LEADING ARTICLE

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Pregnancy Exposure Registries

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Abstract

Scientifically valid data on the safety of drug use during pregnancy are a significant public health need. Data are rarely available on the fetal effects of *in utero* exposure in human pregnancies, particularly when a drug is first marketed. Data from animal reproductive toxicology studies, which function as a screen for potential human teratogenicity, are usually all that is available in a product's labelling. For practising clinicians, translating known animal risks into an accurate assessment of teratogenic risks in their patients is very difficult, if not impossible. Without human data on the effects of *in utero* drug exposure, it is difficult for physicians and other healthcare providers (e.g. genetic counsellors) to adequately counsel patients about fetal risks. Therefore, a pregnant woman may decide to unnecessarily terminate a wanted pregnancy or forego needed drug therapy. In spite of the lack of data on the safety of drug use during human pregnancies, pregnant women are exposed to drugs either as prescribed therapy or inadvertently before pregnancy is known (over one-half of pregnancies are unplanned). Because little is known about the teratogenic potential of a drug in humans before marketing, post-marketing surveillance of drug use in pregnancy is critical to the detection of drug-induced fetal effects. The existing passive mechanism of spontaneous reporting of adverse drug effects is inadequate to routinely detect drug-induced fetal risks or lack of such risks. Therefore, post-marketing pregnancy exposure registries are being increasingly used to proactively monitor for major fetal effects and to describe margins of safety associated with drug exposure during pregnancy. However, differing methodological rigour has been applied to the development of pregnancy exposure registries. It is important that all pregnancy registries develop epidemiologically sound written study protocols *a priori.* It is only through the use of rigourous methodology and procedures that data from pregnancy exposure registries will withstand scientific scrutiny. Successful recruitment of an adequate number of exposed pregnancies, aggressive follow-up, and complete and accurate ascertainment of pregnancy outcome are critical attributes of a well-designed registry.

While women are now included in clinical trials during the development of a new drug, pregnant women are still actively excluded.[1] Especially for early studies of new products of unknown human teratogenic potential, the participation of pregnant women may not be feasible because of fetal safety concerns.[2] If pregnancy does occur during the trial, the usual procedure is to discontinue treatment and

drop the patient from the study. Consequently, when a drug is first marketed, except for products developed to treat conditions unique to pregnancy, there are usually no human data on the fetal effects of *in utero* exposure to that drug. The only data on fetal effects initially available in the product label come from animal reproductive toxicology studies.

Animal studies function as a screen for potential human teratogenicity and are a required part of the drug development process. The positive and negative predictive values of animal studies for humans are often uncertain.[3] Animal models can be misleading when screening for drug-induced fetal effects by detecting associations that ultimately turn out to be false positive or false negative in humans.[4] The strongest concordance between animal findings and human effects is when there are positive findings from more than one species, although even in this case the results cannot always be used to predict specific human effects or incidence in humans.[5] For practising clinicians, translating known animal risks into an accurate assessment of teratogenic risk in their patients is very difficult, if not impossible.

In spite of the lack of information on the safety of drug use during pregnancy, pregnant women are exposed to drugs. With drugs used for preventive or active treatment in women of childbearing age, it is not uncommon for exposure to the fetus to occur during the critical period of organogenesis (3–8 weeks post-conception),[6] because the woman might not be aware of her pregnancy at that time. A recent survey reported that 49% of women aged 18–44 years used at least one prescription drug during the preceding week while 3% had used five or more.[7] Approximately 10% of women aged 15–44 years of age become pregnant annually, with about half of these unplanned pregnancies.[8] This pregnancy rate varies considerably by age group and ranges from 1–18% per year.[9] Some women also enter pregnancy with medical conditions that require ongoing or episodic treatment (e.g. asthma, epilepsy, hypertension) and new medical problems may develop or old ones may be exacerbated by pregnancy (e.g. migraine headaches, depression). Studies also show that most pregnant women knowingly use either prescribed or over-the-counter drugs during pregnancy.[10-12]

Because little is known about the teratogenic potential of a drug in humans before marketing, post-marketing surveillance of the drug use in pregnancy is critical to the detection of drug-induced fetal effects. In the US, drug companies are required to report all adverse drug experiences, including fetal effects, to the US FDA. Historically, most information about the risks of drugs in pregnancy has arisen from these types of isolated case reports.[6] This passive mechanism of surveillance has been well described.[13] For identification of truly rare or unusual outcomes, this system offers many advantages. However, some of the well-known limitations of spontaneous reporting are particularly problematic when trying to evaluate drug risks in pregnancy. Limitations include the lack of denominator data, absence of controls, selection and recall bias associated with retrospective reporting, barriers to reporting and poor case documentation.

To overcome these limitations, post-marketing pregnancy exposure registries are increasingly used to proactively monitor for major fetal effects and to describe margins of safety associated with drug exposure during pregnancy. The FDA website has a list of current pregnancy exposure registries.[14] In August 2002, because of differing methodological rigour that has been applied to the development of existing pregnancy exposure registries, the FDA published guidance on Establishing Pregnancy Exposure Registries to encourage the development of formal written study protocols *a priori* to help ensure the use of standard procedures that will withstand scientific scrutiny.[15] While written as guidance for FDA-regulated industry, the document has broad utility for any researchers interested in monitoring drug exposures during pregnancy. This article is based on that guidance document.

1. What is a Pregnancy Exposure Registry?

A pregnancy exposure registry is a prospective observational study that actively collects information on medical product exposure during pregnancy and associated pregnancy outcomes. Pregnancy exposure registries differ from other post-marketing surveillance techniques, such as spontaneous reporting of adverse drug reactions and case-control surveillance. In a pregnancy exposure registry, pregnant women are enrolled prospectively (i.e. after exposure to a product but before the outcome is known, including the conduct of any prenatal tests that could provide some knowledge of the outcome of pregnancy) and followed to the end of their pregnancies. Data on the pregnancies and their outcomes are collected at set points in time with live births sometimes monitored for up to a year or longer. This prospective orientation with systematic collection of information is the major strength of the pregnancy exposure registry design, providing both a numerator (number of adverse outcomes) and a denominator (total number of exposed pregnancies), which allows for the calculation of an estimated risk. The other surveillance methods are retrospective with cases reported or enrolled based on an adverse outcome (e.g. an infant born with a birth defect) from an unknown number of exposed pregnancies. Retrospective cases are biased toward adverse outcomes because normal outcomes are not reported to birth defect registries and are unlikely to be reported to spontaneous adverse event reporting systems.

Pregnancy exposure registries have several functions. They can serve as a hypotheses-generating tool to signal possible problems for further investigation. They can also monitor for suspected risks raised by animal studies, premarketing clinical studies or post-marketing case reports. Additionally, they can be used to identify factors that affect the risk of adverse outcomes, such as dose, timing of exposure or maternal characteristics. However, they are best suited to detect major teratogens or conversely to provide some margin of assurance that a drug is not a major teratogen. Providing reassurance that a particular drug is not another thalidomide or isotretinoin is critically important. However, given their cohort design, pregnancy exposure registries are seriously constrained in their ability to detect teratogens that might more modestly increase the risk of a specific defect (e.g. cleft palate). They are unlikely to enrol a sufficient number of exposed pregnancies to provide meaningful reassurance that a particular drug does not increase the risk of a specific defect by 2- to 5-fold. This is an important limitation of this approach.

The ultimate goal of a pregnancy exposure registry is to provide clinically relevant human data that can be used in a product's labelling to provide medical care providers with useful information for treating or counselling patients who are pregnant or anticipating pregnancy. In the US, such data have been used to support a change from the originally assigned Pregnancy Risk Category[16] (e.g. acyclovir and budesonide inhalational powder from Category C [positive animal data, no human data] to Category B [positive animal data but adequate and well-controlled studies in humans failed to show a fetal risk]).

2. When to Establish a Pregnancy Exposure Registry

The decision to establish a pregnancy exposure registry includes consideration of both the need for pregnancy risk information and the feasibility of successfully completing the study. A pregnancy exposure registry is recommended when it is likely that a drug will be used as therapy for a new or chronic condition in women who are or may become pregnant. A product is also a good candidate for a pregnancy exposure registry when inadvertent exposures during pregnancy are expected to be common (i.e. the drug is likely to be used frequently by women of childbearing age) or when the product presents special circumstances (e.g. there is a potential for infection of mother and fetus by administration of a live, attenuated vaccine). The need for a

pregnancy exposure registry increases when a product in one of these categories may have the potential to cause harm during pregnancy.

When the purpose of the pregnancy exposure registry is to assess margins of safety of a product or to monitor for potential harm, it is appropriate to initiate the registry as soon as possible, such as at the time of initial marketing, when a new indication is approved, or when patterns of use reveal that the product is used by women of reproductive age.

In some cases, a regulatory authority may ask a drug company to conduct a pregnancy exposure registry as part of a clinical study before approval or, more typically, as part of a post-marketing drug approval commitment. Companies can also initiate registries independently, as part of their overall post-marketing surveillance programme.

3. Designing a Pregnancy Exposure Registry

The design of a pregnancy exposure registry should reflect its underlying objectives. The principles of epidemiological research and those of observational research, in particular, apply to the design and conduct of a pregnancy exposure registry.[17-19]

A thoughtfully developed, formal, written protocol based on sound epidemiological methods and consistently applied procedures, from recruitment of an adequate number of participants to interpretation of registry results, will ensure the conduct of a scientifically rigourous study. Because most fetal effects are relatively rare, even small or minor flaws in registry design and execution can have a large effect on the final results.

3.1 Background Section of the Protocol

The background section of the protocol provides the context for understanding why the registry is being conducted and its goals and objectives. All pertinent information considered in developing the protocol should be summarised in the background section, including the following:

- Findings from animal reproductive toxicity studies, other relevant pharmacological and toxicological studies such as those that address structure activity relationships, and any human data (e.g. pregnancy exposures reported during clinical trials).
- What human fetal effects might be expected to be seen based on what is known about the drug.
- The characteristics of the patient population expected to use the product, in terms of the number and proportion of all women by age group with the diagnosis for which the drug is used as well as the number and proportion of these women who might be expected to take the drug of interest.
- An estimate of potential annual product exposure in pregnant women in order to estimate the length of time needed to recruit a sufficient number of exposed pregnancies.
- The expected characteristics of exposure during pregnancy (dose, timing, duration) and the likelihood that the treatment would be discontinued at recognition of pregnancy.
- The medical condition for which the product has a labelled use and its impact on the pregnant woman and the fetus, including the effects of non-treatment.
- The potential benefits of the product, if there are benefits unique or particularly relevant to pregnant women.

3.2 Patient Recruitment

Recruitment of an adequate number of pregnant women is critical to the success of a registry. By definition, all women should be enrolled prospectively. However, it can be expected that both prospective and retrospective reports will be received in spite of the desire for enrolment prior to knowledge of the outcome. Cases where the condition of the fetus has already been assessed through some prenatal testing (e.g. targeted ultrasound, amniocentesis) are usually considered retrospective, even if the tests were normal. Because it can be difficult to obtain enrolment before prenatal testing on a consistent

basis, to achieve the desired sample size, it may be necessary to include pregnancies with some initial normal prenatal tests as prospective cases. However, inclusion of pregnancies with some *a priori* knowledge of normal outcome as prospective cases and exclusion of those with prenatal tests indicating a defect will potentially bias the results toward a lower overall defect risk.[20] Data analysis should address whether enrolment after prenatal testing biased the results.

Determination of an adequate sample size depends on the stated objective of the registry. For example, if the goal is to evaluate the occurrence of major malformations then the sample size should be based on enrolling sufficient pregnant women with drug exposure at the time of embryonic development and major organogenesis (3–8 weeks postconception). Several different formulas can be used to calculate the required sample size.[21,22] A statistician should be consulted to determine which method should be used based on the specific requirements of the registry. The proposed sample size should be sufficient to show either 'no' difference based on an acceptable limit for the confidence interval of the difference between the exposed and comparison group, or alternatively, to detect a clinically significant difference (e.g. a multi-fold increase in the outcome of concern). The statistical power of the registry based on the estimated sample size should be specified in the protocol.

When calculating the number of pregnant women to enrol prospectively to achieve the desired sample size, it is important to be aware that it will be necessary to over-enrol pregnancies to end up with a sufficient number of live-births, if the fetal effect of concern occurs only in live born infants. In general, only about 62% of clinically recognised pregnancies will result in a live birth, 22% will end in elective termination and 16% will result in fetal loss (i.e. spontaneous abortions and fetal death/stillbirth).[9] These population estimates vary considerably by maternal age and health. In addition, these rates are based on the general population and may not apply to specific disease groups (e.g. epilepsy, diabetes mellitus).

An active recruitment plan is essential to enrolling a sufficient number of exposed pregnant women into the registry. Simple, easily accessed enrolment mechanism(s) will increase the number of exposed pregnancies enrolled. The expected frequency of product exposure in pregnant women will determine the length of time needed to enrol an adequate number. Use of a variety of strategies over time will be needed to ensure as broad coverage as possible. Some strategies that have been used with varying success by current registries include announcement of the registry and contact information in the medical product labelling, similar notices in the product circular, promotional materials and product internet pages, announcements in lay and professional magazines, journals and newsletters, personal mailings to specialists, and exhibits at professional meetings. Regular feedback to health-professional reporters on the status of the registry can help to maintain their interest in enrolling new patients; several existing registries do this on a routine basis.[23] Registries are encouraged to work with the US Centers for Disease Control and Prevention (CDC), the international Organisation of Teratogen Information Services (OTIS), and other relevant organisations such as patient advocacy groups (e.g. American Diabetes Association) and medical societies (e.g. American Rheumatology Society), to endorse or assist in the conduct of pregnancy exposure registries, thereby facilitating patient recruitment. To increase awareness of existing registries, the FDA posts information on all registries of which it is aware on its pregnancy registry internet page.[14]

To prevent problems with regulatory authorities, registry recruitment materials should neither actively promote use of an individual product in the special population of pregnant women (unless the package insert contains supporting information) nor imply that product safety and efficacy data exist beyond the information contained in the currently approved labelling.

3.3 Source of Information

Exposed pregnancies can be enrolled and information surrounding the pregnancy and its outcome provided by healthcare providers,[24] pregnant patients[25,26] or a combination of both.[27] The ultimate objective of a pregnancy exposure registry is to obtain complete, valid information for all enrolees on pregnancy outcome and the medical status of any births. The source of information can influence the ability to meet this objective, i.e. the person who enrols an exposed pregnancy may not be the best source of information on the outcome. All alternatives for obtaining information, including the use of patient medical record release forms should be examined to determine the best mechanism to capture pregnancy and outcome data while minimising loss to follow-up.

Enrolment by healthcare providers is the most convenient and least expensive method. However, there are important drawbacks to this approach. When contacted for follow-up information the enrolling healthcare provider may not remember which patient was enrolled or may not be highly motivated to complete and mail a questionnaire, so a substantial loss to follow-up may occur. Personal telephone contact with the enrolling physician several times during pregnancy and the use of a unique ID that allows the healthcare provider to identify a particular patient while protecting confidentiality should help decrease loss to follow-up. A healthcare provider may also have a real or perceived medical, legal or ethical conflict of interest if (s)he prescribed the product, or (s)he may be reluctant to seek out and disclose information on pregnancy outcome without maternal consent, even when no specific patient identifiers are part of the collection. In addition, exposures occurring during pregnancy are usually reported by the prenatal healthcare provider or by a specialist treating a specific condition in the mother (e.g. neurologist treating migraine); these providers often know little about the infant after delivery. To increase the likelihood of obtaining accurate pregnancy outcome information the enrolling healthcare provider could be asked to obtain signed medical record release forms from the pregnant woman for the registry to acquire medical records from the delivery hospital, prenatal healthcare provider and paediatric healthcare providers, if applicable.

When pregnant women are used as the source of information, informed consent is typically obtained from the women on enrolment. When the pregnancy is completed, if applicable, the women are also asked to sign medical record release forms for the delivery hospital, prenatal healthcare providers, paediatric healthcare provider and/or any specialists. This strategy can confirm patient motivation, minimise loss to follow-up and facilitate cross-validation of information reported by the woman, for example, by allowing for examination of maternal and paediatric medical records or interviews with the appropriate healthcare providers. However, a potential methodological problem with this approach is that self-referrals and nonparticipation of patients who do not give consent can introduce selection bias. Also, obtaining information directly from pregnant women is more expensive as a result of the need for more intensive follow-up and medical validation of self-reports.

3.4 Data Collection

Figure 1 and table I provide a list of maternal data elements and pregnancy outcome information to consider when designing a data collection form for pregnancy exposure registries. What is collected and the source(s) of information depend on a variety of factors and should be modified appropriately for the specific condition or exposure of interest. Data collection should be as complete as possible, without sacrificing the quality of information for quantity of data. To be able to evaluate timing of exposure, it is critical to obtain data that allow the calculation of the date of conception as well as accurate dates of any drug therapy.

If using an internal comparison group (see section 3.7), care should be taken to collect all information in an identical manner from both exposed- and

General	Medical history	Family history	Obstetric history	Current pregnancy
Patient ID Name and telephone number of reporter Date of initial contact Date of follow-up contact Additional contact information (e.g. friend, neighbour) Birth date Race Occupation	For example: • hypertension • diabetes mellitus • seizure disorder • thyroid disorder • allergic disorders • heart disease • connective tissue disease • autoimmune disease • hepatitis • known risk factors for adverse pregnancy outcomes including environmental or occupational exposure • other	Fetal/neonatal abnormalities: • type • maternal/paternal • spontaneous abortions • malformations • multiple fetuses/ births	No. of pregnancies Outcome of each pregnancy: • live birth • spontaneous abortion • elective termination • ectopic pregnancy • molar pregnancy Previous pregnancies: • complications • fetal/infant abnormalities • type of abnormalities	Last menstrual period Estimated delivery date Complications during pregnancy: • adverse drug reaction Number of fetuses Labour/delivery complications: • premature labour or delivery Disease course during pregnancy Obstetric complications: • pre-eclampsia Pregnancy weight gain Medical product exposure: • prescription, OTC, dietary supplements • name, dosage, route, date of first use, duration, indication Recreational drug use: • tobacco, alcohol, illicit drugs • amount, frequency

Fig. 1. Maternal data elements to consider when designing a pregnancy exposure registry. **OTC** = over the counter.

comparison-group women. The registry protocol should include a detailed description of how information will be obtained. This description will help minimise variation. When information is obtained directly from the pregnant woman, a medical record abstraction or an interview with the patient's healthcare provider should be undertaken to confirm critical information obtained from the woman.

3.5 Pregnancy Outcomes

Pregnancy outcomes include spontaneous abortions (loss of embryo or fetus before 20 weeks of gestation), elective terminations, fetal deaths/stillbirths (loss of fetus after 20 weeks of gestation) and live births. Within each of these categories the fetus or infant can be evaluated as to the presence or absence of anomalies or other fetal effects. The protocol should specify *a priori* which pregnancy outcomes and fetal effects will be assessed. Also, the inclusion and exclusion criteria[28] and measures of severity, if applicable, for congenital malformations or other abnormalities of interest should be considered as they have major implications for study design and data analysis.

If spontaneous abortion is to be evaluated as an outcome of interest it is important to identify ex-

Table I. Pregnancy outcome information to consider when designing a pregnancy exposure registry

Source of information:
Maternal healthcare provider
Infant healthcare provider
Mother
Other
Date of receipt of information
Gestational outcome:
Live born
Fetal death/stillborn
Spontaneous abortion
Elective termination
Date of birth or termination
Gestational age at birth or termination
Anomalies diagnosed at termination
Sex
Pregnancy type:
Singleton, twin, triplet, etc.
Assessment at birth:
Anomalies diagnosed at birth
Birth weight and length (small, appropriate or large for gestational age)
Condition at birth (1- and 5-minute APGAR scores, umbilical cord vessels and gases, need for resuscitation, admission to intensive care nursery)
Assessment after birth:
Anomalies diagnosed after birth
Developmental assessment
Infant illnesses
Hospitalisations
Drug therapies

APGAR = activity, pulse, grimace, appearance, respiration.

posed pregnancies as early in gestation as possible since most spontaneous abortions occur during the first trimester.[29] In analysis it is important to take into consideration gestational age at enrolment. It would be expected that pregnancies enrolled earlier in gestation would have a higher rate of spontaneous abortions than those enrolled later. Fully evaluating spontaneous abortions as an outcome can be very difficult if not impossible since a pregnancy registry would never be able to pick up drug-induced fetal losses that occur before pregnancy is known.

For congenital malformations, the length of time for ascertainment following pregnancy completion should be specified and a specific classification scheme such as the CDC birth defects code list[30] used. Overall, major congenital malformations (i.e. those incompatible with life or requiring medical/surgical intervention) occur in approximately 4% of live born infants with individual major anomalies occurring much less frequently.[31] Minor anomalies (i.e. those with no functional or cosmetic significance) may be 10–20 times more common than major ones and 20% of infants with one or more minor congenital anomalies also have a major birth defect.[32] It has been suggested that grouping defects that share embryology and pathogenesis increases the likelihood that a teratogenic effect will be seen.[33] One registry uses this method in their data analyses.[34] Limiting ascertainment of infant outcome to condition at birth will limit the number and type of major malformations reported. One study showed that pooled data from four registries dependent on information at birth from maternal healthcare providers detected fewer cases of multiple defects and fewer internal defects compared with data from a population-based birth defects surveillance system.[20] The study also showed that the percentage of all cases with defects reported to these registries increased from 60% at 3 months of age to 86% at 12 months of age.[20]

It is critical that all congenital anomalies and other complex abnormalities be reviewed and classified by a specialist in the field. The presence of multiple minor malformations can alert an expert to look closer for a major malformation; or certain combinations of defects may constitute a syndrome or have a common aetiology recognisable only by a specialist. Misclassification or inappropriate grouping of outcomes may lead to erroneous conclusions. If using an internal comparison group (see section 3.7), the method of assessment and type of personnel responsible for assessment of infants need to be identical for both the exposed and comparison groups. Blinding of assessors to exposure will decrease the probability of bias.

3.6 Patient Follow-Up

The objective(s) of the registry will determine the type, extent, and length of patient follow-up. Follow-up may stop at birth or may continue through the first year of life of the infant or longer depending on feasibility. Maintaining regular telephone contact periodically throughout pregnancy should minimise loss to follow-up and maximise the number of pregnancies with complete outcome information. Maternal healthcare providers are a good source of information on pregnancy outcomes, such as spontaneous abortions, elective terminations, live births and pregnancy complications. They are not a good resource for information on infant conditions not readily diagnosed at or soon after birth. The healthcare provider of the infant is the best resource for full information on the health status of the infant.

The protocol should include a plan and rationale for follow-up contacts during and/or after pregnancy. Aggressive follow-up of cases is essential. Obtaining alternative contact information (e.g. relative, friend) for the pregnant woman may help decrease loss to follow-up. The plan should contain the number, frequency and timing of follow-up contacts, who will be contacted, how contact will be made, and how and what data will be collected at each contact. The follow-up contact(s) should obtain details on the pregnancy course, outcome, status of the infant and any evidence of abnormalities. Follow-up information can be obtained by mailed questionnaires, telephone interviews, reviews of medical record abstractions, reviews of birth records or a combination of these.

All pregnancies enrolled in the registry should be followed up in the same manner. Losing track of a particular subgroup of women can bias registry results if the reason they are lost is in some way related to their pregnancy outcome (e.g. normal outcomes may be more likely to be lost to follow-up because of less interest in reporting normal outcomes compared with abnormal ones). Additionally, losing a large proportion of registry participants wastes resources and can invalidate an otherwise well-designed pregnancy exposure registry.

3.7 Comparison Groups

With a pregnancy exposure registry, it is critical to use a comparison group. Comparison groups can be either internal to the study (e.g. defined and followed up along with the exposed group of interest) or external to the study (e.g. information collected outside of the study by other investigators that is deemed relevant to the issue under investigation). The proposed comparison group(s) should be specified in the protocol. As there is usually no one ideal comparison group, the inclusion of more than one comparison group can be instructive and may help improve the validity of the registry.

Internal comparison groups can include the following: (i) unexposed, concurrently enrolled pregnant women matched or stratified in relation to the exposed group to control for important covariates; (ii) pregnant women with the same indication or underlying risk factors but who are not taking the drug of interest within a multi-drug registry; or (iii) pregnant women exposed during different trimesters within the same registry (e.g. first trimester exposures compared with second and third trimester exposures).

External comparison groups can include the following: (i) surveillance systems (e.g. data from the National Birth Defects Prevention Network [NBDPN][35] or CDC Metropolitan Atlanta Congenital Defects Program[36]); (ii) general background rates of grouped or individual outcomes (e.g. data from the CDC National Center for Health Statistics [NCHS][37] or the International Clearinghouse for Birth Defects Monitoring Systems[38]); or (iii) data from other pregnancy exposure registries.

Enrolment of a concurrent internal comparison group of unexposed pregnant women with the same indication, while most desirable methodologically, may not be possible. A background rate or the prevalence of congenital anomalies in a population based surveillance system or other pregnancy expo-

sure registry may often be the only available comparator.

If background rates or information from a surveillance system are chosen as a comparison group, it is important to be aware of the limitations of whatever existing system is used (e.g. the NBDPN does not collect information on all congenital anomalies, while the NCHS may have accurate data on spontaneous abortions, but only on those requiring hospital care) so that appropriate analyses can be designed. Additional considerations when choosing a comparison group from an existing system are the ascertainment methods used by the system, how outcomes are defined and identified, the characteristics of the underlying population from which the cases are taken and the time period at which the data were collected. The potential impact of any differences on the interpretation of data from the pregnancy exposure registry should be acknowledged and discussed in the protocol.

3.8 Data Presentation and Analysis

There are no published epidemiological standards for calculating and evaluating risk estimates using prospective data from a pregnancy exposure registry. However, one publication offers some ideas on potential methods.[39] The protocol should describe the planned analytical and statistical methods to be used.

Risk estimates should only be calculated from cases enrolled prospectively. All prospective cases included in the denominator must be 'at risk' of developing the outcome of interest in the numerator, e.g. for major malformations, all cases in both the numerator and denominator must have had first trimester drug exposure; for spontaneous abortions, all cases must have enrolled in the registry by some set time during the first trimester. When registry data are presented the statistical power of the study to detect or rule out a stated increased risk should always be included. While retrospective reports cannot provide a meaningful risk calculation, they can provide important qualitative data and should be included in any registry report. For instance, infants born with a specific constellation of anomalies can be evaluated as a case series.

3.9 Privacy and Human Subject Protection Issues

The importance of informed consent and use of an institutional review board (IRB) are important considerations in the design of a pregnancy exposure registry, even for those registry designs thought to fall in the category of surveillance as opposed to a targeted study.[40] All investigators planning pregnancy exposure registries should consult an IRB to ensure that the collection of data and all other procedures associated with the registry will withstand scientific and ethical scrutiny. The protocol should comply with ethical principles and any applicable regulatory requirements regarding human subjects research (e.g. the US federal regulations for the protection of human subjects[41]). If informed consent is to be obtained from the patient, the text of the informed consent form should be included in the registry protocol.

The recently promulgated US Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule has raised concerns about the ability to monitor the safety of FDA-regulated products. However, the HIPAA Privacy Rule specifically permits the disclosure of protected health information by covered entities such as physicians or hospitals for public health purposes related to the quality, effectiveness and safety of FDA-regulated products to both the manufacturers and directly to the FDA.[42] This includes collecting or reporting adverse events, tracking FDA-regulated products and conducting post-marketing surveillance to comply with requirements or at the direction of the FDA. The US Department of Health and Human Services, Office of Civil Rights, which has jurisdiction for enforcing the Privacy Rule, has issued a guidance that is available on the Internet.[43]

3.10 Use of an Independent Data Monitoring Committee

To ensure scientific integrity and appropriate patient protection, each registry should have an independent data monitoring committee. The committee could advise and participate in establishing a registry, as well as assist in the review of data, classification of any birth defects and the dissemination of information to ensure that results are interpreted and reported accurately. The role and duties of the committee should be specified in the protocol. Members of the committee could include experts in obstetrics, embryology, teratology, pharmacology, epidemiology, paediatrics, clinical genetics, any relevant therapeutic areas and consumers representing the disease state being treated.

3.11 Multidrug Pregnancy Exposure Registries

A multidrug pregnancy exposure registry usually collects information on exposure to various drug therapies in specific diseases, such as HIV,[44] epilepsy[27] or asthma.[45,46] The antiretroviral drug registry is an example of a multidrug registry that is conducted by a contractor with funding from the drug companies that make the various drug products. In some cases, a general multidrug registry, such as that conducted by a teratogen information service, collects information on drugs for unrelated indications. Multidrug registries have advantages over single drug registries with respect to efficiency and economy.

To help avoid redundancy and to prevent overburdening patients, physicians and scientific experts with multiple requests to participate in individual studies, companies should work together to develop multidrug registries whether they are manufacturers of the same generic product or manufacturers of several similar products used to treat the same condition. Combining resources with one mechanism for enrolling patients can increase the ability to achieve adequate sample sizes.

Going beyond the idea of a one generic drug/multiple manufacturers or multiple drugs/one disease types of multidrug registries, it has also been suggested that rather than conducting a separate pregnancy exposure registry for each new drug, a centralised pregnancy exposure registry should be established for drugs of unknown human teratogenicity that are likely to be used by women of reproductive age.[20]

More recently, a call was made for the development of a more comprehensive public-private teratogen surveillance system that combines case-control surveillance with pregnancy exposure registries to provide critical information on high and moderate teratogenic risks of new drugs.[47]

4. US Regulatory Reporting Requirements

4.1 Individual Case Reports

The FDA considers pregnancy exposure registry reports (both prospective and retrospective) as derived from active solicitation of patient information.[48] Accordingly, a company holding marketing authorisation for an approved drug or licensed biological product must submit to the FDA, within 15 calendar days, reports of adverse events from the registry that are both serious and unexpected by regulatory definition and where a reasonable possibility exists that the drug or biological product caused the adverse event.[49] Current reporting requirements in the regulations consider any congenital anomaly within the definition of a serious adverse event.[50] Pregnancy exposure registries that are run independently of a company holding marketing authorisations are not subject to post-marketing regulatory reporting requirements. However, investigators running such registries are encouraged to forward reports of any serious adverse events including congenital anomalies to the manufacturer of the drug or to report directly to the FDA MedWatch office (1-800-FDA-1088 or http://www.fda.gov/medwatch).

4.2 Status Reports

Any company conducting a pregnancy exposure registry required by the FDA or conducted as part of a written post-marketing study commitment must submit an annual status report to the FDA.[51] Companies conducting pregnancy exposure registries not subject to annual reporting requirements are encouraged to include a status report in the periodic safety report.[52] The status report should describe the study design and summarise the status of the planned, initiated, in progress or completed pregnancy exposure registry conducted by or otherwise obtained by the sponsor during the reporting period. Any publications based on data from the pregnancy exposure registry should be included. The status report should also provide a descriptive summary of progress to date, interpretation of findings and appropriate analyses with comments on the clinical significance of the findings.

5. Labelling

The FDA is working to improve the quantity and quality of data available on the use of drugs during pregnancy and is in the process of revising the pregnancy labelling regulations to promote the presentation of more useful clinical information and require the incorporation of human pregnancy data into the labelling, as it becomes available.[53] As part of the periodic safety update report, companies are already required to routinely review all available data and evaluate positive and negative experiences that are reported during pregnancy and lactation with their products.[52] Data from ongoing and existing pregnancy exposure registries should be included in this periodic evaluation and any clinically relevant information incorporated into the product labelling. Examples of some current labelling containing human pregnancy data based on registries or other observational data can be found in the FDA guidance on establishing pregnancy exposure registries.[15]

6. When to Discontinue a Pregnancy Exposure Registry

Several situations may lead to the decision to discontinue a pregnancy exposure registry. These include: (i) sufficient information has accumulated to meet the scientific objectives of the registry (e.g. sufficient sample size); (ii) the feasibility of collecting sufficient information diminishes to unacceptable levels because of low exposure rates, poor enrolment or unacceptable loss to follow-up; or (iii) other methods of gathering appropriate information, such as case-control surveillance, become achievable or are deemed preferable. The criteria to determine when to end the study should be predetermined and specified in the protocol. If the registry is conducted by a drug company as a regulatory requirement then the decision as to when to actually end the study should be made jointly by the drug company and the regulatory authority.

7. Conclusion

Scientifically valid data on the safety of drug use during pregnancy are a significant public health need. Without such information physicians and other healthcare providers (e.g. genetic counsellors) are unable to adequately counsel patients about fetal risks. Therefore, a pregnant woman may decide to unnecessarily terminate a wanted pregnancy or forego needed drug therapy while pregnant. When a drug is first marketed, well-designed pregnancy exposure registries provide the most feasible, efficient mechanism to collect data on exposed human pregnancies. Successful recruitment of exposed pregnancies, aggressive follow-up and complete, accurate ascertainment of pregnancy outcome provide scientifically valid data that can offer reassurance that a drug is not a major teratogen or provide important clinical information on potential fetal risks.

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References

1. Department of Health and Human Services, Food and Drug Administration. Guideline for the study and evaluation of gender differences in the clinical evaluation of drugs. Fed Regist 1993; 58 (139): 39406-16
2. Mastroianni AC, Faden R, Federman D, editors. Risks to reproduction and offspring. In: Women and health research: ethical and legal issues of including women in clinical trials. Washington, DC: Natl Acad Sci Press, 1994: 175-202
3. Mitchell AA. Special considerations in studies of drug-induced birth defects. In: Strom BL, editor. Pharmacoepidemiology. 3rd ed. Chichester: John Wiley & Sons Ltd, 2000: 749-63
4. Ward RM. Difficulties in the study of adverse fetal and neonatal effects of drug therapy during pregnancy. Semin Perinatol 2001; 25 (3): 191-5
5. Rogers JM, Kavlock RJ. Developmental toxicity. In: Klaassen CD, editor. Casarett & Doull's Toxicology: the basic science of poisons. 6th ed. New York; McGraw-Hill, 2001: 351-85
6. Schardein JL. Chemically induced birth defects. 3rd ed. New York: Marcel Dekker Inc., 2000
7. Kaufman DW, Kelly JP, Rosenberg L, et al. Recent patterns of medication use in the ambulatory adult population of the United States. JAMA 2002 Jan 16; 287 (3): 337-44
8. Colley GB, Brantley MD, Larson MK. 1997 family planning practices and pregnancy intention. Atlanta (GA): Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 2000
9. Ventura SJ, Mosher WD, Curtin SC, et al. Trends in pregnancies and pregnancy rates by outcome, United States, 1976-96. National Center for Health Statistics. Vital Health Stat 2000; 21 (56): 1-47
10. De Vigan C, De Walle HEK, Cordier S, et al. Therapeutic drug use during pregnancy: a comparison in four European countries. J Clin Epidemiol 1999; 52 (10): 977-82
11. Lacroix I, Damase-Michel C, Lapeyre-Mestre M, et al. Prescription of drugs during pregnancy in France. Lancet 2000; 356: 1735-6
12. Mitchell AA, Hernandez-Diaz S, Louik C, et al. Medication use in pregnancy; 1976-2000 [abstract]. Pharmacoepidemiol Drug Saf 2001; 10 Suppl. 1: S146
13. Kennedy D, Goldman S, Lillie R. Spontaneous reporting in the United States. In: Strom B, editor. Pharmacoepidemiology. 3rd ed. Chichester; John Wiley & Sons Ltd, 2000: 151-74
14. US Food and Drug Administration. Office of Women's Health. List of pregnancy registries [online]. Available from URL: http://www.fda.gov/womens/registries/default.htm
15. US Food and Drug Administration. Guidance for industry: establishing pregnancy exposure registries. August 2002 [online]. Available from URL: http://www.fda.gov/cder/guidance/3626fnl.pdf [Accessed 2003 Jan 2]
16. 21 Code of Federal Regulations (CFR). 201.57(f)(6) [online]. Available from URL: http://www.access.gpo.gov/nara [Accessed 2003 Jan 2]
17. International Society for Pharmacoepidemiology. Guidelines for good epidemiology practices for drug, device, and vaccine research in the United States. Pharmacoepidemiol Drug Saf 1996; 5: 333-8
18. Strom BL, editor. Pharmacoepidemiology. 3rd ed. Chichester: John Wiley & Sons Ltd, 2000
19. Hartzema AG, Porta M, Tilson HH, editors. Pharmacoepidemiology: an introduction. 3rd ed. Cincinnati (OH): Harvey Whitney Books, 1998
20. Honein MA, Paulozzi LJ, Cragan JD, et al. Evaluation of selected characteristics of pregnancy drug registries. Teratology 1999; 60: 356-64
21. Strom BL. Sample size considerations for pharmacoepidemiology studies. In: Strom BL, editor. Pharmacoepidemiology. 3rd ed. Chichester: John Wiley & Sons Ltd, 2000: 31-9
22. Gail M. Computations for designing comparative poisson trials. Biometrics 1974; 30: 231-7
23. Sumatriptan/naratriptan and lamotrigine pregnancy registries interim reports. PharmaResearch Corporation, Wilmington (NC), USA 28403. 800-336-2176
24. Reiff-Eldridge R, Heffner CR, Ephross SA, et al. Monitoring pregnancy outcomes after prenatal drug exposure through prospective pregnancy exposure registries: a pharmaceutical company commitment. Am J Obstet Gynecol 2000; 182: 159-63
25. The North American Pregnancy and Epilepsy Registry. A North American registry for epilepsy and pregnancy, a unique public/private partnership of health surveillance. Epilepsia 1998; 39 (7): 793-8
26. Chambers CD, Braddock SR, Briggs GG, et al. Postmarketing surveillance for human teratogenicity: a model approach. Teratology 2001; 64 (5): 252-61
27. Shields KE, Gahil K, Seward J, et al. Varicella vaccine exposure during pregnancy: data from the first five years of the pregnancy registry. Obstet Gynecol 2001; 98: 14-9
28. Holmes LB. Editorial: need for inclusion and exclusion criteria for the structural abnormalities recorded in children born from exposed pregnancies. Teratology 1999; 59: 1-2
29. Ellish NJ, Saboda K, O'Connor J, et al. A prospective study of early pregnancy loss. Hum Reprod 1996; 11: 406-12
30. US Centers for Disease Control and Prevention. Metropolitan Atlanta congenital defects program procedure manual and guide to computerized anomaly record. Atlanta (GA): 1998: A32-A100
31. March of Dimes Birth Defect Foundation. Quick reference: birth defects and genetics [online]. Available from URL: http://www.modimes.org [Accessed 2003 Jan 2]

32. Leippig KA, Werler MM, Can CI, et al. Predictive value of minor anomalies: I. Association with major malformations. J Pediatr 1987; 110: 530-7

33. Khoury MJ, Moore CA, James LM, et al. The interaction between dysmorphology and epidemiology: methodologic issues of lumping and splitting. Teratology 1992; 45 (2): 133-8

34. Scheurle A, Tilson H. Birth defect classification by organ system: a novel approach to heighten teratogenic signaling in a pregnancy registry. Pharmacoepidemiol Drug Saf 2002; 11: 1-11

35. National Birth Defects Prevention Network [online]. Available from URL: http://www.nbdpn.org [Accessed 2003 Jan 2]

36. Edmonds LD, Layde PM, James LM, et al. Congenital malformations surveillance: two American systems. Int J Epidemiol 1981; 10: 247-52

37. CDC National Center for Health Statistics [online]. Available from URL: http://www.cdc.gov/nchs [Accessed 2003 Jan 2]

38. International Clearinghouse for Birth Defects Monitoring Systems [online]. Available from URL: http://www.icbd.org [Accessed 2003 Jan 2]

39. Goldstein DJ, Sundell KL, DeBrota DJ, et al. Determination of pregnancy outcome risk rates after exposure to an intervention. Clin Pharmacol Ther 2001; 69: 7-13

40. International Society for Pharmacoepidemiology. Data privacy, medical record confidentiality, and research in the interest of public health. 1977 [online]. Available from URL: http://www.pharmacoepi.org/resources/privacy.htm [Accessed 2003 Jan 2]

41. US Federal Regulations on the Protection of Human Subjects. 45 Code of Federal Regulations (CFR) parts 46 & 164 and 21 CFR parts 50 & 56 [online]. Available from URL: http://www.access.gpo.gov/nara [Accessed 2003 Jan 2]

42. US Health Insurance Portability and Accountability Act. 45 Code of Federal Regulations (CFR) 164.512 [online]. Available from URL: http://www.access.gpo.gov/nara

43. Standards for privacy of individually identifiable health information [online]. Available from URL: http://www.hhs.gov/ocr/hipaa/guidelines/guidanceallsections.pdf [Accessed 2003 Dec 12].

44. White A, Eldridge R, Andrews E. Birth outcomes following zidovudine exposure in pregnant women: the antiretroviral pregnancy exposure registry. Acta Paediatr Suppl 1997; 421: 86-8

45. Lipkowitz MA. The American College of Allergy, Asthma, and Immunology Registry for allergic, asthmatic pregnant patients (RAAPP). J Allergy Clin Immunol 1999; 103: S364-72

46. Scialli AR. The Organization of Teratology Information Services (OTIS) registry study. J Allergy Clin Immunol 1999; 103: S373-6

47. Mitchell AA. Systematic identification of drugs that cause birth defects: a new opportunity. N Engl J Med 2003 Dec 25; 349 (26): 2556-9

48. US Food and Drug Administration. Guidance for industry. Postmarketing adverse experience reporting for human drug and licensed biological products: clarification of what to report, August 1997 [online]. Available from URL: http://www.fda.gov/cder/guidance/1830fnl.pdf [Accessed 2003 Jan 2]

49. 21 CFR 310.305(c)(1), 314.80(c)(2)(iii) and (e), and 600.80(c)(1), (c)(2)(iii) and (e) [online]. Available from URL: http://www.access.gpo.gov/nara [Accessed 2003 Jan 2]

50. 21 CFR 314.80(a) and 600.80(a) [online]. Available from URL: http://www.access.gpo.gov/nara [Accessed 2003 Jan 2]

51. 21 CFR 314.81(b)(2)(vii), 314.98(c), 601.70, and 601.28 [online]. Available from URL: http://www.access.gpo.gov/nara [Accessed 2003 Jan 2]

52. US Food and Drug Administration. Guidance for industry: E2C clinical safety data management: periodic safety update reports for marketed drugs. November 1996 [online]. Available from URL: http://www.fda.gov/cder/guidance/1351fnl.pdf [Accessed 2003 Jan 2]

53. Kweder SL, Kennedy DL, Rodriguez E. Turning the wheels of change: FDA and pregnancy labeling. The International Society for Pharmacoepidemiology, Scribe Newsletter 2000; 3 (4): 2-4, 10

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