicaid claims

database, no excess of major anomalies was seen [11]. In the MFMU study, only 60 women were enrolled with cromolyn exposure; although no significant differences were seen in any perinatal outcome measured, power was limited [10]. In crude analysis, a significant excess of preterm deliveries was noted among 22 cromolyn users in the study by Bracken and colleagues [13]; however, after adjustment for confounders in multivariable analysis, the association was no longer significant (adjusted OR, 1.01; 95% CI, 0.98–1.03). In the same study, no increased risk for low birth weight was found among 18 exposed subjects.

Leukotriene modifiers

This new class of drugs has limited published human data available regarding pregnancy safety. Fewer than 10 exposed pregnancies were enrolled in the cohort that was studied by Bracken and colleagues [13]; this provided limited power to assess the risk for preterm delivery or low birth weight in that study. A pregnancy registry is being maintained for montelukast by the drug manufacturer. As of July, 2004, 151 prospectively ascertained pregnancies have been completed, of which 116 involved first-trimester exposures. Seven major malformations were reported in this group [25]. The data on leukotriene modifiers are too limited to draw any conclusions.

Medications used for the treatment of rhinitis in pregnancy

Antihistamines

Data from the Collaborative Perinatal Project and several generally small human studies have contributed some knowledge about the safety of older or first-generation antihistamines, including chlorpheniramine, triprolidine, tripelemine, and hydroxyzine, none of which has been associated with an increased risk for major congenital malformations [12,26]. A few studies have suggested an increased risk for overall birth defects for selected antihistamines, including brompheniramine [12], diphenhydramine [27], and promethazine [28]; however, at least as many studies have contradicted these findings for major birth defects overall [12,29].

The second-generation antihistamines were introduced only recently; therefore, little data have been published on the use of these medications in pregnancy. One small cohort study of 33 cetirizine-exposed pregnancies, published by Einarson and colleagues [30], noted no increased risk for major birth defects compared with outcomes in 38 unexposed pregnancies. Another small cohort study by Pastuszak and colleagues [31] focused on astemizole; they found no increased risk of major birth defects in infants of 114 exposed women compared with infants of 114 unexposed controls.

The Swedish Medical Birth Register data was used by Kallen [32] to evaluate pregnancy outcome with early exposure to a broad range of antihistamines, including clemastine (n=1230), deschlorpheniramine (n=226), alimenazine (n=35), cetirizine (n=917), terfenadine (n=1164), loratadine (n=1769), and fexofenadine (n=16). No significant increased risks were found for preterm delivery, low birth weight, perinatal death, or all malformations when these medications were used early in pregnancy to treat allergy. Among women who used loratadine, about twice as many male infants were born with hypospadias than would be expected from the general population rates.

Another cohort study, conducted by Diav-Citrin and colleagues [33] and published in 2003, compared pregnancy outcome among 210 women who were exposed to loratadine (77.9% in the first trimester) with 267 women who were exposed to other antihistamines and 929 women who were not exposed to either. No significant differences were found between groups regarding major anomalies overall, preterm delivery, or birth weight. At the same time, a study that involved four centers was published by Moretti and colleagues [34]. This study compared 161 first trimester loratadine-exposed pregnancies with a similar number of unexposed women. No differences were found in overall malformations, gestational age, or mean birth weight; no infant in the exposed group had hypospadias. A further evaluation of hypospadias risk in association with loratadine was performed in the U.S. National Birth Defects Prevention Study case control setting [35]. In 563 male infants who had hypospadias and 1444 male infant controls, the adjusted OR for loratadine exposure was 0.96 (95% CI, 0.41–2.22), and showed no association between the exposure and this particular malformation.

Decongestants

Among the decongestants, phenylephrine has been associated with an increased risk for birth defects in the Collaborative Perinatal Project and one other case-control study [14,36]; however, other studies have not confirmed this association [30]. Pseudoephedrine, as a vasoactive medication, has been linked to some major birth defects that are believed to have a vascular disruptive etiology (eg, gastroschisis and small intestinal atresia). Werler and colleagues [36] found an OR of 1.8 (95% CI 1.0–3.2) for early pregnancy exposure to pseudoephedrine among 206 patients who had gastroschisis compared with 798 nonmalformed controls. This association was accentuated when the product used also contained acetaminophen (OR, 4.2; 95% CI, 1.9–9.2); a similar pattern of associations was found for small intestinal atresia. Although the link between this decongestant and gastroschisis has been reported in several studies, it is still unclear if this is a causal relation. If it is—because defects like gastroschisis are so rare and occur in perhaps two or three infants per 10,000 births—the absolute risk is small. For every 10,000 women who are exposed to pseudoephedrine early in pregnancy, an estimated two or three additional children would be affected over and above the two or three that would be expected.

Intranasal allergy medications

In addition to oral decongestants, Werler and colleagues [37] examined the association between intranasal decongestants, including oxymetazoline, xylometazoline, tetrazyline, nephazoline, and phenylephrine, and the risk for gastroschisis. Although the number of exposed women was small for each medication, no statistically significant association was found between these agents and the defect. There is limited pregnancy outcome information in the literature on the use of intranasal steroids or intranasal cromolyn. Although it is not clear how the absorbed dose of these medications, delivered in this manner, compares with an inhaled form of the same drug, pregnancy safety information on these medications, when used in the inhaled form, may provide some information.

Summary

Given the unique nature of pregnancy with respect to obtaining safety data regarding medication exposures, developing comprehensive information on the wide variety of medications that might be of clinical benefit during pregnancy is a challenging and on-going task. For many of the most commonly used asthma and allergy medications that were covered in this article, there is at least limited human data available. Even for relatively well-studied medications, there are many unanswered questions, and few studies exist that are large enough to rule out at least a doubling of risk for specific outcomes, particularly congenital anomalies. This challenge becomes even more daunting when evaluating risks of individual products is considered the optimal goal, as opposed to “lumping” all medication exposures within a class. All of these issues call for more human pregnancy data that are collected more efficiently so that the answers that clinicians and pregnant women need are available more readily.

In the meantime, health care providers and pregnant women must work with the information that is available to evaluate the risks and benefits of a particular medication and alternative choices for treatment of asthma or allergy during pregnancy, while considering the potential for adverse effects if the woman with severe or uncontrolled asthma is under-treated. To assist in making a risk/benefit assessment, the clinician can draw on existing resources that provide systematic periodic review of new data on medications in pregnancy as it becomes available, and synthesize the entire body of data on a particular drug into concise summary statements. Two such resources are TERIS (Teratogen Information System) [38] and Reprotox [39]; both on-line services are managed by experts in the field of teratology. An additional resource for clinicians and pregnant women is the Organization of Teratology Information Specialists [40], a network of risk-assessment counselors in the United States and Canada who specialize in research and the communication of risks that are associated with exposures in pregnancy.

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