Assuring Access to Safe Medicines in Pregnancy and Breastfeeding

Janet Nooney[1], Shannon Thor[2], Corinne de Vries[3], John Clements[1], Leyla Sahin[2], Wei Hua[2], Darcie Everett[2], Cosimo Zaccaria[3], Robert Ball[2], Agnes Saint-Raymond[3], Lynne Yao[2], June Raine[1] and Sandra Kweder[2,*]

Scientists and regulators in Europe and the United States 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. The health of the child begins with the health of the mother.

Scientists and regulators in Europe and the United States continue to seek methods and strategies to improve knowledge for rational use of medicines for pregnant and breastfeeding populations, an important subset of women's health. Regulatory agencies have made strides toward improvement (**Table 1**), but much more is needed. Recognizing the importance of international collaboration, the authors, representing the Medicines and Healthcare products Regulatory Agency (MHRA) [Correction added on 22 May 2021, after first online publication: The abbreviation of a government agency (MHRA) has been corrected to Medicines and Healthcare products Regulatory Agency.], the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA) met for 2 days in 2020 to consider how to address these important public health issues more globally. Our discussions revealed common thinking on the direction needed for progress. We write here to raise the key issues at hand and the foundations for launching a path for change.

HISTORICAL BACKGROUND

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 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.[13] 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 United States.[14]

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

NONCLINICAL

New medicines are usually supported by nonclinical studies to assess potential reproductive toxicity, from conception through embryo-fetal stages, birth, and sexual maturation.[15,16] Generally intended as informed screening tests, these can also provide insight to potential risks associated with *in utero* exposure. However, it is well known that outcomes in animal testing do not necessarily correlate with clinical outcomes, resulting in uncertainty about translating findings to human risk. This is the case for many reasons, some rooted in different species pharmacology and physiology, but many in how testing is conducted and assessed. For example, animal studies focus on maternal, not fetal exposure; mechanistic insights are limited; studies are limited in size; and exposure is typically throughout pregnancy, making it difficult to assess how shorter exposures may relate to human use.

Current nonclinical approaches also focus on using a limited number of doses that result in establishing possible harm rather than likely harm in the fetus at clinically relevant doses, which in some cases is an important distinction. Unfortunately, rather than facilitating informed clinical studies in pregnant women to proceed, the approach serves as a barrier. Any adverse effect from preclinical data, even at

[1]Medicines and Healthcare products Regulatory Agency, London, UK; [2]US Food and Drug Administration, Silver Spring, Maryland, USA; [3]European Medicines Agency, Amsterdam, The Netherlands. *Correspondence: Sandra Kweder (sandra.kweder@fda.hhs.gov)

Linked article: This article is linked to Improving Knowledge on Safety is Key to Enabling Drug Access for Pregnant and Breastfeeding Women by Chappell, L.C. & Tong, S., *Clin. Pharmacol. Ther.* **110**, 866–868 (2021).

Received January 7, 2021; accepted January 29, 2021. doi:10.1002/cpt.2212

Table 1 Highlights of recent pregnancy and lactation activities in the United States 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[1]	2014	US, US Food and Drug Administration
Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)[2]	2016	US, US Department of Health and Human Services
Report of the Commission on Human Medicines' Expert Working Group on Hormone Pregnancy Tests[3]	2017	UK, Commission on Human Medicines
PRGLAC Report to Congress[4]	2018	US, Department of Health and Human Services
Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials: Draft Guidance for Industry[5]	2018	US, US Food and Drug Administration
Drug Safety in Pregnancy in a Large, Multisite Database: Mother-Infant Linkage in Sentinel[6]	2018	US, US Food and Drug Administration
ConcePTION – Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology and Breastfeeding to Improve Outcomes Now[7]	2019	Europe, Innovative Medicines Initiative
Guideline on Good Pharmacovigilance Practices: Pregnant and Breastfeeding Women[8]	2019	Europe, European Medicines Agency
Postapproval Pregnancy Safety Studies: Guidance for Industry[9]	2019	US, US Food and Drug Administration
Clinical Lactation Studies, Considerations for Study Design: Guidance for Industry[10]	2019	US, US Food and Drug Administration
Programme of Work: Research to Support the Safer Use of Medicine during Pregnancy[11]	2019	UK, Medicines and Healthcare products Regulatory Agency
Strategic Reflection: EMA Regulatory Science to 2025[12]	2020	Europe, European Medicines Agency

exposures higher than those anticipated in pregnant women (and similarly in animal breastfeeding studies) tends to result in recommendations to avoid use and further investigative studies (animal, mechanistic, or human) are rarely pursued to elucidate clinical risk.

A paradigm shift is needed 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, better understanding of how results from nonclinical studies "translate" into impact for use in humans. Such an understanding could enable more refined consideration of inclusion of women of childbearing potential and/or pregnant women in clinical trials where currently there is routine exclusion.

Relatively straightforward changes could be implemented while developing approaches to more complex scientific and ethical issues. For example, regulators could ensure that relevant questions on nonclinical 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 modeling.

This is not an impossible task. Advances in technology mean adverse biological effects are being studied using increasingly data-rich quantitative methods, data sharing, and multidisciplinary approaches to analyzing outputs. Such tools are already modernizing testing in nonreproductive toxicology, including animal exposure relevant to human use to refine risk assessments, alternative non-mammalian assay systems and even new imaging technologies that could be applied to *in utero* animal fetal assessments.

Finally, a wealth of data exists on compounds that have failed in development for a variety of reasons and may no longer be commercially viable. Although not often in the public domain, this information could be shared and used in developing new models for better understanding of mechanisms disrupting fetal development. Similar public preclinical:clinical pregnancy databases on marketed drugs might be even more important than failed drugs. Suitable "safe harbors" and "honest brokers" could support such data sharing projects to develop and qualify more human relevant methods. We believe it is time for discussion of how such databases and projects might be established and funded.

CLINICAL

The historical rationale for excluding pregnant or breastfeeding women from clinical trials has been to protect the fetus or child from potential harms associated with new medicines. This has extended to inclusion of women only if they do not intend to become pregnant during the trial, typically requiring contraception throughout and for some time following the trial. Although reasonable in very early development, work to collect data that inform the risk associated with use in pregnancy or breastfeeding is rarely proposed by developers. Women who do become pregnant in trials tend to be discontinued quickly and lost to follow-up, despite guidance encouraging otherwise (**Table 1**). This results in lost potential therapeutic benefits to the subject as well as the opportunity to collect important data, such as the pharmacokinetic profile of the test agent in pregnancy. Whereas this may not have consequences for low morbidity conditions, it does for women with serious conditions, such as seizure disorders, systemic infections, or cardiac conditions, making the concept of establishing a framework for guiding when early study in pregnancy is most needed.

Scientific reasons to study medicines in pregnancy and breastfeeding relate most commonly to the systematic physiologic changes of pregnancy that can markedly affect pharmacodynamics or pharmacokinetics of medicines (**Table 2**). Complicating these is the fact that many diseases are affected by pregnancy, affect pregnancy outcome, or both, including rheumatologic and autoimmune disorders, blood dyscrasias, and even asthma, for example. In addition, the extent to which medicines are present in breastmilk, how infants metabolize them, and their effects on infant physiology are far more complex than usually considered. Further, in circumstances, such as serious or life-threatening disorders or those treated in clinical practice despite the absence of clinical evidence in pregnancy, inclusion of pregnant women in clinical trials should be an option to consider. 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. Collectively, these scientific factors illustrate why we must move beyond decades of thinking driven by old biases and fear and use sound ethics and safety provisions to make changes encouraging inclusivity.

Work has begun that could be leveraged to launch incremental change. In addition to the activities noted in **Table 1**, there are frameworks from the World Health Organization,[18] the Drugs for Neglected Diseases initiative,[19] and the US Department of Health and Human Services[20] that serve as foundations for international dialogue on improving inclusivity. In addition, International Conference on Harmonization (ICH)-E8 "General Considerations for Clinical Trials"[21] is currently undergoing a revision that will include removing language that recommends exclusion of pregnant women from clinical trials.

Perhaps most encouraging is work of the US Task Force on Research Specific to Pregnant Women and Lactating Women,[2] which has shown there is overwhelming support by stakeholders for pregnant and breastfeeding women to be presumed eligible for participation in clinical research. Developers, investigators, and regulators must now address how to do so. Without question, success depends on simultaneously addressing liability barriers, which will require collaboration across governments and healthcare professional/patient advocacy organizations to encourage creative thinking to address the important needs of these populations.

POSTMARKETING

Spontaneous adverse event reporting has long been the primary source informing profiles of medicines in pregnancy and breastfeeding. Such data can be clinically useful, for example, in potentially signaling visible structural defects at birth. However, such data's well-known limitations, magnified in pregnant or breastfeeding populations, include incomplete data on lifestyle factors, genetic predisposition, timing of exposure, and detailed information on birth outcomes (including healthy births). Adverse effects of medicine exposure in pregnancy can also manifest as pregnancy loss, or as neurocognitive or functional effects, which may vary or only reveal themselves as a child develops. Failure to consider each of these can skew a picture of a medicine's safety, yet rarely are such data pursued.

Patient registries (especially prospective exposure follow-up studies), may be product or disease based and are excellent tools when they have robust enrollment, methods, and follow-up. Registries are more successful when they are resourced for intensive recruitment and retention efforts. As pregnancies are not rare events, more efficient and effective approaches should be considered by product developers to facilitate recruitment and retention, such as developing partnerships with disease registries, linking to electronic health record systems, incorporating new tools (e.g., mobile apps), and using advanced social and behavioral science techniques to overcome barriers. For example, the registries for lamotrigine and levetiracetam helped establish these products as lower risk to fetuses in mothers treated for epilepsy compared with valproate, carbamazepine, and topiramate, which has since been corroborated by data from the UK epilepsy in pregnancy registry.[22]

Table 2 Physiologic changes in pregnancy that may alter pharmacokinetics and pharmacodynamics of medicines[17]

Parameter	Increase	Decrease	Comments
Body weight	X		Weight dependent dosing
Body fat composition	X		
Gastric emptying		x	Prolonged gastric transit time
Total body water	X		Increased blood volume and related alterations in many blood laboratory values
Extracellular fluid	X		
Heart rate, stroke volume and cardiac output	X		
Glomerular filtration rate	X		Increased renal clearance
Albumin concentration and protein binding		x	May alter physiologic availability of some drugs
Hepatic enzyme activity	x (CYP450 pathways; Xanthine oxidase; N-acetyltransferase)		Examples include increased CYP2D6 activity. Changes can be marked and substantially alter metabolism of drugs.

Most changes manifest in the first trimester and peak in the second trimester and reflect a continuum of change as pregnancy progresses, with return to baseline at various rates in the postpartum.

The Antiretroviral Pregnancy Registry, which is supported by manufacturers of antiretrovirals, publishes their data every 6 months and has been useful in generating pregnancy safety data that have been added to labeling.

Regulatory systems must be examined and optimized 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. Efforts to conduct such work have begun but are limited in capture. For example, the Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology, and Breastfeeding to Improve Outcomes Now (ConcePTION)[7] project is a public private partnership of European regulatory and public health agencies, industry, and academia. It seeks not only to catalogue resources and opportunities, but also to address methods and infrastructure development (including a human breastmilk biobank) and to build bridges and interfaces that will catalyze research in this area. In the US Sentinel System, mother-infant linkages are established to enable assessment of drug safety in pregnancy in a large, multisite database.[6]

Despite methodological differences, current postmarket approaches, such as spontaneous reports, registries, and analyzing electronic healthcare data are best when they complement each other with the most up-to-date signal detection and evaluation methods applied to each. In addition, no one region is likely to have resources, financial or patient numbers, to answer the full scope of questions related to medicines use in pregnancy and breastfeeding. 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.

For these reasons, 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.

CONCLUSION

Obtaining data and information about medicines in pregnancy and breastfeeding has been fraught with barriers and controversy for decades, yet our first statement, that "The health of the child begins with the health of the mother," is widely accepted. 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. Some may suggest that for meanigful change to occur legislation, regulation, and incentivization need to be addressed as was the case for pediatrics. Such considerations were beyond the scope of our early discussions as regulators focusing on global perspectives.

Our agencies share aspirations for change, recognizing that we are at the beginning of a long journey and specific actions will require more and broader discussion with many stakeholders to take shape. As such, our shared path forward must focus on:

- Approaching the use of medicines in pregnancy and breastfeeding from a benefit and risk perspective to meet the needs of clinical decision making.
- Fresh approaches to nonclinical reproductive toxicology.
- Systematic consideration of possible use of medicine by pregnant and breastfeeding women and, as warranted, planning for formal investigations in these populations.
- Addressing regulatory and liability barriers to promote clinical trial inclusion and participation of pregnant and breastfeeding women and women who may become pregnant.
- Supporting clinical decisions, rational use, and appropriate dosing through systematic and timely study of medicines likely to be used in this population.
- Examining and optimizing the regulatory system to ensure timely and efficient use of all available data resources.
- Challenging 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.

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. We intend to develop and implement a strategy that enables us to lead such efforts with women, healthcare professionals, industry, and public health experts, and hope to be met with enthusiastic engagement by partners around the globe.

ACKNOWLEDGMENTS

Michael D. Nguyen and Simone Pinheiro of the European Medicines Agency, and Jane Woolley, Katherine Donegan, David Jones, Sue Cole, Lisa Campbell, Sarah Mee for their work in preparing materials and organization of the workshop held in 2020, as well as their ongoing committment to furthering scientific excellence in addressing safety and access to medicines by pregnant women.

CONFLICT OF INTERESTS

The authors declared no competing interests for this work.

FUNDING

No funding was received for this work.

DISCLAIMER

This article reflects the views of the authors and should not be construed to represent views or policies of the FDA, the MHRA, or the EMA.

1. US FDA. Content and Format of Labeling for Human Prescription Drug and Biological Products: Requirements for Pregnancy and Lactation Labeling. (2014).
2. US HHS. Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC). (2017).

3. UK Commission on Human Medicines. Report of the Commission on Human Medicines' Expert Working Group on Hormone Pregnancy Tests. (2017).
4. US HHS. PRGLAC Report to Congress. (2018).
5. US FDA. Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials: Draft Guidance for Industry. (2018).
6. US FDA. Drug Safety in Pregnancy in a Large, Multisite Database: Mother-Infant Linkage in Sentinel. (2018).
7. ConcePTION – Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology and Breastfeeding to Improve Outcomes Now. Europe Innovative Medicines Initiative. (2019).
8. EMA. Guideline on Good Pharmacovigilance Practices: Pregnant and Breastfeeding Women. (2019).
9. US FDA. Postapproval Pregnancy Safety Studies: Guidance for Industry. (2019).
10. US FDA. Clinical Lactation Studies, Considerations for Study Design: Guidance for Industry. (2019).
11. UK MHRA. Programme of Work: Research to Support the Safer Use of Medicine during Pregnancy. (2019).
12. EMA. Strategic Reflection: EMA Regulatory Science to 2025. (2020).
13. Donegan, K., King, B. & Bryan, P. Safety of pertussis vaccination in pregnant women in UK: observational study. *BMJ* **349**, g4219 (2014).
14. CDC. Influenza vaccination coverage among pregnant women — 29 States and New York City, 2009–10 Season. *MMWR* **61**, 113–118 (2012).
15. ICH Harmonized Tripartite Guideline: Non-clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3(R2).
16. ICH Harmonized Guideline: Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals S5(R3).
17. US FDA. Guidance for Industry Pharmacokinetics in Pregnancy-Study Design, Data Analysis, and Impact on Dosing and Labeling. (2004).
18. World Health Organisation. Guidelines for the management of pregnant and breastfeeding women in the context of Ebola virus disease. (2020).
19. Couderc-Pétry, M., Eléfant, E., Wasunna, M., Mwinga, A., Kshirsagar, N.A. & Strub-Wourgaft, N. Inclusion of women susceptible to and becoming pregnant in preregistration clinical trials in low- and middle-income countries: a proposal for neglected tropical diseases. *PLoS Negl. Trop Dis.* **14**, e0008140 (2020).
20. Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research US HHS. (2001).
21. ICH Harmonized Tripartite Guideline: General Considerations for Clinical Trials.
22. Scheuerle, A.E. *et al*. Levetiracetam Pregnancy Registry: final results and a review of the impact of registry methodology and definitions on the prevalence of major congenital malformations. *Birth Defects Res.* **111**, 872–887 (2019).