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What Is the Role of Post Marketing Surveillance in Detecting Teratogenic Exposure?

Christina D. Chambers *University of California, San Diego, School of Medicine La Jolla, California*

Once a new medication is marketed, if the medication is used by women in their childbearing years, there are likely to be pregnant women who take the drug. Exposures to new medications can occur unintentionally during the early weeks of pregnancy before a woman knows that she is pregnant. A pregnant woman may also take a new medication intentionally for some disease or condition that requires treatment. Without human pregnancy clinical trial data to establish the safety of a medication for the developing fetus, post-marketing surveillance studies are a common method for gathering data on potential teratogenicity as quickly and as efficiently as possible.

One type of post-marketing surveillance study is a called a “pregnancy registry.” Pregnancy registries are studies in which pregnant women who have taken a specific medication or received a certain vaccine are asked to enroll in the registry. Information is collected about the woman’s pregnancy, her medication and other exposures, the outcome of that pregnancy, and the health of the newborn baby. Information is typically collected on all pregnancy outcomes, whether the pregnancy ends in miscarriage, stillbirth, or a live born baby or babies, and information is collected on any complications that occur, including birth defects. The number of specific poor outcomes, such as babies born with birth defects, among women who took the drug of interest is evaluated to determine if these events are more frequent than expected and if it is plausible that the excess number of affected infants might be due to a teratogenic effect.

Every pregnant woman has a small (about 3%) risk of having a child with a birth defect regardless of the medications she takes or vaccines she receives. In order to determine if a specific new drug or vaccine exposure might be increasing that risk, pregnant women exposed to the drug or vaccine under study are compared to another group of pregnant women. This reference group can be the general population of pregnant women, or can be a comparison group of pregnant women who are enrolled in the registry but who have not taken the medication or received the vaccine under study.

The objective of a pregnancy registry is to determine, as early as possible after a drug or vaccine is marketed, whether or not there is any indication of a teratogenic risk in humans. A pregnancy registry may be the most efficient method for post-marketing surveillance if a drug is used for a very rare condition or is used only infrequently in the population of women who might become pregnant. A pregnancy registry can also be a good method for identifying a new human teratogenic exposure if the medication causes a unique and severe pattern of birth defects or a very high incidence of specific birth defects.

However, because new medications might be infrequently used in pregnant women and because pregnancy registries rely on women and/or their health care providers to volunteer for the study, the number of women who enroll in any given registry often is very small. Small numbers of participants can limit the ability of a pregnancy registry to detect human teratogenic exposures, particularly if the drug exposure occurs in only a small proportion of exposed pregnancies. Thus, an important function of a pregnancy registry is to identify potential “signals” or suggestions of an excess risk, and

to call for additional studies to confirm or refute that signal. By the same token, pregnancy registries can never definitively establish safety but can provide some reassurance that a specific drug does not carry a high risk for a severe pattern of birth defects.

Another approach to post-marketing surveillance takes advantage of the technological advances in electronic insurance claims data and medical and pharmacy records storage. Large databases that include pregnancy information, such as linked prescription and birth records, can compare pregnancy outcomes between pregnant women who have been prescribed a new drug or received a new vaccine of interest and those who have not within the same healthcare database. This approach offers many of the advantages of a pregnancy registry at potentially far less cost and need not rely on volunteers to enroll.

Some limitations of healthcare database studies include the difficulty in determining if the drug or vaccine was actually taken or received by the mother and when in gestation. Database studies oftentimes lack access to information on other important exposures such as whether or not the mother smoked cigarettes or drank alcohol during pregnancy. In addition, just as with pregnancy registries, if the drug or vaccine of interest is infrequently given to women of childbearing age, even very large databases may have access to only small numbers of pregnant women exposed to any particular drug or vaccine. Therefore, large databases may still have difficulty in identifying new teratogenic exposures unless the risk is high for a severe and easily recognizable teratogenic effect.

Other sources of information, for example the National Birth Defects Prevention Study case-control study, may also be informative in identifying human teratogenic exposures. In recent years, there has been increased interest in using a combined or complementary approach to post-marketing surveillance employing two or more of these post-marketing surveillance methods in parallel to study a new drug or vaccine. This combined approach can help address the limitations of each approach individually, and potentially provide informative safety information more quickly.

Despite the challenges of performing post-marketing surveillance for human teratogenicity, the public health need for such information is great. In the absence of randomized clinical trials that include pregnant women, synthesis of information from post-marketing studies along with population-based studies, pre-clinical developmental toxicity studies, and other predictive techniques, as described in this Primer, are needed to optimize the capacity to recognize a potential teratogenic effect with a new pharmaceutical agent or conversely to provide reassurance that a new drug does not pose a substantial risk.

Suggested Reading

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