

The Safety of Medications in Pregnant Women: An Opportunity to Use Database Studies

Andrea V. Margulis, MD, ScD,^a Elizabeth B. Andrews, PhD^b

Information on the safety of medications that pregnant women may need is key to protecting the health of the woman and her fetus. When new drugs are first marketed, this information is scarce, because pregnant women are generally excluded from randomized clinical trials. Broader inclusion of pregnant women in clinical research is being discussed by regulatory authorities and funders.¹ But even with greater inclusion of pregnant women in clinical trials, safety data from those trials would be limited by the combination of study size, low frequency of many key outcomes, and strict conditions for enrollment. Postapproval observational studies still would be needed to assess drug safety in routine health care. These assessments can be conducted as pregnancy exposure registries or by using existing health databases. Currently, because of our overreliance on pregnancy exposure registries and underuse of database studies, we are missing an opportunity to provide information that would help women and their physicians make better informed decisions about treatment in pregnancy.

Pregnancy exposure registries, usually sponsored by a single pharmaceutical company, are a primary method requested by the US Food and Drug Administration (FDA) for postapproval safety studies in pregnant women.² However, these registries often fail to enroll a sufficient number of exposed pregnancies, and when they do, it is often difficult to interpret results because they generally do not include an internal comparison cohort and rely on comparisons to external data sources, such as the Metropolitan Atlanta Congenital Defects Program.² The pregnancy registries that have been most successful in enrolling large numbers of pregnancies and have included internal comparators are multisponsored registries of multiple medications for the same indication. A notable example is the North American Antiepileptic Drug Registry (NAAEDR).

Studies using existing databases can be conducted more quickly and with fewer resources and can be more scientifically robust than registry studies. The international drug safety research community, including regulatory bodies, academia, and pharmaceutical companies, has embraced studies that capitalize on large repositories of administrative and clinical data to conduct safety surveillance and formal epidemiologic

^aRTI Health Solutions, Barcelona, Spain; and ^bRTI Health Solutions, Research Triangle Park, North Carolina

Both authors conceptualized, drafted, and reviewed the piece; approved the final manuscript as submitted; and agree to be accountable for all aspects of the work.

DOI: <https://doi.org/10.1542/peds.2016-4194>

Accepted for publication Mar 9, 2017

Address correspondence to Andrea V. Margulis, MD, ScD, RTI Health Solutions, Diagonal 605, 9-1, 08028 Barcelona, Spain. E-mail: amargulis@rti.org

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: Drs Margulis and Andrews are full-time employees of RTI Health Solutions, a unit of RTI International, which is an independent nonprofit research institute that conducts research for clients in government and business, including the pharmaceutical industry.

FUNDING: This article received funding from Roche. Roche has had no involvement in the writing and did not see the content until after it was submitted for publication.

POTENTIAL CONFLICT OF INTEREST: Drs Margulis and Andrews are full-time employees of RTI Health Solutions, a unit of RTI International, which is an independent nonprofit research institute that conducts research for clients in government and business, including the pharmaceutical industry.

To cite: Margulis AV and Andrews EB. The Safety of Medications in Pregnant Women: An Opportunity to Use Database Studies. *Pediatrics*. 2017;140(1):e20164194

studies. Such studies are often required by regulatory bodies as conditions of drug approval. Data repositories include electronic medical records, commercial and governmental health insurance claims, and population-based registries (eg, birth records, cancer registries, and mortality files). Mother and infant records can be linked, which facilitates the study of pregnancy medication exposure, pregnancy outcomes, and infant outcomes. Multiple outcomes can be evaluated, multiple comparison groups can be assembled from extant records, and multiple databases can be combined to increase the number of pregnant women monitored for the medication of interest.

An example of this approach is the FDA-sponsored Sentinel Initiative, which included health records on more than 178 million individuals in 2014 for monitoring the safety of marketed medications.³ The 21st Century Cures Act, passed by the US Congress in December 2016, extends the influence of the Sentinel Initiative and other evidence from clinical experience in regulatory decisions. The same type of infrastructure used in the Sentinel Initiative and other research networks in the United States and Europe can be tailored to evaluate pregnancy outcomes to ensure identification of pregnancies early in the first trimester, explore infant outcomes by using linked mother-infant records, and validate outcomes against clinical and other source records when health care claims may be subject to errors.

The value of multidatabase studies was demonstrated in a study required by the FDA that used 4 US databases to evaluate the association between topiramate (a medication long used for epilepsy and migraine and recently approved in combination with phentermine to treat obesity) and oral clefts in offspring.⁴ Data were analyzed within each database by using a common

study protocol, and results were combined to estimate incidence rate ratios comparing topiramate-exposed pregnancies with 2 comparator cohorts. In 2 databases, computer claims indications of oral cleft were validated against medical charts to confirm that the claims data were accurate. The study, which was completed in <2 years, included nearly 2000 mother-infant pairs with topiramate exposure in the first trimester of pregnancy. Results indicated that topiramate may be associated with a modest increase in oral clefts: for every 1000 pregnancies with topiramate exposure in the first trimester, an additional 1 or 2 cases might occur. These results and other studies were integral to the US drug approval decision for Qsymia (phentermine and topiramate), and information is now included in the package insert and educational materials available to patients and physicians. In contrast, during 15 years of operation (1997–2012), the multidrug NAAEDR collected information on only 347 neonates born to women who had taken topiramate.⁵ A single-exposure registry would have required many years and accumulated far fewer topiramate-exposed pregnancies, and would likely not have been as informative as the NAAEDR or the database study.

Regulators and sponsors have been slow to embrace the use of database studies for pregnancy safety questions. In 2014, the FDA sponsored a workshop to discuss challenges posed by postapproval studies in pregnant women. FDA staff reported that, of 59 products with pregnancy exposure registries, only 22 stated their targeted number of enrollees in the registry protocol, and only 3 of these had achieved it.⁶ Of the 17 products whose registries ended, 59% closed for feasibility reasons. It was noted that other study designs must be considered to produce enough data to inform

product labels. A search in the FDA's Postmarket Requirements and Commitments database showed that for 9 products approved in 2015 or the first half of 2016, the FDA required all manufacturers to establish exposure registries. One manufacturer was also required to do a database study. The planned completion dates are 2030 for the registry and 2022 for the database study. European regulatory authorities have been taking a similar approach. The repository for observational postapproval studies requested by European regulatory authorities is the European Union Electronic Register of Post-Authorization Studies. We searched this register on September 30, 2016, and found 9 studies that included pregnant women, had a safety component, and had contracts signed in 2015 or 2016; 7 were pregnancy registries, and 2 were database studies.

We believe it is time for regulatory agencies and study sponsors to consider database studies as the main source for safety data for most pregnancy, neonatal, and infant outcomes and to support an efficient infrastructure and process applicable to multiple disease areas, drugs, and biologicals. Large databases are available for research, methods for conducting multidatabase studies are well developed, and collaborations among multiple scientific disciplines and data custodians have been fruitful. However, retrospective data sources do not capture well some pieces of data (eg, number of seizures in pregnancy). Prospective registry studies could be reserved for research in which this type of information is critical. Not all scientific questions can be addressed within a single data source or from 1 country; both registries and database studies are challenged by drugs infrequently used in pregnancy and can be inconclusive. In such cases, regulators should encourage

multinational collaboration, which can yield much more information than country-specific projects.

As researchers involved in multiple types of studies of medications in pregnancy (EBA led the first industry-sponsored pregnancy registry), we believe it is time to turn our attention and resources to multidatabase studies to evaluate many medications for conditions often encountered by women of childbearing potential. These programs can efficiently generate robust results to inform treatment decisions in pregnancy with far greater impact on the population at large than reliance on only pregnancy exposure registries.

ACKNOWLEDGMENTS

We thank Adele Monroe for her editorial help and Susana

Perez-Gutthann and Ken Rothman, all from RTI Health Solutions, for their helpful comments.

ABBREVIATIONS

FDA: Food and Drug Administration
NAAEDR: North American Antiepileptic Drug Registry

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Pediatrics 2017;140;

DOI: 10.1542/peds.2016-4194 originally published online June 1, 2017;

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