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Better Data Needed from Pregnancy Registries

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Abstract

This article is a consensus position statement from the Research Committee of the Organization of Teratology Information Specialists (OTIS). The Committee believes that more specific information on the timing and dose of drug exposures from pregnancy birth defect registries sponsored by pharmaceutical companies (herein called *pregnancy registries*) would improve the estimation of risk for developmental toxicity (i.e., growth alteration, structural anomalies, functional/neurobehavioral deficits, or death). Specifically, the Committee believes that the exposure timing should be stated in gestational weeks and days rather than simply weeks. In addition, the Committee believes that the exposure dose should be stated in patient-specific terms, such as body weight (mg/kg) or body surface area (mg/m^2) rather than simply dose strength. Although the focus of this position is pregnancy registries, it also is applicable to any source of medication-induced embryo-fetal toxicity.

Keywords

pregnancy registries; exposure timing; exposure dose

INTRODUCTION

Pregnant women are exposed to a drug during gestation when treatment is initiated in one of three ways: (a) before conception and continued into pregnancy, (b) when the woman is not known to be pregnant, or (c) when the woman is known to be pregnant. In any of these situations, estimating the risk from the exposure is based on: (i) the reported human pregnancy experience with the drug or other drugs in the same pharmacologic class or subclass, (ii) the gestational age when the exposure occurred, (iii) the dose of the drug, (iv) the potential for the drug to cross the placenta to the embryo-fetus, (v) animal reproduction data, and, for risk-benefit assessment, (vi) the risk from untreated or undertreated disease. The first three factors are the most important because human pregnancy experience is sine qua non for providing the best risk estimate of developmental toxicity. Unfortunately, these critical factors are often not or only partially available. In contrast, the latter three factors usually are available or can be estimated; although they are important adjuncts, their predictive value for developmental toxicity is not comparable to human pregnancy data.

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The sources of pregnancy drug exposure data are case reports, case-control studies, cohort studies, computerized databases, and pregnancy registries. Case reports are important for raising signals of potential drug-induced developmental toxicity for a specific drug. Retrospective case-control studies are useful for evaluating rare outcomes, but they often rely on maternal recall for exposure data that may be different between cases and controls. However, in some designs, such as nested case control studies that are often used with administrative databases, issues regarding recall bias can be avoided. Cohort studies are usually prospective (i.e., subjects are enrolled before the outcome is known) and are commonly used for evaluating risk, but their size is frequently small and the selection of appropriate comparison groups (unexposed pregnancies) is important. Computerized databases, such as Medicaid, which can have the advantage of accessibility to large numbers of exposed pregnancies and relatively large numbers of outcomes, can raise concerns regarding misclassification; this must be addressed for certain types of exposures or outcomes, uncertainties surrounding the actual exposures, and their timing. Alternatively, traditional pregnancy registries typically involve prospective data collection and, depending on the frequency of exposure, can accrue relatively large numbers of subjects, making them ideal sources of information about pregnancy risks. However, registries are sometimes limited by the absence of important information, such as the timing and dose of the exposure. Moreover, many registries lack appropriate comparison groups (unexposed pregnancies) with sufficient information to calculate relative risks.

Timing of Exposures

The gestational timing in days and/or weeks of an exposure combined with accurate gestational age is the most critical factor for determining whether the exposure had the potential to cause developmental toxicity. Although the critical period of organogenesis (20–55 days after conception or 34–69 days from the first day of the last menstrual period) is the most vulnerable period (Schardein, 2000a), developmental toxicity can occur at any time during gestation with the only requirement being that the toxic exposure coincides with a critical development event (Rodier, 2005).

Obstetricians and others caring for pregnant women routinely date pregnancies from the first day of the last menstrual period or, by the more accurate method, ultrasonography. In either case, the gestational age is described in weeks and days from the first day of the last menstrual period, such as 30 days (4 2/7 weeks), with the understanding that conception occurred on day 14. Ultrasound dating is significantly more accurate than dating by the last menstrual period, with a range of error of approximately 3 days during early pregnancy. The accuracy is inversely related to fetal age, with the range of error increasing with gestation (Manning, 2004).

The gestational timing of structural anomalies is also measured in days and weeks, but in terms that the anomalies must have occurred before the end of the stated period. A drug exposure that occurred after the period could not produce the defect. For example, the neural tube defect meningomyelocele results from events that occur before day 28 following conception (Jones, 2006; Schardein, 2000b). Thus, an event or exposure that occurred at a post-conception age of approximately 35 days or more (allowing for an error in dating) could not have caused the defect. Examples of a few other anomalies and the post-conception days before which the causative event or exposure must have occurred are ventricular septal defects (6 weeks), transposition of great vessels (34 days), cleft lip (36 days), cleft palate (8 weeks), omphalocele (10 weeks), diaphragmatic hernia (6 weeks), and hypospadias (12 weeks) (Jones, 2006; Schardein 2000b).

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Exposure Dose

A broadly accepted principle of teratology is that there is a dose-effect relationship with developmental toxicity. That is, for each drug there is a threshold dose below which there are no adverse fetal effects and above which there is increasing severity and frequency of developmental toxicity. The threshold dose is called the *no observed effect level* (NOEL) or *no observed adverse effect level* (NOAEL). Although it is rarely stated as such, the lowest dose that produces abnormal development is called the *lowest observed adverse effect level* (LOAEL). The NOEL is routinely determined in experimental animal studies. Excluding drugs that only produce effects in humans, such as some monoclonal antibodies (e.g., abciximab), the U.S. Food and Drug Administration requires at least one rodent species (mice or rats) and one nonrodent species (usually rabbits) to be tested (U.S. Environmental Protection Agency, 1991). At least three doses are chosen. Typically, the highest dose will cause slight maternal toxicity (e.g., reduced body weight), the lowest dose corresponds to the approximate human dose, and the middle dose fits between these doses. However, depending on the toxic potency of the drug, all three doses may be a fraction of the maximum human dose. The doses are based on body weight (e.g., mg/kg), body surface area (BSA) (e.g., mg/m^2), or systemic exposure from the area under the plasma concentration versus time curve (AUC) (e.g., μg/mL). Moreover, because of the genetic homogeneity of the experimental animals, the NOEL applies to the entire study population.

Obviously, experimental human studies to determine a NOEL would be unethical. Thus, if a NOEL is suggested by reported experience, it must have been based on observations in which the spectrum of defects thought to be caused by the drug occurred only at certain doses within the therapeutic range. However, human teratology studies, including pregnancy registries, typically describe doses based on the strength of the drug (e.g., milligrams), not as patient-specific doses based on body weight or BSA (dosing based on AUC would be prohibitively expensive). This practice gives an incomplete picture of the dose because the body weights and surface areas of patients are highly diverse. For example, consider a 100-mg dose given to two women, one who weighs 55 kg and the other 110 kg, and both are 62 inches tall. The weight-adjusted dose for the smaller woman would be 1.8 mg/kg, whereas the dose would be 0.9 mg/kg for the larger one. Based on weight, the smaller woman's dose would be twice as much (100% greater) as the larger woman's dose. If dosing were based on BSA, the doses would be 65 and 46 mg/m^2 from the surface areas of 1.55 and 2.19 m^2, respectively (Halls, 2008). Thus, based on BSA, the dose for the smaller woman would be 1.41-fold (41% greater) the larger woman's dose. In both cases, higher plasma concentrations of the drug would be expected in the smaller woman and, consequently, higher concentrations in her fetus. Thus, although a woman's body weight changes during pregnancy, birth defect registries should at least specify the patient-specific dose during the critical period for birth defects.

An observational NOEL for humans may not be applicable to the entire population because of genetic diversity resulting in marked differences in drug absorption, metabolism, and excretion. However, it might provide some benefits in counseling if effects of the diversity were not great.

Application to Pregnancy Registries

Pregnancy registries are valuable sources of human pregnancy experience because of their prospective nature, enrollment over a wide geographical area, and potentially large number of subjects. Registries can identify early signals, although even the largest registries have limited power to identify low to moderate increased risks especially for rare outcomes. Prospective pregnancy registries, which typically rely on a volunteer sample, can estimate the birth proportion of birth defects and compare this with an unexposed group. However,

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the registries cannot verify the true birth prevalence of birth defects in association with an exposure because not all exposed pregnancies are recruited to the registry. In addition, there may be selection bias involved in those who volunteer for the study, or who complete the study, compared with those who do not. Thus, the results may be neither valid nor representative of the target population of all exposed pregnancies. Furthermore, interpretation of pregnancy registry data can be limited by high rates of lost-to-follow-up pregnancies that may have had outcomes different from those with documented outcomes, by lack of appropriate unexposed comparison pregnancies, by limited information on important confounders, and by little or no information on spontaneous abortions, elective abortions, and fetal deaths without birth defects. However, a primary limitation of most pregnancy registries relates to a lack of detailed information on exposure timing and dose.

Table 1 has information on five pregnancy registries. Four of the five registries reported exposures by trimesters and three specified the time of exposure in weeks, but only for exposed pregnancies that resulted in adverse outcomes. None of the registries specified timing of exposure in weeks and days. Moreover, the timing of exposures in weeks and days for pregnancies ending in normal outcomes was not specified in any registry. The maternal dose, in terms of milligrams or other units of dose strength, was reported in two registries, but only for those cases ending in an adverse outcome. None of the registries reported patient-specific doses in terms of body weight or BSA. However, this could be easily done because only the patient's height and weight are needed to calculate doses based on BSA or body weight. Surprisingly, none of the registries mentioned dose if the outcome did not involve developmental toxicity. The absence of specific dosage information for all patients enrolled in a pregnancy registry prevents any attempt to establish a NOEL.

Summary

For many drugs, pregnancy registries are the primary source of human pregnancy experience, particularly for newly-marketed drugs. Although they are an important source of information, their value could be markedly increased by providing more exact measurement of the exposures in weeks and days as well as patient-specific dosing information during the critical periods in terms of body weight, BSA, or drug serum levels, if available, for all exposures.

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Table 1

Exposure Timing and Dose Information from Pregnancy Registries

Pregnancy registries	Timing by trimester	Timing by weeks/days	Patient dose	Patient-specific dose*	Dose for all patients
Lamotrigine	Yes	Weeks only if DT	Yes (mg) (DT only)	No	No
Montelukast	Yes	Weeks only if DT	No	No	No
Rizatriptan	No	No	No	No	No
Sumatriptan Naratriptan	Yes	Weeks only if DT	Yes (mg) (DT only)	No	No
Bupropion	Yes	No	No	No	No

Lamotrigine Registry: http://pregnancyregistry.gsk.com/lamotrigine.html.

Montelukast Registry: http://www.merckpregnancyregistries.com/singulair.html

Rizatriptan Registry: http://www.merckpregnancyregistries.com/maxalt.html

Sumatriptan/Naratriptan/Treximet Registry: http://pregnancyregistry.gsk.com/sumatriptan.html

Bupropion Registry: http://pregnancyregistry.gsk.com/bupropion.html

*Patient-specific dose = mg/kg, mg/m^2, or serum concentrations.

DT, developmental toxicity.