

Databases in the assessment of the effects of drugs during pregnancy

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There is limited information on the effects of marketed drugs in pregnant women, largely because premarketing studies are not conducted in this population unless the agent is intended for specific use during pregnancy. Current information on the use of available medications during pregnancy includes 3 types of data: (1) case reports, (2) case-control studies, and (3) cohort studies. Assessments of pregnancy risk related to medication use most commonly involve case reports, and each year the Food and Drug Administration catalogs approximately 1000 suspected adverse drug experiences during pregnancy. The Food and Drug Administration, working with Michigan Medicaid, has developed a database of several hundred thousand pregnancy outcomes. Results of this study for asthma medications used between 1980 and 1992 are presented. However, interpretation of the results is complicated, and substantially more data are required, particularly as new medications become available. (*J Allergy Clin Immunol* 1999;103:S360-1.)

Premarketing studies on drugs have not been conducted in pregnant women, unless the drugs under consideration have a specific indication for use in pregnancy. Consequently, teratogen reference material contains few human data,^{1,2} with the exception of *Brigg's 4th edition*.³ Published controlled trials assessing use of asthma medications during pregnancy are limited to trials on the use of adrenergics in tocolysis.⁴

Postmarketing information includes 3 types of data^{5,6}: case reports, case-control studies, and cohort studies.

1. *Case reports* are the initial and customary source of information leading to a suspicion of human pregnancy risk. Each year the Food and Drug Administration computerizes about 1000 suspected adverse drug experiences during pregnancy. A total of 186 adverse events have been related to asthma therapies through 1993: 45 reports for albuterol, 15 for theophylline, 75 for prednisone, 35 for prednisolone, 6 for beclomethasone, and 10 for cromolyn. The only unusual clustering of adverse reactions is for 5 reports of heart defects observed with theophylline use; however, 3 of these came from a single published report.⁷ Case reports indicate an association between use of tocolytic adrenergic agents and maternal tachycardia and pulmonary edema. Nearly 100 published case studies have reported the occur-

rence of neonatal goiter associated with exposure to iodinated glycerol,⁸ which was often found in cough treatments in combination with theophylline. This risk has finally been reduced by removing iodinated glycerol from cough mixtures.

2. *Case-control studies* compare drug exposure frequency with a suspected outcome to the exposure frequency without that outcome. None of these studies has addressed asthma therapies.*⁹ However, 2 case-control studies showed an association between maternal use of decongestants (pseudoephedrine and phenylpropanolamine) and gastroschisis,^{10,11} even though data from the prospective Medicaid cohort of 940 women who received pseudoephedrine during the first trimester of pregnancy did not identify any increased risk.³
3. *Cohort studies* compare the frequency distribution of adverse outcomes for a given exposure with the outcome frequency distribution in patients who did not have that exposure. Fetal effects need to be examined in light of the timing of exposure relative to the period of embryogenesis or fetal development. Long-term exposures, such as those for asthma management, are more likely to overlap with a critical embryogenic period than are short-term exposures. Confounding factors, such as concurrent drug exposures and the effects of the underlying illness, complicate interpretation of the results.

Several workshops on the topic of asthma management during pregnancy have been held, but the workshops are based on information from studies that have insufficient primary data (including studies that were not well controlled) and have compared therapeutic categories without reference to concurrent exposures. The National Institutes of Health Collaborative Perinatal Project,¹² which included 50,000 pregnancies, is the most cited reference in these workshops. However, because this project ended in 1960, it does not cover newly marketed agents or provide data based on the current recommendations for use of asthma treatments.¹³

From 1980 to 1992, the Food and Drug Administration has accumulated data on several thousand maternal asthma cases and pregnancy outcomes for recipients of Michigan Medicaid. The Michigan Medicaid database includes information regarding fill date for each prescription, indication (to an extent), dosage form, timing, dose, concomitant medications, provider, and treatment

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*A recent case-control study⁹ has associated the first-trimester use of oral corticosteroids with an increased risk of oral cleft.

frequency. It does not include data on date of conception, nor does it provide first-trimester history for about 40% of the women, because they sought prenatal care later in their pregnancies. The prospective maternal prescription data are particularly valuable, although these data do not include information on compliance, exact timing of drug administration, or drugs obtained in ways other than through outpatient Medicaid prescriptions.

The analysis methodology was based on linking maternal records with pediatric billing records for patients with birth defects, with pediatric patients being followed up for periods varying from 1 to 7 years. The quality of diagnosis of birth defects varied according to the nature of the defect. Except for birth defects that were obvious in infancy (eg, oral clefts or polydactyly), diagnosis invoices may have reported suspicions rather than confirmed diagnoses. To reduce this ambiguity, at least 2 defect invoices were required to include these data in the analyses. For possible associations, more details could be obtained through pediatric case files, which provide the number and timing of birth defects and the supporting diagnoses.

Data files were examined from 4264 women who had spontaneous abortions during the time frame from 1980 to 1983 to determine whether prescriptions had been received by these women within 90 days preceding the spontaneous abortion. These data were compared with the 90-day (first-trimester) data available from 55,736 deliveries during that period. Computerized data analysis showed a twofold association of spontaneous abortions with use of any asthma treatments. Of interest, iodinated glycerol was the only cough medicine to show this association, possibly because it was often compounded with theophylline. Even if these results are replicated in other studies, whether the spontaneous abortion association is due to asthma itself or to the treatments remains to be clarified.

Data from the Michigan Medicaid Study for currently available asthma medications are shown in Table I. The data suggest a possible association between theophylline and heart defects, oral clefts, and urinary tract defects—associations not evident with other asthma medications.⁵ However, in surveillance studies of many therapeutic agents and many possible outcomes, associations can arise by chance. These associations raise signals that require replicated data from additional studies. At the same time, even extensive data can lack sufficient power to detect and define the true risks. No attempt has yet been made to examine possible late functional sequelae of exposure to asthma medications. For these reasons, interpretation of results from the Michigan Medicaid surveillance study, which included 333,000 deliveries, is still limited because of insufficient sample size. Substantially more data are required and must be obtained on a timely basis as new agents become available.

TABLE I. Data from the Michigan Medicaid Surveillance Study regarding asthma medications³

Medication	No. exposed	No. of malformations	No. of expected malformations
Bronchodilators			
Albuterol	1090	48	43
Atropine	381	18	16
Epinephrine	35	0	1.5
Isoetharine	22	0	1
Isoproterenol	16	1	0.7
Metaproterenol	361	17	15
Terbutaline	149	7	6
Theophylline	1240	68	53
Anti-inflammatory medications			
Beclomethasone	395	16	16
Cromolyn	191	7	8
Methylprednisolone	222	14	9
Prednisone	236	11	10

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