Editorial

How Did Research on Medication Safety in Pregnancy Define, Develop and Advance the Field of Pharmacoepidemiology?

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According to the Centers for Disease Control and Prevention,[1] in the United States, 90% of pregnant women take medication during pregnancy. Nearly every pregnant woman faces the decision about whether to take medication and requires information to determine how to best protect her own health and the health of the fetus.

Guidance on the safety of medications utilized during pregnancy was once scarce, and the consequences of this lack of information were sometimes devastating. The infamous "thalidomide disaster" in 1961 is one example. Thalidomide was marketed in Europe as a mild hypnotic and after its release, a dramatic increase was seen in the frequency of a severe and previously rare birth defect known as *phocomelia,* the absence of limbs or parts of limbs.[2] Epidemiologic studies associated its cause with *in utero* exposure to thalidomide,[3–9] which led to regulatory changes in both the United States and Europe. In the United Kingdom, the Committee on the Safety of Medicines was established in 1968, and in the United States the Kefauver-Harris Amendments strengthened the requirements for the proof of drug safety. These legislative changes led to what has become the current drug-approval process.

The field of *pharmacoepidemiology*, the study of the use of and the effects of drugs in large numbers of people,[10,11] emerged in response to the need for research on the impact of medication usage on the public's health. The advent of pharmacoepidemiology followed a long period during which information regarding medication safety was provided solely by preapproval clinical trials, and medication use in clinical practice settings was not incorporated into regulatory direction. The reliance on preapproval clinical studies, which generally excluded large proportions of the population, such as pregnant women, resulted in inadequate safety data as study-inclusion criteria limited generalizability. Even with the expanded inclusion of pregnant women in clinical research, safety data are limited as the small samples observed are often inadequate for the detection of rare outcomes. Today, large-scale pharmacoepidemiologic studies spanning continents guide the World Health Organization's recommendations on the safe use of medications in pregnancy, such as the use of the highly effective artemisinin antimalarial treatments previously precluded from use in pregnant women based solely on embryotoxicity studies in animals.[12]

We chose to introduce the field of pharmacoepidemiology to the readers of *Clinical Therapeutics* with two papers that illustrate the development of the field through seminal research on medication safety in pregnancy. The historical importance of early studies on *in utero* exposure to medications and adverse pregnancy and birth outcomes is described, as is the development of new and evolving data sources and methods that can be applied to other research areas as well. Multiple robust administrative data sources exist for use in performing population-based studies in pregnant women, with linkage to outcomes among their infants.[13] The paper by Wood et al[14] provides an overview of these various data sources, such as spontaneous reporting systems, teratology-information services, primary case–control or birth-cohort studies, pregnancy-exposure registries, and electronic health data. Refinements and technologic improvements in observational-data sources, such as combining data sources across institutional or

national borders, developing and using more sophisticated study designs, the need for better risk communication, and future directions for improved data sources, are presented and discussed in that article.

One of the most important contributions of pharmacoepidemiology has been the development of cutting-edge methods for bias control in observational-data studies. Wood et al[14] introduce these concepts, with a focus on how to address what is known as "confounding by indication," which occurs when we attribute a poor outcome to a drug, when, in fact, the reason for taking the drug causes the outcome. For example, attributing a higher risk for stroke to the use of antihypertensive medications could be spurious due to confounding by indication, because the risk for stroke will be higher among patients who are prescribed antihypertensive therapy. This concept, as well as a general discussion of how to address unmeasured confounding, is explained clearly, with examples and practical guidance on the general use of methods of reducing bias. How, for instance, should readers of the Journal interpret possible selection biases in pharmacoepidemiology studies of a pregnancy outcome that included only live births to women required to have been continuously enrolled in a health insurance plan? Wood et al[14] and others[15] acknowledge the benefit of augmenting or linking claims data with other sources, such as birth registries, electronic health records, and other primary data-collection sources to address these challenges.

The article by Lupattelli et al[16] continues the theme of how research on medication safety in pregnancy has advanced pharmacoepidemiology, through a discussion of methods for handling missing data. The examples given are applicable to many research areas, as all studies on health outcomes are susceptible to missing data, regardless of the data source utilized. The article describes how incomplete information on confounders, outcomes measures, pregnancy duration, or even cohort-selection criteria, can result in biased results. General missing data mechanisms and methods are described, as well as how missing data were handled in recent research. An applied example on missing data analysis within the Norwegian Mother and Child Cohort Study is given, and practical advice for those dealing with missing data is provided.

As observational-data sources evolve, medication-safety research will become less dependent on small-sample clinical studies and pregnancy registries, and postapproval observational studies will be used more frequently for evaluating drug safety in pregnancy. This trend increases the need for practical guidance[17] on the interpretation of observational research as pharmacoepidemiologists navigate "old-world" epidemiologic problems borne anew in electronic health data and other robust, administrative data sources. The pharmacoepidemiologic studies in this issue[14,16] provide a historical perspective on some of the most important contributions of pharmacoepidemiology, and also provide practical guidance by introducing and exemplifying methodologic approaches to analyzing and interpreting observational data that are translatable to many fields. Finally, as the US Food and Drug Administration has termed its medication safety surveillance database the *Sentinel Initiative,* the role of pharmacoepidemiologists might be best explained to patients as being sentinels for medication safety, *en garde*, keeping watch to prevent any future "thalidomide disasters," and providing timely and accurate medication safety information for public health.

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