# Postmarketing surveillance for drug safety in pregnancy: The Organization of Teratology Information Services Project

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## Brief Reports

# Postmarketing Surveillance for Drug Safety in Pregnancy: The Organization of Teratology Information Services Project

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**BACKGROUND:** Although medications are frequently used during pregnancy, premarketing studies exclude pregnant women, with the result that maternal and fetal risks of medications are largely unknown prior to marketing. **METHODS:** To demonstrate the feasibility of using Teratology Information Services (TISs) to identify potential subjects who may participate in postmarketing surveillance studies regarding medications taken during pregnancy, maternal characteristics and pregnancy exposure data routinely collected from callers to member agencies of the Organization of Teratology Information Services (OTIS) were pooled for two one-month periods. **RESULTS:** A total of 3536 calls inquiring about 7746 different agents were received from pregnant women. Of the 40 medications about which pregnant women most frequently asked, the top two were nonprescription acetaminophen and pseudoephedrine, three were prescription drugs with a U.S. Food and Drug Administration pregnancy label category D designation, and five were prescription antidepressants. **CONCLUSIONS:** TISs are well positioned to prospectively ascertain medication exposures in large numbers of pregnant women and may be an exceptional resource for conducting postmarketing surveillance for the safety of medications taken during pregnancy. *Birth Defects Research (Part A) 70:944–947, 2004.* Published 2004 Wiley-Liss, Inc.†

**Key words:** pregnancy exposures; teratogens; drug safety

## INTRODUCTION

Despite concerns regarding the potential prenatal effects of any drug taken by a woman during pregnancy, several studies have demonstrated that women commonly use several medications over the course of gestation (Bonati et al., 1990; Lacroix et al., 2000). For the majority of agents, safety data for human pregnancy are unavailable (Webster and Freeman, 2001). In response to consumer anxiety and to learn about the prenatal effects of medications for which little or no data are available, a number of Teratology Information Services (TISs) have been established in the United States, Canada, Europe, South America, and Australia. These services utilize trained teratogen information specialists in a variety of university and other health care settings to disseminate the most current data regarding medication safety during pregnancy. To facilitate collaboration, TISs in the United States and Canada have incorporated into the Organization of Teratology Information Services (OTIS) (Leen-Mitchell et al., 2000).

Over the last 15 years, individual and collaborative groups of TISs have completed several pregnancy outcome studies by asking callers with specific exposures to participate in research (Chambers et al., 1996; Einarson et al., 1998; Shuhaiber et al., 1998; Jones et al., 2002). Although



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The findings and conclusions of this study are those of the authors and do not reflect the views of the FDA.

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Table 1
Participating OTIS Member Teratogen Information Services: The States/Province Served by Each

| |
|---|
| Arizona Teratology Information Program |
| CARE Northwest (Washington, Alaska, Idaho) |
| California Teratogen Information Service |
| Connecticut Pregnancy Exposure Information Service |
| Florida Teratogen Information Service—University of Florida |
| Florida Teratogen Information Service—University of Miami[a] |
| Florida Teratogen Information Service—University of South Florida[a] |
| Illinois Teratogen Information Service |
| Indiana Teratogen Information Service |
| Michigan Teratogen Information Service |
| Missouri Teratogen Information Service |
| Motherisk Program (Ontario, Canada)[b] |
| Nebraska Teratogen Project |
| Pregnancy Health Line (New Jersey, Delaware, Pennsylvania)[b] |
| Pregnancy Risk Network (New York) |
| Pregnancy Risk Line (Utah, Montana) |
| Texas Teratogen Information Service |

[a]Participated only in January 2000 study period.
[b]Participated only in September–October 2001 study period.

protocols in these studies have varied, TISs have gained considerable experience in the recruitment and retention of exposed and nonexposed subjects and data collection using a cohort design. However, to date, TISs have not established a systematic method for identification and recruitment of study subjects through the OTIS network. We examined the feasibility of pooling data routinely collected by OTIS member TISs to ascertain a geographically diverse sample of women reporting specific prenatal exposures, which may provide an adequate recruitment base for conducting postmarketing surveillance for the safety of medications taken during pregnancy.

## MATERIALS AND METHODS

During two one-month periods (January, 2000 and September 17–October 19, 2001), selected to represent historically peak caller activity periods, pregnancy exposure data and maternal characteristics collected in a standard manner from callers to OTIS member TISs were de-identified and pooled. These data included the number of callers, number of pregnant callers, maternal and gestational ages, and drug or environmental exposures. Participating TISs are listed in Table 1. Product trade names were changed to generic names. Medications were classified according to a drug compendium, Drug Facts and Comparisons (2002). Nonmedication agents were listed under separate categories. For a composite view of the variety of agents about which TISs were contacted, pregnancy exposure data from the two one-month periods were combined.

## RESULTS

Callers to participating TISs are characterized in Table 2. The categories of agents about which inquiries were made are listed in Table 3. Of 11,265 inquiries made by 5796 individual callers, 3536 callers were pregnant women, who inquired about 7746 different agents. The remaining 2260 callers were primarily health care providers and postpartum women who called with questions about exposures during breastfeeding. The 40 medications taken as single or multiple component products about which pregnant women most frequently inquired are listed in Table 4. Although 60% of those medications are prescription products, the top two are available over-the-counter. The specific drug most frequently inquired about was acetaminophen, as either a single- or multiple-component product.

As noted in Table 3, when tabulated by category, drugs from the central nervous system category, which included analgesics, were the subset most commonly asked about. Medications classified as respiratory agents included, but were not limited to, decongestants, antihistamines, cough medicines, and drugs used to treat asthma. The miscellaneous category included, but was not limited to, occupational exposures not otherwise categorized, paternal exposures, infectious disease, and hyperthermia. The most common chemicals about which inquiries were received were hair dyes, followed by pesticides, paint, solvents, methyl-mercury associated with fish consumption, acrylics for fingernail care, lead, and household bleach. The most frequent inquiries regarding herbal/natural products were for echinacea, menthol, chamomile tea, evening primrose, acidophilus, St. John's Wort, and ginseng.

## DISCUSSION

Our findings demonstrate the ability of OTIS member TISs to ascertain large numbers of pregnant women representing a broad geographic area. These women inquired about a wide variety of drug, chemical, herbal/natural products, and other environmental exposures. Furthermore, the exposures for which contact with a TIS was initiated most often occurred in the first trimester.

It is unknown to what extent TIS inquiries represent exposures in the general population of pregnant women—an important consideration in evaluating potential biases inherent in this source of data. To our knowledge,

Table 2
Characteristics of all Callers to OTIS Member TIs for Two One-Month Study Periods

| Characteristic | Study periods: January, 2000 | Study periods: September–October, 2001 |
|---|---|---|
| Total no. of callers | 1499 | 4297 |
| % of callers pregnant at time of contacting TIS | 79.5 | 54.5[a] |
| Maternal age of pregnant caller (years ± SD) | 29.7 ± 6.8 | 31.7 ± 5.4 |
| Mean gestational age at time pregnant callers contacted TIS (weeks ± SD)[b] | 13.5 ± 8.9 | 15.0 ± 9.8 |

[a]Data reflect the inclusion in the September to October 2001 study period of the Motherisk Program, Ontario Canada, where 53% of the calls are from nonpregnant women and men (33% breastfeeding, 7% planning pregnancy, 13% nonpregnant seeking information). Excluding Motherisk data from this study period, 75% of callers were pregnant.
[b]Gestational age was calculated from the first day of the last menstrual period.

Table 3
Broad Categories of Agents

| Category | No. of inquiries by pregnant callers[a] | % of inquiries by category among pregnant callers[a] | Total no. of inquiries[b] |
|---|---|---|---|
| Central nervous system agents (including analgesics) | 1664 | 21.5% | 2703 |
| Respiratory agents | 942 | 12.2% | 1394 |
| Miscellaneous | 906 | 11.7% | 1165 |
| Chemicals | 711 | 9.2% | 919 |
| Recreational (including alcohol, cigarettes, caffeine, and illicit drugs) | 689 | 8.9% | 787 |
| Systemic antiinfective agents | 501 | 6.5% | 869 |
| Nutrients and nutritional agents | 404 | 5.2% | 507 |
| Dermatological agents | 393 | 5.1% | 553 |
| Biologic and immunologic agents (including vaccines) | 369 | 4.8% | 601 |
| Endocrine/metabolic agents | 342 | 4.4% | 486 |
| Natural and herbal products | 264 | 3.4% | 389 |
| Gastrointestinal agents | 226 | 2.9% | 357 |
| Diagnostic aids | 162 | 2.1% | 214 |
| Cardiovascular agents | 61 | 0.79% | 125 |
| Renal and genitourinary agents | 44 | 0.57% | 77 |
| Hematological agents | 25 | 0.32% | 49 |
| Ophthalmic and otic agents | 23 | 0.29% | 38 |
| Antineoplastic agents | 20 | 0.26% | 32 |
| Total | 7746 | 100% | 11,265 |

[a]Number and percents represent spontaneous inquiries; callers were not prompted regarding exposure to recreational agents.
[b]Inquiry: number of questions about a specific exposure; individual callers may ask questions about more than one specific exposure; thus more than one inquiry was made by some callers.

there are no published U.S. population-based data on the overall frequency of specific medications used in early pregnancy. As the majority of pregnancies in the United States are unplanned (Forrest, 1994), women may continue their usual medication usage patterns into the early weeks of an unrecognized pregnancy. Therefore, the representativeness of TIS inquiries is addressed here by comparison to women of child-bearing age in the Slone Survey, a population-based survey of medication use in ambulatory adult U.S. residents (Kaufman et al., 2002).

Acetaminophen and pseudoephedrine, the top two drugs about which TISs were contacted, were the first and fourth most commonly used medications among women 18–44 years of age in the Slone Survey. In addition, 16 of the most frequently used drugs by women in this age group were identical in both the Slone Survey and the present study. Of the 40 drugs about which most inquiries were made to TISs, 60% were prescription medications as were 70% of the 37 drugs used most often by women of reproductive age in the Slone Survey. To the extent that medications used by women of reproductive age are representative of early pregnancy exposures, these data provide some evidence that the exposures about which women contacted a TIS are characteristic of exposures in the general population of pregnant women.

Differences between the studies may reflect that TIS callers were women who were pregnant, with immediate concerns about the risks of specific exposures, while the Slone Survey sampled U.S. adult women in the same age range. Five of the top 10 prescription drugs for which inquiries were made to a TIS were antidepressants, as opposed to none of the top 10 used by 18- to 44-year-old women in the Slone Survey. Three of the top 40 medications about which inquiries were made to TISs—alprazolam, clonazepam, and lorazepam—have a pregnancy category D designation, defined as "positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks" (U.S. Food and Drug Administration, 2003). Of these, only alprazolam was listed in the 37 most commonly used medications among reproductive-aged women in the Slone Survey.

Information about diverse nonmedication agents was requested by callers to OTIS member TISs. For some of these agents, such as alcohol, cocaine, and radiation, teratogenic potential has been documented (Jones and Smith, 1973; Brent, 1986; Addis et al., 2001). For other common inquiries, such as household and workplace chemical agents and natural/herbal products, little or no information is available regarding their effects on pregnancy outcome.

It is unknown what proportion of pregnant women with exposure to any given agent contact a TIS, what percentage of those women would agree to participate in a pregnancy outcome study, and to what extent those women would differ from women who either do not call a TIS or would not agree to study participation. Clearly, these issues can impact on the generalizability and statistical power of a sample of exposed pregnant women who might be recruitable through the OTIS network. However, the large number of pregnant women who call TISs about first trimester exposures and the diversity of agents about which they call, demonstrates that prospec-

Table 4
Forty Most Common Prescription and Over-the-Counter Drug Inquiries by Pregnant Callers

| Rank | Drug[a] | No. of pregnant callers | % of all pregnant callers by drug[b] | Total no. callers |
|---|---|---|---|---|
| 1 | Acetaminophen | 290 | 8.0% | 412 |
| 2 | Pseudoephedrine | 151 | 4.3% | 246 |
| 3 | **Oral contraceptives** | 112 | 3.2% | 155 |
| 4 | **Codeine derivatives** | 110 | 3.1% | 166 |
| 5 | Dextromethorphan | 106 | 3.0% | 175 |
| 6 | **Fluoxetine** | 81 | 2.3% | 148 |
| 7 | Ibuprofen | 80 | 2.3% | 130 |
| 8 | **Vaccine-influenza** | 78 | 2.2% | 137 |
| 9 | Vitamin A | 77 | 2.2% | 95 |
| 10 | **Paroxetine** | 73 | 2.1% | 138 |
| 11 | Prenatal vitamins | 69 | 2.0% | 71 |
| 12 | **Amoxicillin** | 62 | 1.8% | 83 |
| 13 | Diphenhydramine | 58 | 1.6% | 84 |
| 14 | **Sertraline** | 53 | 1.5% | 101 |
| 15 | Pyrethrins | 49 | 1.4% | 73 |
| 16 | **Albuterol** | 49 | 1.4% | 59 |
| 17 | Aspirin | 47 | 1.3% | 71 |
| 18 | Salicylic acid | 47 | 1.3% | 61 |
| 19 | Doxylamine | 47 | 1.3% | 56 |
| 20 | Chlorpheniramine | 45 | 1.3% | 74 |
| 21 | Guaifenesin | 45 | 1.2% | 67 |
| 22 | **Vaccine-MMR** | 41 | 1.2% | 62 |
| 23 | Vitamin C | 40 | 1.1% | 50 |
| 24 | **Alprazolam**[c] | 39 | 1.1% | 57 |
| 25 | **Bupropion** | 38 | 1.1% | 60 |
| 26 | Vitamin B-6 | 36 | 1.0% | 44 |
| 27 | **Venlafaxine** | 34 | .96% | 75 |
| 28 | **Acyclovir** | 33 | .93% | 52 |
| 29 | **Clonazepam**[c] | 31 | .88% | 44 |
| 30 | **Prednisone** | 30 | .85% | 52 |
| 31 | **Citalopram** | 28 | .79% | 69 |
| 32 | **Fluticasone** | 28 | .79% | 49 |
| 33 | **Tretinoin** | 27 | .76% | 34 |
| 34 | **Lorazepam**[c] | 25 | .71% | 45 |
| 35 | **Nitrofurantoin** | 25 | .71% | 42 |
| 36 | **Levothyroxine** | 25 | .71% | 38 |
| 37 | **Loratadine** | 24 | .68% | 53 |
| 38 | **Erythromycin** | 23 | .65% | 41 |
| 39 | Phenylephrine | 21 | .60% | 38 |
| 40 | **Gabapentin** | 21 | .60% | 35 |

[a]Bold type indicates drugs available by prescription only.
[b]Percent based on a total of 3536 pregnant callers.
[c]Has an FDA pregnancy category label D designation which is defined as "positive evidence of human fetal risk based on adverse reaction data from investigational or marketing studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks."

tively ascertained pooled data from OTIS member TISs has the potential for development into a systematic method of identifying exposed pregnant women across the United States and Canada. Furthermore, utilizing the OTIS network in this manner may provide an exceptionally valuable resource for recruitment of exposed women as subjects to participate in postmarketing surveillance studies for the safety of medications used in pregnancy.

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