Assuring Access to Safe Medicines in Pregnancy and Breastfeeding

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Abstract

Scientists and regulators in Europe and the United States (U.S.) continue to seek methods and strategies to improve knowledge on rational use of medicines for pregnant and breastfeeding populations, an important subset of women's health. Regulatory agencies have made strides toward improvement, but much more is needed. Recognizing the importance of international collaboration, we have begun to consider how to address these important public health issues more globally.

Introduction

The health of the child begins with the health of the mother. Yet, there is a persistent dearth of data to support clinical decision making in pregnant and breastfeeding women, risking inadequate, inappropriate, or lack of treatment, any of which can result in significant health consequences for the mother or child. Many factors contribute to this, including the temporary nature of pregnancy. Most importantly the histories of thalidomide and diethylstilbestrol (DES) continue to cast long shadows on clinical, regulatory, and public attitudes surrounding research and medicinal treatment involving pregnant and breastfeeding women. They were the basis for "special protections" for women in rules and regulations governing research, largely preventing exploration of ethical ways to study such populations to obtain robust and reliable data. Similarly, the extreme nature of the cases in which infants were affected are likely to have been driving factors in the liability barriers to data collection by industry. Without data, regulators are unable to confidently ensure robust information in labeling.

On the other hand, there have been recent efforts to close these information gaps. For example, observational data on pertussis vaccination in pregnancy was critical in removing a "not recommended in pregnancy" categorization of pertussis vaccines in Europe. Clinical trials of vaccines to prevent H1N1 influenza during the 2009 pandemic contributed to the body of knowledge on the safety of inactivated influenza vaccines in pregnancy, which supported public health outreach that led to increased seasonal and pandemic influenza vaccine coverage among pregnant women in the U.S.

Still, when considering use of the majority of medicines the woman and healthcare provider are placed in an impossible position – needing to make healthcare decisions in an information vacuum.

Materials and Methods

Recognizing the importance of international collaboration, a group of regulators from Medicines and Healthcare products Regulatory Agency (MHRA), European Medicines Agency (EMA), and U.S. Food and Drug Administration (FDA) launched a collaboration with a 2-day event in 2020 to address these important public health issues more globally (Photo 1).

The group reviewed recent efforts in each region towards improvement (Table 1). Regulators evaluated the current state of nonclinical, clinical, and postmarket approaches, noting limitations and future strategies for each. The group then created a focused list of shared aspirations for change (Table 2).

Table 1. Highlights of Recent Pregnancy and Breastfeeding Activities in US and Europe

Activity	Year	Region and Agency
Content and Format of Labeling for Human Prescription Drug and Biological Products: Requirements for Pregnancy and Lactation Labeling	2014	US, Food and Drug Administration
Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)	2016	US, Department of Health and Human Services
Report of the Commission on Human Medicines' Expert Working Group on Hormone Pregnancy Tests	2017	UK, Commission on Human Medicines
PRGLAC Report to Congress	2018	US, Department of Health and Human Services
Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials: Draft Guidance for Industry	2018	US, Food and Drug Administration
Drug Safety in Pregnancy in a Large, Multisite Database: Mother-Infant Linkage in Sentinel	2018	US, Food and Drug Administration
ConcePTION – Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology and Breastfeeding to Improve Outcomes Now	2019	Europe, Innovative Medicines Initiative
Guideline on Good Pharmacovigilance Practices: Pregnant and Breastfeeding Women	2019	Europe, European Medicines Agency
Postapproval Pregnancy Safety Studies: Guidance for Industry	2019	US, Food and Drug Administration
Clinical Lactation Studies, Considerations for Study Design: Guidance for Industry	2019	US, Food and Drug Administration
Programme of Work: Research to Support the Safer Use of Medicine during Pregnancy	2019	UK, Medicines and Healthcare products Regulatory Agency
Strategic Reflection: EMA Regulatory Science to 2025	2020	Europe, European Medicines Agency

Results and Discussion

Nonclinical discussions highlighted the need for a paradigm shift from theoretical or ill-defined risk as an absolute barrier for use in pregnancy and breastfeeding to generating and interpreting data to inform sound clinical testing and use. This includes, foremost, developing a better understanding of how results from nonclinical studies 'translate' into impact for use in humans. Regulators could begin to ensure relevant questions on non-clinical data are highlighted and discussed early in development, holding sponsors accountable for addressing them when appropriate to the intended use of a product, whether through further animal testing or modelling. Also, the need for databases or projects that establish suitable "safe harbors" and "honest brokers" for sharing data on compounds that have failed in development, which could aid in future modeling and understanding of fetal development disruption.

Clinical discussions focused on ways to combat the persistent exclusion of women from clinical research which can have real consequences for women with low or high morbidity conditions. As with other populations, the use of medicines in pregnant and breastfeeding women must be based on a benefit to risk evaluation with attention paid to the benefits of treatment vs the risks of leaving the disease untreated. The scientific community must beyond decades of thinking driven by old biases and fear and use sound ethics and safety provisions to make changes encouraging inclusivity, such as establishing a framework for guiding when early study in pregnancy is most needed.

During postmarket discussions, regulators noted the need for examination and optimization of regulatory systems to ensure timely and efficient use of all available data resources, especially new tools applied to large healthcare databases to promote integrated approaches and cross-disciplinary activities. Such work will benefit greatly from global collaboration, not only in data collection, but in development of research and methods in this emerging field. Common protocols and analytic methods that allow data to be compared across systems are best forged through international partnerships, which can also catalyze academic work and may allow for global information sharing. A strong international roadmap for partnership to establish an infrastructure that enables integrated approaches between systems as well as between regions would greatly improve safety data collection and has the potential to advance public health in these populations.

Photo 1. Regulators from FDA, EMA, and MHRA gather at MHRA's London headquarters in January 2020.

Table 2. Shared Strategies for Improving Access to Safe Medicines in Pregnancy and Breastfeeding

Strategy	Research Area
Approach use of medicines in pregnancy and breastfeeding from a benefit and risk perspective to meet the needs of clinical decision-making.	Cross-cutting
Promote fresh approaches to non-clinical reproductive toxicology.	Non-clinical
Emphasize systematic consideration of use of medicine by pregnant and breastfeeding women and, as warranted, plan for formal investigations in these populations.	Clinical
Address regulatory and liability barriers to clinical trial enrollment of pregnant and breastfeeding women and women who may become pregnant.	Clinical
Support rational prescribing through systematic and timely study of medicines likely to be used in this population.	Non-clinical, Clinical
Optimize the regulatory system to ensure timely and efficient use of all available data resources.	Postmarket
Challenge medicine developers and researchers to partner globally to develop robust modern methods in electronic data collection and analysis to jump start research in this area.	Postmarket

Conclusion

Obtaining data and information about medicines in pregnancy and breastfeeding has been fraught with barriers and controversy for decades, yet it is widely accepted that the health of the child begins with the health of the mother. Focus on the latter must drive change, with generation of evidence-based information that women and their healthcare providers can confidently use to make treatment decisions.

FDA, EMA, and MHRA agree on the focus for a path forward (Table 2), recognizing this is the beginning of a long journey and specific actions will require more and broader discussion with many stakeholders to take shape.

Underpinning the goal of improving access to safe and effective medicines in pregnancy and breastfeeding is the necessity for broad and transparent dialogue among stakeholders. The group intends to display leadership in such efforts with women, healthcare professionals, industry, and public health experts and hopes to be met with enthusiastic engagement by partners around the globe.