Bias Against the Null Hypothesis in Retrospective Registries of Gestational Drug Exposure

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Abstract

Objective: The findings in retrospective pregnancy registries related to prenatal drug exposure (collected after pregnancy outcome is known) are commonly reported in regulatory documents and in the medical literature. However, there is little information about the accuracy of the estimates of risk from such registries. We therefore sought to compare the rates of major congenital malformations reported in retrospective and prospective registries for the same drug to quantify the potential bias of retrospective reports.

Methods: We searched for all fetal safety reports related to medications for which information from both prospective and retrospective registries was available. These were published either in the peer-reviewed literature or as pharmaceutical company documents between 1984 and 2011.

Results: For all drugs registries studied, estimates of major congenital malformations from retrospective registries tended to be higher than the rates in prospective registries; median estimates of risk were higher by a factor of 4.18 ± 1.23 (range 2.13–5.97).

Conclusions: The present study confirms a major and consistent bias against the null hypothesis in studies of teratogenic risk using retrospective registries, and this must be considered when interpreting such data. Spontaneous reporting of outcomes after exposure to a drug is highly selective towards adverse events, which families with normal pregnancy outcomes are less likely to report.

Résumé

Objectif : Les constatations tirées de registres rétrospectifs d'exposition prénatale aux médicaments (dont les données sont recueillies une fois l'issue de la grossesse connue) sont régulièrement citées dans des documents réglementaires et dans la littérature médicale. Toutefois, les renseignements quant à l'exactitude de l'estimation des risques effectuée à partir de ces registres sont limités. Nous avons donc cherché à comparer le taux de malformations congénitales majeures déclarées dans des registres rétrospectifs et prospectifs pour un même médicament afin de quantifier le biais potentiel associé aux rapports rétrospectifs.

Méthodologie : Nous avons cherché tous les rapports sur l'innocuité pour le fœtus portant sur des médicaments pour lesquels nous disposions de données tirées de registres rétrospectifs et prospectifs. Il s'agissait de documents produits par des pharmaceutiques ou d'articles publiés dans des revues évaluées par les pairs entre 1984 et 2011.

Résultats : Dans l'ensemble, les estimations du taux de malformations congénitales majeures basées sur les données de registres rétrospectifs avaient tendance à être supérieures à celles associées aux registres prospectifs. L'estimation médiane du risque était supérieure d'un facteur de 4,18 ± 1,23 (étendue: 2,13–5,97).

Conclusions : La présente étude a confirmé l'existence d'un biais important et constant contre l'hypothèse nulle dans les études sur le risque tératogène fondées sur des registres rétrospectifs. Il faut être conscient de ce biais au moment d'interpréter les données de ces registres. La déclaration spontanée de l'issue de grossesse après l'exposition à un médicament dépend grandement de la survenue d'événements indésirables; en effet, les familles sont moins susceptibles de déclarer une issue de grossesse normale.

Key Words: Retrospective registries, pregnancy, malformation, drug safety

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INTRODUCTION

Typically, medications for use in humans are introduced to the market supported by reproductive animal data, which are often not predictive of the risk of human malformation. Furthermore, in pre-marketing clinical trials, accidental exposures to a medication during pregnancy are typically very rare.[1] However, because 50% of all pregnancies are unplanned,[2] large numbers of women are exposed inadvertently to medications in early pregnancy. Moreover, many pregnant women suffer from conditions

that require continued treatment during pregnancy. When a new drug enters the market, case reports of fetal exposure begin to emerge, but unless a very highly teratogenic signal and a unique phenotype are evident (such as was noted with thalidomide or isotretinoin),[3] it takes years before a prospective cohort study of first trimester fetal exposure becomes available.

Historically, most information about the risks of drugs in pregnancy has arisen from findings of spontaneous adverse event reports (case reports). This mechanism of passive surveillance has been well-described[4] and is advantageous in the identification of a rare or unusual fetal outcome. A major limitation of retrospective case series is the lack of denominator data, which precludes estimation of the size of risk with use of the drug compared to the risk in the general population.

Retrospective registries of exposure during pregnancy (enrolment in which follows notification by families or physicians after the pregnancy outcome is known) are typically established by drug companies as part of the regulatory process and their contents are often reported in the peer-reviewed literature.

The main concern regarding the interpretation of findings in these registries is that families with malformed children exposed to a given drug in pregnancy, or their physicians, will be more likely to report the malformation to registries than families with healthy children prenatally exposed to the same drug.[5] However, there is little information available on the precision of the estimates from such registries. In 1999, our group documented that the rate of major malformation associated with the antifungal itraconazole was 13% in the retrospective report collected by the manufacturer but was only 3.2% in the prospective report collected by the same company.[5] Since then, however, the hypothesis that retrospective registries are biased towards higher rates of malformations has not been further confirmed.

Because most medications are not teratogenic,[6] a potentially false teratogenic signal may elicit anxiety and may lead women not to treat serious medical conditions. In at least one class of drugs (the statins), a report of adverse fetal outcomes based on retrospective surveillance[7] led to high levels of anxiety. However, the adverse fetal outcomes were later shown in a meta-analysis of prospective studies not to be associated with exposure to statins.[8]

The objective of the present study was to compare the rates of major congenital malformations reported in retrospective and prospective registries for the same drug to quantify the potential bias of retrospective reports.

METHODS

We performed a search of the electronic database PubMed from inception to December 31, 2013, for all available full English texts, using the following search terms: "retrospective pregnancy registry," "prospective pregnancy registry," "reporting bias," "drug company," and "drug registry," alone and in combination with "and congenital malformations" or "and embryopathy." In addition, several pregnancy registry annual reports that were documented by drug companies and received by the Motherisk program at the Hospital for Sick Children in Toronto were reviewed for the period 1984 to 2011. Motherisk regularly receives these reports upon their release.

For this analysis, we included published articles and registry reports that provided data on rates of major malformations in the offspring of women who were exposed to the specific drug during the first trimester of pregnancy, derived from both retrospective and prospective registries for the same drug.

The following information was recorded from the registries for each drug: the total number of major malformations among live born infants (the numerator); the number of stillbirths or terminated pregnancies; and the total number of reported live births, stillbirths, elective pregnancy terminations, and miscarriages (the denominator).

The reported rates of major malformations in the retrospective and prospective reports from the same registry for the same drug were compared using a Fisher exact test. Odds ratios and 95% confidence intervals were also calculated. The distribution of malformations in each report was compared to the normal distribution of birth defects reported in the United States to identify whether there was a specific pattern of malformations.[9]

RESULTS

The electronic search identified a total of 1316 published articles. After removing all animal studies, case reports, controlled observational studies, and review articles without original data, 122 articles were reviewed in detail. Five drugs or classes of drug identified in peer-reviewed published articles fulfilled the inclusion criteria (itraconazole, fluoxetine, acyclovir, statins, and mefloquine).[5,10–13] Three drugs from drug company annual reports also met the inclusion criteria (quetiapine, quadrivalent human papillomavirus vaccine, and montelukast sodium). In all cases, the rates of major malformations after exposure to these drugs were significantly higher in data reported retrospectively than in data reported prospectively (Table).