

The Organization of Teratology Information Services (OTIS) Registry Study

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Some population-based studies of the risks of gestational medication use are limited by differential recall or enrollment of mothers of children with abnormalities. Prospective acquisition of exposure information, before knowledge of pregnancy outcome, is the most unbiased manner in which to obtain denominator-based outcome information. The Organization of Teratology Information Services (OTIS) Registry Study will prospectively evaluate pregnancy outcomes in relation to exposures to asthma medications. Patients will be enrolled by participating Teratology Information Services. Information regarding medication exposure, asthma severity, and other important medical events will be assessed during pregnancy by means of standardized interviews, supplemented by medical records. Outcome information will be obtained from copies of the pediatric records. Data analysis will evaluate relative risks of adverse outcomes in exposed compared with unexposed asthmatic and nonasthmatic subjects. (*J Allergy Clin Immunol* 1999;103:S373-6.)

This article describes a study that began early in 1998. The study makes use of the ability of Teratology Information Services to prospectively ascertain pregnancy exposures to medications and to evaluate pregnancy outcome. The study is funded by an unrestricted grant from Rhône Poulenc Rorer.

RATIONALE

The use of asthma medications by women of child-bearing age is common. Exposure to pharmaceuticals during pregnancy may occur inadvertently or may be occasioned by therapeutic necessity. Preclinical data have been useful in estimating the potential of a pharmaceutical agent to produce developmental toxicity but are most effectively used in conjunction with data on the outcome of human pregnancy after exposure to a given agent. An example is angiotensin-converting enzyme (ACE) inhibitors. These agents were found in preclinical studies to produce developmental toxicity in rabbits consistent with maternal hypotension and fetal hypoperfusion. Because rabbits are known to be uniquely sensitive to hypotensive effects, the data were not considered particularly important for estimating human risk. Beginning

Abbreviations used

ACE: Angiotensin-converting inhibitor

OTIS: Organization of Teratology Information Services

in the early 1980s, a number of case reports of abnormal fetuses and children exposed to ACE inhibitors began to appear.¹ Around the same time, there was a suspicion that renal insufficiency in the infant might accompany treatment during pregnancy with these agents.² Finally, in 1991, Dr Mason Barr brought together the suspicions, based on case reports and pathology studies, that ACE inhibitors produced a fetopathy characterized by fetal renal insufficiency and hypocalvaria.³ On March 13, 1992, the US Food and Drug Administration issued a warning about the use of ACE inhibitors during pregnancy and the occurrence of this fetopathy.

The identification of a fetal malformation syndrome associated with maternal use of pharmaceuticals during pregnancy often proceeds from an accumulation of case reports that result in the eventual recognition of a causal relationship. In some instances, the recognition is relatively rapid. For example, the association of thalidomide use during pregnancy and phocomelia was firmly established within 4 years of the marketing of the drug in Europe and Australia, based on the dramatic increase of an otherwise very unusual malformation. In most cases, however, the association between maternal drug use and developmental toxicity escapes detection because the increase in adverse effects is more modest. For example, valproic acid and carbamazepine use during pregnancy have been associated with about a 10-fold increase in meningomyelocele in the offspring, but this increase only brings the prevalence of this abnormality to 1% to 2% in exposed children. The relatively low "attack rate" means that most exposed children are healthy and the association with pharmaceutical exposure is difficult to detect. In fact, both valproic acid and carbamazepine were marketed for well over a decade before their association with congenital malformations was identified.

One of the most important impediments to the identification of pharmaceutical-toxicity associations is the lack of denominator-based information. When case reports of children with abnormalities after exposed pregnancies occur, it is not possible to know whether the association is coincidental because congenital anomalies and other adverse pregnancy outcomes occur at a relatively high

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PREGNANT WOMEN WITH ASTHMA

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- If you are willing to be a part of this Study, call the *Teratogen Information Service nearest you *or* call 1-888-523-4TIS for further information.
- Patients will be ascertained by Teratogen Information Services located throughout the United States.

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**Teratogen Information Services (TIS) Provide Scientific Information to Physicians and Pregnant Women About Asthma (and other) Medications During Pregnancy.*

FIG 1.

background rate in the general population. Denominator-based information permits a calculation of a rate at which adverse effects are associated with an exposure and a comparison with general population rates or with rates in a ref-

erence group. This kind of information would be expected to lead to the early identification of an association between a pregnancy exposure and an adverse outcome.

It is also important to identify exposures for which

there is no apparent increase in the risk of adverse outcome. Because many pregnancy exposures are inadvertent, considerable anxiety accompanies the discovery that a medication was used early in an unrecognized pregnancy. In addition, there are frequent occasions when medication use during pregnancy is important in order to optimize the health of the woman. The availability of denominator-based information is necessary to estimate the risk, if any, to the inadvertently exposed pregnancy and to assist in therapeutic decisions about drug choice for pregnant women who require pharmacologic therapy.

There are a number of denominator-based information sources; however, not all are equal. Some retrospective studies attempt to correlate outcomes with exposures by inquiring about exposures among the mothers of children with and without targeted abnormalities. Such studies require that the abnormality of interest be identified a priori. In addition, such inquiries may be biased by more complete or perhaps embellished recall among the mothers of children with abnormalities. Registries of drug exposure attempt to ascertain all instances of drug use during pregnancy; however, these registries can be limited by an increased likelihood of the reporting of adverse events associated with an exposure. Women with normal pregnancy outcomes may be less likely to identify themselves to a registry.

Prospective acquisition of exposure information, before knowledge of pregnancy outcome, is the most unbiased manner in which to obtain denominator-based outcome information. By following up pregnancies in which an exposure has been identified, it is possible to estimate the rate at which abnormal pregnancy outcomes occur after the exposure of interest. A reference rate can also be calculated based on outcomes after prospectively ascertained exposures to other agents, for example, to other agents used for the same condition or to agents believed not to increase the rate of adverse pregnancy outcome (eg, acetaminophen, β -lactam antibiotics).

TERATOGEN INFORMATION SERVICES

A network of organizations for the provision of information on pregnancy exposures has arisen from the individual efforts of genetics departments, state health agencies, and other interested health providers. These organizations function in a manner similar to poison control centers in that telephone inquiries are received and responses given without charge. Most of the calls are received from women who are pregnant and have been exposed inadvertently to a pharmaceutical agent during early pregnancy.

Although the teratology information services in this country operate independently, the Organization of Teratology Information Services (OTIS) was formed more than 10 years ago to facilitate education and training in this area and to establish quality assurance criteria. A parallel effort has been coordinated by the Council of

Regional Networks for Genetic Services, which has worked with OTIS to develop a framework for the provision of teratology information services.⁴ This framework sets forward the performance of surveillance on exposed pregnancies as a research responsibility of teratogen information services.

To date, surveillance activities of teratology information services have resulted in several publications that report pregnancy outcome after exposure to a number of agents including carbamazepine,⁵ lithium,⁶ carbon monoxide,⁷ chloroquine,⁸ fluoxetine,⁹⁻¹¹ and clarithromycin.¹²

METHOD OF STUDY

Selection of exposures of interest

The exposures under investigation are the inhaled corticosteroids triamcinolone acetonide, beclomethasone, flunisolide, fluticasone, and budesonide. Information is also collected on pregnancy outcome after exposure to other medications used for asthma including inhaled β -agonists (eg, albuterol, metaproterenol, terbutaline, pirbuterol, salmeterol, and bitolterol), cromolyn, nedocromil, theophylline, leukotriene receptor antagonists, and systemic corticosteroids. Women exposed to asthma medications other than inhaled corticosteroids will serve as a reference group controlled for the presence of asthma, and a second control group will consist of nonasthmatic women who inquire about exposures not believed to increase the incidence of adverse pregnancy outcome (eg, acetaminophen, dental x-rays).

Identification of exposed pregnancies

Participating teratology information services have been identified by OTIS as having an interest in surveillance activity and the capability to perform this type of research. Subjects may enroll by calling the Teratogen Information Service in their area or by calling a central toll-free number (Fig 1). Subjects with the necessary exposure criteria will be enrolled prospectively over a period of up to 4 years.

Follow-up methods

Follow-up of prospective pregnancies includes regular contact by study personnel to maintain information on pregnancy events (eg, other medication exposures, asthma severity) and to maintain subject interest in the study purpose. Because this study is a nationwide effort, it is anticipated that there will be populations who change their addresses or telephone numbers frequently, and contact throughout pregnancy by study personnel will facilitate retention of these pregnant subjects in the sample.

Subjects are required to enroll before 20 weeks' gestation (term = 38 to 42 weeks) and are called every 2 months during the pregnancy, as well as after the anticipated delivery date. At each contact, staff record all exposures and medical events since the last contact and complete a standardized evaluation of asthma severity. The asthma severity information includes hospitaliza-

TABLE I. Outcome information

Date of birth or termination
Gestational age at birth or termination
Status (live born, stillborn, spontaneously aborted, voluntarily aborted, ectopic pregnancy, molar pregnancy)
Sex
Pregnancy weight gain of mother
Obstetric complications (eg, pre-eclampsia, premature labor, premature delivery)
Pregnancy order (singleton, twin, triplet)
Anomalies diagnosed at birth or termination
Anomalies diagnosed after birth
Weight at birth
Length at birth
Condition at birth (including when available Apgar scores, umbilical cord gases, need for resuscitation, intensive care nursery admission)
Neonatal illnesses, hospitalizations

tions, unscheduled visits, use of systemic corticosteroids, and peak flow velocities for those women who monitor this parameter. Medical records are examined to supplement information obtained directly from the subject. Responses to maternal interview and copies of the pediatric records are reviewed by an obstetrician and by a dysmorphologist pediatrician who independently evaluate and categorize exposure and outcome information. Disagreements in assignment of exposure or outcome status are negotiated and, if sufficiently frequent, will be analyzed separately. Pregnancy and infant outcome variables are listed in Table I.

Analysis

Rates of adverse outcome (malformation, death, functional impairment, and growth inhibition¹³) will be compared initially by using relative risk methods and 95% CIs.

When a sufficient number of exposed pregnancies are available, stratification will be used for gestational weeks of exposure, exposure to other agents, severity of asthma, gestational age at birth, year of exposure, and maternal race and age by means of regression techniques. Comparisons specifically planned include: (1) outcome in pregnancies exposed to inhaled glucocorticoids versus pregnancies in patients with mild asthma (exposed to inhaled β -agonists only with no unscheduled asthma visits); (2) outcome in pregnancies exposed to inhaled glucocorticoids versus pregnancies exposed to asthma medications other than inhaled glucocorticoids and β -agonists; (3) outcome in pregnancies exposed to inhaled corticosteroids versus pregnancies in nonasthmatic women; and (4) outcome in pregnancies during which asthma is treated versus pregnancies in nonasthmatic women.

There are sentinel abnormalities that may suggest

more detailed investigation. For example, many infants with malformation syndromes are small for gestational age; however, the malformations may not be sufficiently severe to be apparent at birth. Thus an exposure that produces developmental abnormalities may be identified in this surveillance effort only through a shift in birth weight distribution. When such a sentinel shift is detected, more detailed evaluation can be obtained through a standardized dysmorphology examination. This level of evaluation is outside the scope of this study; however, the identification of the sentinel abnormality would give rise to a separate effort to obtain appropriate detailed evaluation.

Although not included in this study, evaluation of neurobehavioral function of prenatally exposed children is considered an important outcome parameter. Records of exposed live-born infants will be maintained by the study coordinator in the event that future support becomes available for the evaluation of neurobehavioral follow-up.

ADDITIONAL INFORMATION

For additional information or to enroll subjects, clinicians are invited to contact Dr Scialli or e-mail, sciallia@gunet.georgetown.edu or to call 888-523-4847.

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