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Published in:
CPT: Pharmacometrics and Systems Pharmacology

DOI:
10.1002/psp4.13214

Publication date:
2024

Document Version
Publisher's PDF, also known as Version of record

Received: 23 May 2024 | Revised: 11 July 2024 | Accepted: 17 July 2024

DOI: 10.1002/psp4.13214

PERSPECTIVE

EMA perspective on the value of model-informed drug development for labeling recommendations regarding medicine use during pregnancy and breastfeeding

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Except for medicines intended for use in pregnancy, pregnant and breastfeeding individuals are routinely excluded from drug development programs. Consequently, when medicines are needed to treat disorders that occur in pregnancy or during the breastfeeding period, or when unintended exposure to medicines occurs in unplanned pregnancies, there is uncertainty regarding the choice of treatment and the potential impact on the child. This article outlines the need for this to change, and opportunities in that direction offered by MIDD (Model Informed Drug Development).

CURRENT REGULATORY LANDSCAPE

At the time of marketing authorization, pregnancy/breastfeeding labeling typically relies mainly on preclinical data. While post-authorization studies are sometimes requested to collect safety data in pregnant and breastfeeding individuals, usually, routine pharmacovigilance (signal detection and post-authorization safety update reports) is relied upon for generating information in this population once the products are on the market.[1,2] The overall consequence is possible under-prescription of medicines in these individuals and missing or ambiguous pregnancy-specific dosing recommendations in the SmPC (Summary of Product Characteristics).[3,4] Hence, before, and long after real-world evidence is available, the use of medicinal products tends to be discouraged during pregnancy and breastfeeding.

This has been recognized as an unhelpful situation by regulators around the world,[5] leading within the European Medicines Agency (EMA) to the development and implementation of a strategy[6] to enhance the SmPC information on the benefits and risks of medicines in pregnancy and breastfeeding. Central to reaching this objective is to improve the related data collection (breadth and informativeness) during the

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product lifecycle. Important milestones include the agreement achieved by the International Conference of Harmonization (ICH) to draft a guideline for responsibly including, or permitting to remain, pregnant and breastfeeding individuals in clinical trials,[7] and the reopening of the Committee for Human Medicinal products (CHMP) guideline on labeling in pregnancy and breastfeeding.[8]

We anticipate that regulatory developments such as those mentioned above, coupled with the significant development and innovation in nonclinical drug development methodologies and MIDD over the last decades, will shift the current labeling paradigms, to improve accessibility and safe use of medicines during pregnancy and breastfeeding. Several regulatory initiatives are underway, and these will be publicized on a dedicated webpage on the EMA public website in summer 2024.

OPPORTUNITIES AND CHALLENGES WITH MIDD TO IMPROVE LABELING IN PREGNANCY/LACTATION

MIDD comprises the strategic use of computational modeling and simulation approaches that integrate data, prior information, and knowledge, including drug, nonclinical, clinical, and disease characteristics, to generate evidence. When adequately implemented, modeling and simulation is considered a powerful tool for characterizing the efficacy and safety of drugs in subgroups underrepresented in clinical studies such as pregnant and breastfeeding participants, who also deserve timely access to safe and effective medicines.

From a physiology and pharmacology point of view, pregnant and breastfeeding individuals represent complex and dynamic systems.[9] MIDD approaches, including population pharmacokinetics/pharmacodynamics, physiologically-based pharmacokinetic modeling, and quantitative systems pharmacology, can integrate available knowledge on the drug pharmacology, in vitro or in vivo nonclinical data and clinical data to quantify these complex systems and enable predictions of drug exposure and clinical response during pregnancy and lactation. These models can be continuously improved based on new data collected in clinical studies that enroll pregnant and breastfeeding individuals. Depending on the remaining uncertainty in the models and related parameters, they can be used to either improve operating characteristics of clinical trials enrolling pregnant and lactating participants or support regulatory claims by complementing (non) clinical evidence for benefit/risk, labeling and need for potential additional risk mitigation measures in these special populations.

Among the different MIDD approaches, physiology-based pharmacokinetic (PBPK) modeling is expected by drug developers and regulators alike to have a prominent role in drug development in pregnant and breastfeeding individuals, given its ability to distinctly describe physiological and pharmacological processes.[10,11] Already, different software providers are including pregnancy and lactation modules in their platforms.[12–14]

PBPK can serve for early-in-development PK prediction by integrating drug parameters, systems knowledge (i.e., changes in absorption, distribution, metabolism, excretion (ADME) in pregnancy, lactating mother, neonate-infant, transplacental or/and mammary gland drug transfer), in vitro data (permeability, metabolism, active transporters, etc.) and in vivo data from nonclinical and clinical experiments. This prediction of drug exposure in special populations, coupled with an understanding of nonclinical toxicology exposure margins and exposure-response relationships (depending on the stage of drug development), can inform decision-making regarding the enrolment of pregnant and lactating participants in clinical studies and contribute to the weight-of-evidence approach advocated in the EMA guidelines. Even in cases where it is not possible to enroll pregnant and lactating individuals, this quantitative framework can facilitate decisions regarding labeling and risk management in these populations.

Despite these developments being welcomed at EMA, the current experience in EMA submissions with PBPK and broader MIDD in this context remains limited. In addition, the MIDD framework proposed above does not come without challenges. Focusing on PBPK, the model predictions in pregnancy and lactation are associated with high uncertainty because of poor understanding and quantification of system parameters and mechanisms involved in transplacental and mammary gland transfer, physiological changes in pregnancy, lactation, and the maturing child. Likewise, the in vitro methods to enable reliable PBPK predictions in these special populations are not well characterized.

The current uncertainties with PBPK in pregnancy and lactation impede their unconditional use and regulatory acceptance. Regulators would expect to be able to quantify the risk of making a wrong decision, for example, in this case agreeing on a dose that leads to under- or overexposure in pregnant women or breastfed infants/neonates with associated risks.

The science is still evolving, but promising efforts are underway to improve knowledge by systematic collection

of physiology data, development, and characterization of new in vitro cell lines for passive and active transport, nonclinical and clinical data generation.[15,16]

CONCLUSION

There is regulatory acceptance that the use of MIDD approaches has the potential to:

- Complement clinical evidence, thus contributing to and accelerating actionable labeling information regarding medicine use and dosage in special populations such as pregnant and breastfeeding individuals.
- Increase confidence in enrolling these special populations in clinical trials.

PBPK is emerging as a tool of choice in this context. However, there is limited regulatory experience with these methods in the specific lactation/pregnancy context of use. In this regard, regulatory activities are ongoing to facilitate use of MIDD approaches and improve pregnancy/lactation labeling for medicines. European regulators are willing to engage early in discussions with platform developers and consortia, via the qualification procedure,[17] to agree on development and application of PBPK models in pregnancy and lactation.

FUNDING INFORMATION

No funding was received for this work.

CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

DISCLAIMER

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agencies or other organizations with which the authors are affiliated. The authors are employees of the European Medicines Agency or of a National Competent Authority.

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How to cite this article: Manolis E, Musuamba FT, de Vries CS, Colin PJ, Oleksiewicz MB. EMA perspective on the value of model-informed drug development for labeling recommendations regarding medicine use during pregnancy and breastfeeding. *CPT Pharmacometrics Syst Pharmacol*. 2024;13:1820-1823. doi:10.1002/psp4.13214