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Opportunities for Systems Biology and Quantitative Systems Pharmacology to Address Knowledge Gaps for Drug Development in Pregnancy

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Abstract

Pregnant women are still viewed as therapeutic orphans to the extent that they are avoided as participants in mainstream clinical trials and not considered a priority for targeted drug research despite the fact that many clinical conditions exist during pregnancy for which pharmacotherapy is warranted. Part of the challenge is the uncertain risk potential that pregnant women represent in the absence of timely and costly toxicology and developmental pharmacology studies, which only partly mitigate such risks. Even when clinical trials are conducted in pregnant women, they are often underpowered and absent biomarkers and exclude evaluation across multiple stages of pregnancy where relevant development risk could have been assessed. Quantitative systems pharmacology model development has been proposed as one solution to fill knowledge gaps, make earlier and perhaps more informed risk assessment, and design more informative trials with better recommendations for biomarker and end point selection including design and sample size optimality. Funding for translational research in pregnancy is limited but will fill some of these gaps, especially when joined with ongoing clinical trials in pregnancy that also fill certain knowledge gaps, especially biomarker and end point evaluation across pregnancy states linked to clinical outcomes. Opportunities exist for further advances in quantitative systems pharmacology model development with the inclusion of real-world data sources and complimentary artificial intelligence/machine learning approaches. The successful coordination of the approach reliant on these new data sources will require commitments to share data and a diverse multidisciplinary group that seeks to develop open science models that benefit the entire research community, ensuring that such models can be used with high fidelity. New data opportunities and computational resources are highlighted in an effort to project how these efforts can move forward.

Keywords

clinical pharmacology, drug development, pregnancy, quantitative systems pharmacology

Introduction

Pregnant women are one of the most at-risk groups in any society, and likewise, unmet medical needs in pregnant women are a global health concern. Receiving essential health care in pregnancy is of special importance because health and well-being of both mother and child are at issue. It has been reported that 64% of pregnant women take at least 1 medication for the treatment of a variety of clinical conditions, including viral (e.g., HIV), fungal, or bacterial infections; smoking cessation; epilepsy; and pregnancy-induced conditions such as hypertension, depression, and gestational diabetes.[1,2] Complicating this issue, the use of over-the-counter medications during pregnancy is also common. A recent study conducted in pregnant women found that 95.8% of participants used prescription medications, 92.6% took over-the-counter medications, and 45.2% used herbal medicines.[1] Approximately 5%–10% of pregnant women receive US Food and Drug Administration (FDA) approved drugs under the previously defined (prior to 2015) category D or X drugs, which are potential teratogens, and the frequency of drug use is higher in early versus late pregnancy.[2,3] Even in light of the newer, more informative nomenclature,[4] this situation is the same. This highlights the fact that despite the risk involved, some drugs are still prescribed to at-risk pregnant women outside the label recommendation, but also there is the reality that many women require drug treatment during pregnancy due to chronic conditions such as epilepsy, diabetes, hypertension, or asthma. To withhold drug treatment would be dangerous for both mother and baby. In addition, women are having babies at a later age, which can boost the number of women with chronic conditions.

Pregnancy represents a dynamic state with respect to physiological changes that occur in both mother and

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Table 1. Summary of relative pregnancy-induced physiologic changes during the near term.

System	Parameter	Nonpregnant	Pregnant
Cardiovascular	Cardiac output (L/min)	4.0	7.0
	Heart rate (beats per min)	70	90
	Stroke volume (mL)	65	85
	Plasma volume (L)	2.6	3.5
	Colloid osmotic pressure (mm Hg)	22.0	18.2
	Total peripheral arterial resistance (dyne s/cm^5)	1530	1210
Respiratory	Total lung capacity (mL)	4225	4080
	Residual volume (mL)	965	770
	Tidal volume (mL)	485	680
	Minute O_2 uptake	201	265
Liver	Portal vein blood flow (L/min)	1.25	1.92
	Hepatic artery blood flow (L/min)	0.57	1.06*
Renal	Glomerular filtration rate (mL/min)	97	144
	Creatinine (mg/dL)	0.7	0.5
Enzyme expression	Inferred primarily based on RNA expression data (ignoring potential differences in protein expression and enzymatic activity), significant differences in metabolic competency in the cytochrome P450 enzymes have been determined.		
Endogenous entities increased during pregnancy	Small molecules (estrogen, progesterone, 17a-hydroxyprogesterone, aldosterone, cortisol, 11-deoxycortisol, androstenedione)		
	Peptides/proteins (neuropeptide Y, calcitonin gene–related peptide, prolactin, human placental lactogen, leptin, growth hormone variant, inhibin, human chorionic gonadotropin)		

*Difference was not statistically significant.

child, and benefit to the targeted condition is heavily weighed against the potential to do harm in either mother or child or both. Knowledge regarding the use of drugs in pregnant women is often generated only after off-label use and not targeted investigation. When clinical trials are conducted, they are often small, underpowered trials focused on safety and exposure matching only[5] as opposed to clinical benefit assessments or optimal dosing considerations. Even the desired therapeutic window as such is complex and difficult to define a priori. Table 1 provides a summary of some pregnancy-induced physiologic changes during the near term.[6–11] More detailed quantitative descriptions are contained in the source references. Most drugs are not tested for use during pregnancy, and consequently, labeling, which may include information about fetal safety, includes nothing about dosing, efficacy, or maternal safety. These are concerns of health care providers considering treatment of disease during pregnancy. The practitioner often treats the pregnant woman with the same dose recommended for use in adults (typically men) or may decide not to treat the disease at all.

Pregnancy is not devoid of disease conditions, either, with research showing that a healthy woman's pregnancy is most complicated by diseases such as psychiatric illness, hypertension, and cancer. A study showed that up to 64% of pregnant women receive at least one prescription for medical needs.[11] Along with increasing age for pregnancy, there is an increase in complex medical problems, subsequently increasing the use of prescription medications by pregnant women. A study conducted in 2011 revealed that of all medications approved by the FDA from 1980 to 2010, 91% did not have enough data on safety, efficacy, and fetal risk of medication taken during pregnancy. Thus, treatments in pregnancy are mainly empirical and not evidence based, simply due to the lack of sufficient studies in pregnant women.[12,13] Very few pharmaceutical company–sponsored drug intervention studies have been conducted or are being planned in areas other than pregnancy-associated conditions. Most of the studies are related to analgesia, hypertension, and anemia, which are directly related conditions. More observational studies in general medical illnesses as well as pregnancy- and labor-associated indications are sorely needed. Observational studies, if conducted rigorously, can pave the way for controlled clinical studies to allow generation of a higher level of evidence. In general, fewer studies are done in the first and second trimesters compared to the third trimester.

The drug pipeline for obstetric disease between 1980 and 2007 found just 17 new drugs undergoing evaluation between the preclinical and preregistration phases.[14,15] This number compares with 660 new drugs for cardiovascular diseases over the same time frame. Of the 17 obstetric drugs, only one represented a new class of drug. With respect to current drug development pipelines, this is still little to report on. Still, many of the drug classes currently being pursued still lack

Table 2. Funding sources and representative gap-filling studies beyond PK-centric exposure matching and safety trials

Funding Organization	Title (Reference)	Objectives
National Institutes of Health, Office of Research on Women's Health	Maternal Morbidity & Mortality web portal: representative funding opportunities listed (https://orwh.od.nih.gov/mmm-portal/funding-opportunities)	• Translational research • Technology and outcomes in LMICs • COVID-19 research • Others
FDA Office of Women's Health (OWH)	OWH-Funded Research: Pregnancy (Prevention/Exposure) (https://www.fda.gov/science-research/womens-health-research/owh-funded-research-pregnancy-preventionexposure)	• Defining SARS-CoV-2 Vaccine-Induced Immunity in Pregnant and Lactating People • Define a biomarker of decidual inflammation to predict recurrent pregnancy loss • Assessing Real-World Use of Pharmaceuticals Among Pregnant Women
Preeclampsia Foundation (https://www.preeclampsia.org/research-funding) Vision grant awarded every year	Prospective Study to Evaluate the Role of CD3-zeta Expression in Preeclampsia Compared to Normotensive Pregnant Controls	• Risk factors for future patient stratification
March of Dimes (https://www.marchofdimes.org/our-work/research)	Benzene and NO_2 Exposure During Pregnancy and Preterm Birth in Two Philadelphia Hospitals, 2013–2017 (Escoto 2022)	• Exposure during pregnancy and preterm birth
Bill & Melinda Gates Foundation Maternal, Newborn & Child Health (https://www.gatesfoundation.org/our-work/programs/gender-equality/maternal-newborn-and-child-health)	Related Grand Challenge Grants (https://grandchallenges.org/grant-opportunities)	• Strengthening Modeling and Analytics Capacity and Ecosystem for Women's Health • Strengthening Contraceptive Research and Development Ecosystem in Africa: Accelerating Innovations in Non-Hormonal Contraception

Abbreviations: FDA, US Food and Drug Administration; LMICs, low- and middle-income countries; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

a strong mechanistic underpinning to support their clinical development (e.g., oxytocin antagonists and $\beta 2$ and $\beta 3$ adrenoreceptor agonists).[14] Many drugs used in pregnancy are borrowed or repurposed from mainstream therapeutics, with comprehensive evidence of efficacy and safety in pregnant women often lacking despite awareness of the pharmacokinetic changes previously described.[15,16]

One of the more promising opportunities for the further development of quantitative systems pharmacology (QSP) models for pregnancy is the diversity of funding sources to increase translational research in pregnancy both preclinically and via targeted clinical investigation. Table 2 highlights some of these sources from prominent funding bodies. An important aspect for this initiative will be the sharing of these data in a coordinated manner so that these data can fulfill their potential not only by addressing the research objectives for which they were designed but as additional resources from which the entire ecosystem can leverage for additional research plans. Having access to publications is not enough in this regard. Recently, the National Institutes of Health issued the Data Management and Sharing policy (effective January 25, 2023) to promote the sharing of scientific data, though past initiatives have yet to elicit the kind of data sharing hoped for by funders.[17] The National Institutes of Health contention is that sharing scientific data accelerates biomedical research discovery, in part, by enabling validation of research results, providing accessibility to high-value data sets, and promoting data reuse for future research studies. As new global funding requirements are likely to stipulate the sharing of the actual data generated and not only summarized tabulations in the future, the construction of QSP models and other quantitative approaches will be greatly facilitated. For researchers in this arena it is likewise important to be informed of new funding opportunities as quickly as they arise. Luckily, more online resources are becoming available to assist in this regard, for example, GrantWatch on the Blog.[18]

QSP models have been able to fill in knowledge gaps in certain difficult-to-study populations including various rare diseases[19,20] and neurological disorders including Parkinson disease and Alzheimer disease.[21–23] Recently, Quinney et al.[24] have addressed the application of QSP in pregnancy and have illustrated the approach and the benefit, although there are still few published examples of the approach applied to investigational drugs in pregnancy. What is clear from the existing published uses cases thus far is that the inputs for development of QSP models to study pharmacotherapy in pregnancy thus far are largely taken from mainstream drug development of the agent in question and seldom vetted against any data in

pregnancy. While a certain amount of leveraging data in nonpregnant states should be expected, this needs to change. Specifically, designing preclinical, translational research plans and conducting longitudinal clinical trials in pregnant women, collecting more and better data across pregnancy states, is a needed emphasis.

Indeed, the relationship between pregnancy and the global burden of disease is a well-recognized global health concern[24] not only from the standpoint of lack of investigation but also from the perspective of the lack of information resources that facilitate the current level of reasonable empiricism afforded to high-income countries. Specifically, in the absence of empirical evidence for most of these drugs, medical providers in the United States routinely depend on case reports, pregnancy registries, observational studies, or anecdotal clinical experience to prescribe medications for pregnant women. These information resources are often unavailable to physicians making similar decisions in low- and middle-income countries.[25] Again, resource inequity coupled with a lack of coordinated data sharing is part of the challenge on a global health scale. The intention of this article is to highlight the potential use and utility of QSP to fill important knowledge gaps for the use of medicines in pregnant women, to highlight data and knowledge gaps for such models, and to provide a road map where such models may be better informed through planned and ongoing prospective research. Finally, we address the benefits of real-world data (RWD) and artificial intelligence (AI)/machine learning (ML) techniques to advance both QSP model development and qualification.

Data Sources for Pregnant Women

Data requirements for comprehensive QSP models have been previously described.[26] Beyond generic QSP models, additional data to describe the necessary model architecture for pregnant women include physiologic data by phase, disease condition data in pregnancy, longitudinal data, developing child data (human and/or animal data) as well as complementary data in the fetus, fetal and placental transfer kinetics, and lactation data if in scope. While sponsors do routinely generate toxicologic data in maternal toxicology/toxicokinetic trials, these are usually focused on drug exposure risks and inherently pharmacokinetic-centric. They offer drug-specific value but do not necessarily fill other physiologic data gaps. To that end, additional targeted research made available by the diverse funding streams highlighted in Table 2 are now being planned or are ongoing to fill some of these gaps. Table 3 highlights a number of targeted investigations with specific objectives in pregnant women, which offer the possibility to address shortcomings of previous trials and contribute to some of the missing components of pregnancy QSP models. An area of potential collaboration could be the investigation of the studies listed in Tables 2 and 3 for their value in generating priors for QSP models, specifically in the category of time-dependent changes in physiologic parameters correlated with drug transport and disposition. Some of this effort is likely in scope for the Maternal and Pediatric Precision in Therapeutics initiative.[27]

As previously mentioned, it is hoped that data from investigations such as those listed in Table 3 are made available to the ecosystem of researchers in this arena. One important recent development is the creation of the Maternal and Pediatric Precision in Therapeutics resource hub for obstetric and pediatric data (https://www.nichd.nih.gov/about/org/der/branches/opptb/mprint), which is intended to provide a home for such data that would be freely accessible to the community. Most of the development compounds targeted for development for pregnant women are focused on a few indications specifically related to the condition of pregnancy. A disturbing trend is the increasing comorbidities in pregnant women in certain common indications where mainstream (nonpregnant) patients are well managed (e.g., diabetes, hypertension, asthma, depression). The use of these drug classes in pregnant women often remains an empiric process in which caregiver experience with the agents in the class often dictate the outcomes in an individual patient.

Systems Biology and QSP Opportunities and Strategies to Address Pregnancy Knowledge Gaps

There are various layers of biological scales and respective systems-based approaches that can advance our understanding of predicting drug concentration and effect or quantify risk. In this section, we outline the opportunities for applying advanced systems biology and pharmacology approaches, coupled with mathematical model representations and data science techniques with the ultimate goal of advancing the application of novel drugs in pregnancy and quantifying risk to mother and fetus.

With the advent of measurement technologies, allowing us to measure an increasingly comprehensive list of metabolites and proteins at scale, coupled with the completion of the human genome project, and characterization of genes, has propelled our understanding of cellular behavior and network behavior of underlying biological pathways and processes.[28] Systems biology has been increasingly used now as a platform technology for discovery of novel targets, elucidation of drug mechanism of action, and translational sciences geared toward advancing new molecular entities into the clinic, through discovery of novel biomarkers of disease or drug action.[29] These mechanistic discoveries are amenable for investigating and quantifying

Table 3. Representative clinical trials in pregnancy targeting current shortcomings

Trial (Reference)	Objectives	Shortcomings to Address
National Institutes of Health, Office of Research on Women's Health Trials (https://orwh.od.nih.gov/mmm-portal/ongoing-studies): • Chronic Hypertension and Pregnancy (CHAP) Project • Final Research Plan: Aspirin Use to Prevent Morbidity and Mortality from Preeclampsia - Preventive Medication • nuMoM2b Heart Health Study • Human Placenta Project • Pregnancy Risk Assessment Monitoring System (PRAMS) • PregSource • Researching COVID to Enhance Recovery (RECOVER)	• Evaluates effectiveness and safety of blood pressure treatment strategy during pregnancy to achieve targets • Maternal health outcomes among women at increased risk of preeclampsia using aspirin during pregnancy • Investigates relationship between experiences during pregnancy and cardiovascular health 2–3 $\frac{1}{2}$ years after pregnancy • Understand the role of the placenta in health and disease • Surveillance project; jurisdiction-specific, population-based data on maternal attitudes and experiences before, during, and shortly after pregnancy • Designed to learn about pregnancy directly from pregnant women • Understand, prevent, and treat postacute sequelae, including long COVID in pregnant women	• Lack of consensus on biomarker/clinical end points • Lack of outcome data in adequately powered trial • Lack of longitudinal data • Lack of translational data linked to outcomes • Lack of longitudinal data linked to reproductive health • Lack of real-world data from patients themselves • Lack of longitudinal data linked to reproductive health
ClinicalTrials.gov (https://clinicaltrials.gov/ct2/home) *Drug and Vaccine Sponsors* BioNTech SE and Pfizer in collaboration with many academic medical centers*Global Investigator-initiated trials* *Mỹ Đức Hospital*	• Safety, Tolerability, and Immunogenicity of BNT162b2 Against COVID-19 in Healthy Pregnant Women 18 Years of Age and Older (https://clinicaltrials.gov/ct2/show/NCT04754594)Evaluation of the Possible Vertical Transmission of SARS-CoV-2 Through Study of Amniotic Fluid and Chorionic Villi of Affected Pregnant Women (https://clinicaltrials.gov/ct2/show/NCT04598347?term=pregnant+women&cond=COVID-19&draw=4&rank=8) • Diagnostic Value of Calponin 2 in Identifying Tubal Pregnancies (CNN2) (https://clinicaltrials.gov/ct2/show/NCT05591599?cond=pregnancy&draw=2&rank=1) • Many others	• Lack of translational data linked to outcomes • Lack of longitudinal data linked to reproductive health • Lack of consensus on biomarker/clinical end points • Lack of outcome data in adequately powered trial

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

disease and drug mechanisms and can be incorporated into broad or fit-for-purpose systems pharmacology models that combine disease and drug mechanistic understanding to address different types of questions, such as impact of dosing level or dosing regimens on dynamics of metabolic or signaling drivers to drug-related improvements, ability to achieve or stay below homeostatic thresholds, or understanding impact and potential benefits of drug on defined segments of disease. These systems biology and pharmacology capabilities are intertwined with physiological systems modeling that focus on interorgan transport and impact of perturbing biology on organ health and system-wide homeostasis, facilitating a more direct link to patient-level end points or symptoms associated with disease burden.[30] How can these advances bridge the gap toward advancing the development and use of novel drugs to pregnancy? There are opportunities here to more fully capture biological and physiological state changes during stages of pregnancy and informing appropriate study of benefit and risk of novel drugs in this population.

There has been much progress in the application of physiological models to both disease physiology and drug development. Physiological modeling has been a cornerstone for appreciating physiological systems, function, and control, owing to the necessity of understanding the dynamic changes of response under normal daily stimuli or disease involvement. Models are indispensable tools for simulating and characterizing system dynamics, understanding control drivers and other applications.[31] Some notable examples of these applications have been toward understanding of blood pressure and heart rate dynamics and control, as well as kidney regulation and control of blood volume.[32] Advanced models have helped physiologists characterize mechanisms of blood flood and distribution, including changes in cardiac function and output and fraction of blood volume into different organs, based on changes in demand. These models are directly applicable to appreciate and quantify physiologic changes to cardiovascular function during the different pregnancy stages, as well as facilitate the quantification of drug distribution with different dosing and regimens under

study. The field of physiologically based pharmacokinetic (PBPK) modeling has made significant advances in the application of physiological modeling to capture transport and blood flow data to model distribution and kinetics of drugs in a wide variety of populations, including pregnancy.[33] When coupled with knowledge of drug metabolism and transporters, and expression of these transporters across tissues and cell types, multiscale PBPK simulation platforms can be an extremely valuable tool for clinical pharmacology.

This brings us to the use and application of systems biology to measure and quantify changes in gene expression, metabolism, and proteomics on a broad scale to comprehensively capture biological changes during stages of pregnancy, and drug impact based on mechanism of action on baseline biological state. Advances in broad-scale measurement of metabolites, proteins, and gene expression, coupled with commensurate advances in statistical and computational modeling and computing power, are revolutionizing the life sciences and, in particular, understanding of clinical disease pathogenesis. The ability to capture and construct a systems-level multiomic network of gene to protein and metabolite in a disease context is providing in-depth understanding of disease necessary to propel discovery of novel targets and assessment of these targets' modulation of human disease biology. Examples of how these advances have made a difference include identification of new targets in the field of cancer immunotherapy and identification of targets to overcome resistance against tuberculosis drug combinations.[34] Systems biology platforms are now actively applied in the search for new therapeutics for nonalcoholic steatohepatitis and long COVID (following infection with the COVID-19 virus, some people continue to experience health problems long after having COVID-19) and are expected to play an important role in the advancement of novel medicines for neurodegenerative diseases[35,36] given the neurologic component of both disease trajectories. In a similar way, computational and systems biology has the potential to advance our understanding of the tissue- and cell-specific changes that occur during different stages of pregnancy, for example, providing a broader and more in-depth understanding of lipid and metabolic changes, and predicting how these underlying changes in metabolism can impact drug efficacy or drug metabolism. In combination with transport and physiological models, this knowledge can aid in quantifying and potentially predicting exposure distribution in pregnancy states and extent of exposure in the fetus, for both small molecules and monoclonal antibodies. Simulating both active and passive transport and diffusion processes and potentially incorporating higher dimensional transport models can increase the ability to predict drug distribution concentration and quantify the relative risk and benefit to therapeutic intervention.

Because of the complexity of QSP models, they require rich experimental data and often rely on in silico prediction tools to obtain the required physicochemical or absorption, distribution, metabolism, and excretion parameters as one would obtain for a PBPK model. Because drug-specific parameters may not always be available, assumptions are often made on the basis of general knowledge. Thus, it is important to validate model predictions with available data. For example, validation of the drug-specific parameters using intravenous and oral data obtained in the nonpregnant population is necessary to demonstrate the adequacy of the model in nonpregnant adults as a comparative population of interest. Also, assessing the sensitivity of model predictions to changes in the system model's key parameters is necessary. Model verification for the nonpregnant subjects is often used as a comparator to study the effect of pregnancy on drug pharmacokinetics/pharmacodynamics, for example.

One of the important frontier areas for QSP model development is the integration of the methodology with AI and ML approaches. While QSP models seek to describe hypothesized or assumed mechanistic relationships in a mathematical formalism, ML applies unbiased algorithms to explore correlations or learn features from experimental data. Although the approaches may appear as disparate approaches, there is value derived from their integration.[37] A recently formed working group has identified four categories of application for integrated QSP-ML approaches: parameter estimation and extraction, model structure, dimension reduction and stochasticity, and virtual populations. While these areas emphasize the quality aspects of model development and validation, they also improve the fidelity in model applications, for example, by bridging mechanistic knowledge gaps with data-driven, yet nonspecific learned relationships. In the context of QSP models to support drug development in pregnant women, this integration is also envisioned to improve outcomes in pregnancy[38] largely through AI/ML-enabled "deep phenotyping" (i.e., describing deviation from healthy morphology or physiology, in this case nonpregnant morphology or physiology).[39]

Future Opportunities

Additional opportunities in the area of omics big data and data sciences include and extend to the incorporation and application of electronic health record (EHR) data. The value of EHR data was and continues to be significantly highlighted throughout the COVID-19 pandemic. Many of these EHR data and analyses have been an indispensable tool for evaluating how different populations are affected by viral infection,

evaluating access to diagnostics and vaccines, and investigating impact of comorbidities and surfacing potential predictors for severe disease or hospitalization.[40] Some of these publications and studies have also described the impact of COVID-19 infection and disease on pregnancy and fetal health, and risk of pre-term delivery.[41] More recently, a cross-institute initiative has been funded to study and map the immune system and changes during pregnancy trimesters, and to use these systems biology-driven maps to advance recommendations for vaccine delivery during pregnancy, for COVID-19,[42] as part of the Maternal 'Omics to Maximize Immunity (MOMI consortium). The combination of EHR and systems biology-driven research holds significant promise, as exemplified here at the intersection of immunology and vaccine research applied to maternal and fetal health. Moreover, the mapping of these immune systems during pregnancy can have further-reaching application in drug development, for example, in the area of immunotherapy.

The gaps in treating pregnancy-related health issues are truly a global concern. Maternal and perinatal conditions are the single largest contributor to the global burden of disease, accounting for 6% of disability-adjusted life years[43] and would account for more if stillbirths were not excluded. Worldwide, there are 536,000 maternal deaths annually, while nearly half the 13.5 million deaths of children under age 5 occur as antepartum, intrapartum, or neonatal deaths. These are disproportionately concentrated in the developing world, where 99% of maternal deaths occur, three quarters due to preventable or treatable conditions such as hemorrhage, hypertensive disorders of pregnancy, sepsis, obstructed labor, and unsafe abortion.[43]

The FDA is working on ways to facilitate greater use of RWD to help understand the safety and efficacy of medications used during pregnancy and lactation. To that end, they have sponsored workshops (https://www.jhsph.edu/research/centers-and-institutes/center-of-excellence-in-regulatory-science-and-innovation/news-and-events/FDA%20OWH-CERSI-Collaborative-Workshop.html) on this topic and issued recent guidance to provide clarity for drug sponsors.[44,45] It can be a challenge for health care professionals and patients to find quality scientific information about the safety of drugs and biological products when used during pregnancy or breastfeeding. Ethical challenges often arise in studying women in these populations, as there are valid concerns about maternal and fetal safety. This is the view of many at the Center for Drug Evaluation and Research Director at the FDA. The lack of data often leads physicians and women to make decisions about prescription drugs without knowing if there are increased maternal and fetal safety risks or risks of drug exposure to nursing infants.

FDA recommendations relevant to the use of RWD in drug development for pregnancy include the following:[46,47] (1) Increase the quantity, quality, and timeliness of research involving therapeutic products used by pregnant and lactating women; (2) optimize pregnancy registries to move away from single-product, single-company pregnancy registries and expand the use of disease-based registries; (3) implement a proactive approach to protocol development and study design to systematically develop a plan for timely collection of data, including pregnancy safety data; and (4) design health record systems to link mother and infant records and leverage large studies and databases. There is now broad regulatory appreciation that RWD plays an important role in filling the data gap, as most pregnancy and lactation-related safety data are collected in the postapproval setting and relying on a single study to optimize safety assessment during pregnancy is not in anyone's best interest, as multiple data streams are needed. It is the RWD in pregnant women that can then be analyzed via AI/ML approaches in order to deliver efforts in the deep phenotyping of pregnant women with respect to their underlying disease trajectories that would help form more credible QSP models to describe and simulate the time course of drug exposure and response. By projecting virtual pregnant women and then qualifying simulations via the RWD, this affords the potential to mitigate some of the risk–benefit associated with prospective clinical trials in pregnant women and likewise facilitate the design of more informative trials when they are conducted.

Discussion

QSP is an important component of a model-based drug development paradigm adopted by many within the pharmaceutical industry. Its benefits are many for numerous existing and novel therapeutic areas but also for subpopulations often viewed as outside the mainstream development target population, including pediatrics and people with rare diseases.[19,20,36,48] These benefits inform not only key decision criteria (study population, indication, study design, and sampling scheme) but also the basis for clinical use (e.g., dosing timing and adjustments) and prescribing information (therapeutic window, contraindications, DDI potential, etc.). In pregnant women, for whom targeted clinical investigation is expected to be a continual challenge, we must leverage in silico techniques as much as possible, especially when they are well vetted against RWD sources or data from prospective clinical evaluation.

Lack of research into pregnancy and reproductive health can have a significant effect on the ability to

provide novel therapies and interventions that can save lives and relieve suffering for many mothers and babies. Given the current diversity in translational research opportunities and ongoing clinical trials in pregnancy, it appears that funders are now responding in an appropriate manner, as highlighted in Tables 2 and 3. Still, more is needed. The UK government's new Women's Health Strategy for England has highlighted the need for more research into a number of issues including pregnancy, though research into pregnancy and reproductive health is chronically underfunded.[49] Likewise, the World Health Organization has proposed broad strategies to improve women's health that aim to generate better maternal and fetal outcomes and facilitate data sharing (https://www.who.int/data/maternal-newborn-child-adolescent-ageing/global-strategy-data).

Avoiding all drug therapies in pregnancy is not possible. Many women need treatment for pregnancy-related issues or chronic underlying conditions. Therefore, it is vital that new techniques can be used to aid understanding of some of the areas that are currently less understood, such as how the medicine might affect the workings of the placenta or whether it can cross the placenta from mother to child. One of the hopes of more consistent investment and deployment of the QSP approach to support drug development in pregnant women is the expansion of the global portfolio of agents being studied as well as the more informative clinical development programs including novel clinical trial designs, relevant biomarkers, and clinical end points and better dosing guidance in pregnant women.

Recently, the case for QSP was clearly articulated by the community of National Institute of Child Health and Human Development investigators that would also accumulate the data resources necessary for this approach to gain credibility across various therapeutic areas.[24] The authors point out a few challenges to the effort including harmonization of phenotype definitions, ethical barriers to clinical investigation, and integration of data and knowledge. As more data in pregnancy are collected and shared,[27] the opportunity to connect QSP modeling resources[37] to such data as they are collected, curated, and transformed into contemporary tools and solutions, including QSP models, should improve. It should also be clear that QSP models are not the only solution for the data gaps in pregnancy. Exciting progress on organ-on-a-chip[50] and placenta-on-a chip[51] technologies offer promising complementary solutions that should be similarly evaluated and held to high standards for the manner in which they can eventually support drug development in pregnancy, for example, by providing valuable tissue-specific and multicellular stimulus–response phenotypic and omic-level data. Not coincidentally, some of the data resources discussed herein will also benefit these approaches and technology. While one cannot assume successful outcomes here, it should be clear that data and knowledge colonialism cannot be allowed to influence a truly global solution to a global problem that affects mother and child.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Data Availability Statement

Data generated herein are based on literature and web review but are available from the principal investigator upon request.

Principal Investigator's Statement

The authors confirm that Jeffrey S. Barrett, PhD, FCP, is the principal investigator responsible for this research and analysis.

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