Drug development research in pregnant and lactating women

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Pregnant and lactating women are considered "therapeutic orphans" because they generally have been excluded from clinical drug research and the drug development process owing to legal, ethical, and safety concerns. Most medications prescribed for pregnant and lactating women are used "off-label" because most of the clinical approved medications do not have appropriate drug labeling information for pregnant and lactating women. Medications that lack human safety data on use during pregnancy and lactation may pose potential risks for adverse effects in pregnant and lactating women as well as risks of teratogenic effects to their unborn and newborn babies. Federal policy requiring the inclusion of women in clinical research and trials led to considerable changes in research design and practice. Despite more women being included in clinical research and trials, the inclusion of pregnant and lactating women in drug research and clinical trials remains limited. A recent revision to the "Common Rule" that removed pregnant women from the classification as a "vulnerable" population may change the culture of drug research and drug development in pregnant and lactating women. This review article provides an overview of medications studied by the Obstetric-Fetal Pharmacology Research Units Network and Centers and describes the challenges in current obstetrical pharmacology research and alternative strategies for future research in precision therapeutics in pregnant and lactating women. Implementation of the recommendations of the Task Force on Research Specific to Pregnant Women and Lactating Women can provide legislative requirements and opportunities for research focused on pregnant and lactating women.

Key words: antiviral drug, clinical trials, drug development, gestational diabetes mellitus, glyburide, lactating women, medications, metformin, pharmacodynamics, pharmacokinetics, pharmacometric tools, pravastatin, preeclampsia, pregnant women, preterm birth, PRGLAC transplacental transfer

Recent History of Drug Development and Research During Pregnancy

There has been an increase in the prevalence of preexisting and chronic conditions (ie, asthma, diabetes, hypertension, heart disease, and substance use disorders) among women of childbearing age in recent years,[1] which require them to continue taking medications during their pregnancy, the postpartum period, and lactation. Between 40% to 60% of pregnant women take 1 or more prescription medications for their preexisting or pregnancy-induced conditions during their pregnancy.[2] More than 70% of women who breastfeed or pump their milk take some form of medication during lactation.[3] However, the majority of medications prescribed to pregnant and lactating women are used "off-label" because more than 90% of clinically-approved medications do not have appropriate drug labeling information for pregnant and lactating women[4] (Figure). Medications that have never been tested in pregnant and lactating women may have potential risks for adverse effects in pregnant and lactating women as well as lead to harmful effects to their developing fetus, neonates, and infants. This may contribute to increased maternal and perinatal morbidity.

Historically, pregnant women largely have been excluded from clinical drug research and new drug development processes[5] primarily because of legal and ethical concerns. This exclusion led to the use of drugs in clinical practice that had not undergone rigorous evaluation for use during pregnancy; this, unfortunately, led women to take drugs that had significant adverse effects. One example was the use of diethylstilbestrol (DES) in pregnant women to protect against miscarriages and other pregnancy-related complications from the 1940s to the 1960s. It was later identified that exposure to DES in utero caused vaginal clear-cell adenocarcinoma in female offspring[6,7] and congenital anomalies in female reproductive tracts such as hypoplastic cervix and Mullerian duct abnormalities.[8,9] Another example is thalidomide. Thalidomide is a sedative drug that was widely used among pregnant women to relieve pregnancy-induced nausea and vomiting in the late 1950s and early 1960s. The lack of human data on the safety and efficacy of the drug during pregnancy led to the prescription of thalidomide to pregnant women; unfortunately, thousands of babies were born with severe upper and lower limb malformations caused by the teratogenic effects of thalidomide.[10] In addition, a wide variety of internal defects such as

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FIGURE
Most women take 1 or more medications during pregnancy and lactation

Most of the medications lack appropriate labeling information for pregnant women and lactating women.

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patent ductus arteriosus, pulmonary stenosis, duodenal atresia, etc were associated with prenatal exposure to thalidomide.[11] The drug was taken off the market in 1961.

In the wake of the worldwide thalidomide tragedy, the US Food and Drug Administration (FDA) increased its regulations on drug approvals for use in pregnant women and released new guidelines in 1977 (General Considerations for the Clinical Evaluation of Drugs), which prevented pregnant women from participating in phase I and early phase II clinical trials.[12] In 1979, the FDA implemented a pregnancy category labeling system that required sponsors to include information on the safety of medications in pregnancy that was largely based on data from animal studies. The FDA labeling rule classified pregnant women as a "vulnerable" population that require special protection in research. Owing to the lack of incentives to conduct research in such a "high-risk," "vulnerable" population and the fears of potential harmful effects to the developing fetus, pharmaceutical companies have been very reluctant to include pregnant and lactating women in drug development research and clinical trials.

To date, the drug safety and efficacy data for pregnant and lactating women for most FDA-approved drugs have been collected from the postmarketing surveillance pregnancy registries. However, over the past several decades, attitudes concerning the inclusion of women in clinical research and trials have changed dramatically. The National Institutes of Health Revitalization Act in 1993, which required the inclusion of women in clinical research and trials, led to considerable changes in research design and practice and led to more women being included in clinical research and trials.[13] Despite these considerable changes, however, the inclusion of pregnant women in drug development research and clinical trials was still limited. In fact, the concern for pregnant women as a result of being categorized as a "vulnerable" population with regards to clinical research and trials remained until a recent revision of the "Common Rule" (the "Common Rule" is a short name for "The Federal Policy for the Protection of Human Subjects" and was adopted by a number of federal agencies in 1991. URL: https://www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html) that removed the classification of pregnant women as a "vulnerable" population.[14]

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Approaches in Obstetrical-Fetal Pharmacology Research

The importance and necessity of creating a systematic framework and infrastructure in which to study medications used in pregnant women was recognized in the early 2000s by the scientific community and federal agencies. A multicenter collaborative research network—the Obstetric-Fetal Pharmacology Research Units (OPRU) Network——was thus established by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) in 2004 as a follow-up on a workshop about drug use during pregnancy hosted by the NICHD in September 2000.[15] The OPRU Network was changed to the Obstetric-Fetal Pharmacology Research Centers (OPRCs) after re-competition in 2015.

With a core mission to improve the safety and efficacy of medications used by pregnant and lactating women, the NICHD OPRU Network and OPRCs investigators have conducted pharmacokinetic (PK) and pharmacodynamic (PD) studies on a number of medications commonly

used during pregnancy and lactation, such as glucose-lowering agents for the treatment of gestational diabetes mellitus (GDM),[16,17] pravastatin for the prevention of preeclampsia,[18] clonidine and atenolol for the treatment of hypertension,[19,20] indomethacin for preterm labor,[21] oseltamivir for influenza infection,[22] and others (Table). Results from these studies have contributed to the understanding of altered PK processes (drug absorption, distribution, metabolism, and excretion) and PD properties of these medications during pregnancy and lactation. For example, significant changes in the PK parameters (decrease in area under the curve and maximum placenta concentration and increase in apparent oral clearance) of glyburide during pregnancy have suggested that higher dosages of glyburide may be needed in a woman with diabetes during pregnancy than when the patient is not pregnant to achieve comparable glycemic management.[16] The study also found that the umbilical cord plasma glyburide concentration was about 70% of that of the maternal plasma glyburide concentration, which was different from previous reports in which no glyburide was detected in cord blood.[16,78] These observations provided a pharmacologic basis for altering the glyburide administration regimen in pregnant women to minimize the side effects (both to the mother and the newborn) while maximizing the pregnant woman's therapeutic response.[30] These study findings have also led to changes in the American College of Obstetricians and Gynecologists Practice Bulletin on GDM[79] and demonstrate how NICHD-sponsored maternal-fetal pharmacology research can have a substantial impact on clinical practice.

Another example of the impact of NICHD-sponsored maternal-fetal pharmacology research has been demonstrated in studies on pravastatin. Specifically, an NICHD-supported pilot trial provided preliminary safety and PK data regarding the use of pravastatin for the prevention of preeclampsia in high-risk pregnant women.[18] The PK data and the favorable maternal-fetal safety profile obtained from the pilot trial by the OPRU Network and OPRCs led to a large, multicenter clinical trial that is currently being conducted by the NICHD Maternal-Fetal Medicine Units Network to further determine whether pravastatin prevents preeclampsia in high-risk pregnant women. Because there currently are no highly effective treatments for preeclampsia, the findings from this study will likely impact the clinical care of patients with preeclampsia in the future. This is also 1 of many examples of how the NICHD leverages existing resources and the expertise of multiple clinical networks to create synergies to advance science and the institute's mission.

Physiological Changes in Pregnancy Affecting Drug Disposition

Pregnancy is a complex process during which a woman's body undergoes profound changes to support the development of the fetus. Through efforts from the OPRU Network, OPRCs, and other investigators, a substantial body of literature now demonstrates that pregnancy-induced physiological changes can affect the PK processes of drug absorption, distribution, metabolism, and excretion (ADME). For example, the delayed gastric emptying and decrease in gastrointestinal motility that occur during pregnancy leads to delayed drug absorption.[80] The increase in maternal body weight and extracellular volume and the decrease in plasma albumin concentrations that occur during pregnancy can alter the volume of distribution of the drug.[80,81] The increase in renal blood flow and glomerular filtration rate that occur during pregnancy leads to increased renal clearance, which can substantially increase the elimination rates of renally-cleared drugs, leading to shorter half-lives.[82] The altered drug disposition starts in the first trimester, continues throughout the pregnancy and into the postpartum period, varies with gestational age, and may lead to potential underdosing or overdosing of medications when using standard adult doses during pregnancy. Pregnancy-induced physiological changes may thus necessitate the adjustment of drug dosing to minimize side effects and maximize the desired therapeutic effects.

Although there are many common changes that occur during pregnancy that are expected to affect the PKs of many drugs (eg, increased renal clearance, increase in the volume of distribution, etc), there are multiple factors that may influence the individual response to drugs. For example, variations in the activities of specific drug transporters and metabolizing enzymes during pregnancy can affect the drug metabolism, transport, and excretion.[83] In addition, individual variations in patients with underlying disease processes can alter the response to drug treatment.[84] Understanding drug-specific PK and PD properties and gestational age-specific variations is also important to improve treatment efficacy and reduce maternal and fetal adverse outcomes. However, owing to practical and logistical reasons, conventional PK and PD studies in pregnant and lactating women have some limitations and challenges (eg, a small sample size, limited sampling from a large number of subjects, and demographic differences [race and age] between the pregnant and nonpregnant groups).[44,85,86]

Pharmacometric Tools in Maternal Pharmacology Research

Pharmacometric tools such as population pharmacokinetics (popPKs) modeling and physiologically based pharmacokinetic (PBPK) modeling have gained popularity in pharmacologic studies for use during pregnancy and lactation in recent years and may offer alternative approaches to overcome these difficulties and challenges. For example, popPK modeling and simulation has been used to estimate the PKs of oseltamivir in pregnant women with influenza infection.[44]

TABLE
Medications studied by the Obstetric-Fetal Pharmacology Research Units Network and Obstetric-Fetal Pharmacology Research Centers

Drug name	Diseases and conditions	Study types	Author, year[a]
Pravastatin	Preeclampsia	• Phase 1 safety and PK study	• Costantine et al,[18] 2016 Costantine and Ananth,[23] 2016 Cleary et al,[24] 2014 Costantine et al,[25] 2013
		• Transplacental transfer	• Nanovskaya et al,[26] 2013
Glyburide	GDM	• Preclinical studies	• Zhang et al,[27] 2015 Shuster et al,[28] 2014 Naraharisetti et al,[29] 2007
		• PK and PD	• Hebert et al,[16] 2009 Caritis and Hebert,[30] 2013 Shuster et al,[31] 2020
		• Glyburide metabolism	• Zhou et al,[32] 2010 Zhou et al,[33] 2010 Zharikova et al,[34] 2009 Jain et al,[35] 2008 Zharikova et al,[36] 2007
		• Placenta drug transporters	• Hemauer et al,[37] 2010 Nanovskaya et al,[38] 2008
		• Glyburide transporters	• Zhou et al,[39] 2008
Metformin	GDM	• Preclinical study	• Zhang et al,[27] 2015
		• PK and PD	• Eyal et al,[17] 2010 Shuster et al,[31] 2020 Liao et al,[40] 2020 Shuster et al,[41] 2020
		• Placenta drug transporters	• Hemauer et al,[37] 2010
Rosiglitazone	GDM	• Placenta drug transporters	• Hemauer et al,[37] 2010
Oseltamivir	Influenza	• PK	• Beigi et al,[22] 2011 Beigi et al,[42] 2014
		• Transplacental transfer	• Nanovskaya et al,[43] 2012
		• PopPK	• Pillai et al,[44] 2015
Hydralazine, atenolol, clonidine, furosemide, labetalol	Hypertension	• PK and PD of antihypertensive agents	• Buchanan et al,[19] 2009 Eyal et al,[20] 2010 Easterling,[45] 2014 Rothberger et al,[46] 2010 Claessens et al,[47] 2010

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PBPK modeling has also been applied to predict drug PK changes throughout pregnancy[87,88] and during lactation,[89] which can provide information to support an informed decision about optimal dosing regimens for pregnant and lactating women. Pharmacometric modeling tools will play an ever-increasing role in predicting the safety and efficacy of drugs during pregnancy and lactation, enabling the design of smaller and safer clinical trials that are likely to succeed in providing clinically relevant data. As our understanding of the physiology of pregnant and lactating women improve, these models will become increasingly predictive and powerful. As discussed below, this area is a high priority for future NICHD-sponsored research.

TABLE
Medications studied by the Obstetric-Fetal Pharmacology Research Units Network and Obstetric-Fetal Pharmacology Research Centers *(continued)*

Drug name	Diseases and conditions	Study types	Author, year[a]
17-α hydroxyprogesterone caproate (17-OHPC)	Preterm birth	• PK, PD	• Feghali et al,[48] 2014 Caritis et al,[49] 2014 Caritis et al,[50] 2012
		• Quality assessment of compounded 17-OHPC	• Chang et al,[51] 2014 Caritis et al,[52] 2013
		• Hepatic transporters, metabolism and disposition	• Sharma et al,[53] 2013 Sharma et al,[54] 2010 Sharma et al,[55] 2008 Yan et al,[56] 2008
		• Biotransformation and placental perfusion	• Fokina et al,[57] 2012
		• Assays of drug plasma concentration	• Zhang et al,[58] 2008 Zhang et al,[59] 2007
		• Transplacental transfer	• Hemauer et al,[60] 2008
Telavancin, vancomycin	MRSA infections	• Preclinical PK study of telavancin	• Wang et al,[61] 2014
		• Placental transfer of vancomycin and telavancin	• Nanovskaya et al,[62] 2012
Indomethacin	Preterm birth	• PK	• Rytting et al,[21] 2014
		• Assays of drug plasma concentration	• Wang et al,[63] 2013
Doxorubicin	Cancer	• PK	• Ryu et al,[64] 2014
Tacrolimus	Organ transplant	• Placental drug transfer and drug excretion to breast milk	• Zheng et al,[65] 2013
		• PK	• Hebert et al,[66] 2013 Zheng et al,[67] 2012
Cisplatin	Cervical cancer	• Drug excretion in breast milk	• Hays et al,[68] 2013
Famotidine	Gastroesophageal reflux disease (GERD)	• Assays of drug plasma, urine, and umbilical cord concentration	• Wang et al,[69] 2013
Nifedipine	Preterm birth	• PK and PGx	• Haas et al,[70] 2013 Haas et al,[71] 2012
Metronidazole	Bacterial vaginosis	• PK	• Wang et al,[72] 2011
Triptan	Serotonin syndrome	• Review of FDA Adverse Event Reporting System	• Soldin et al,[73] 2008
Amoxicillin	Anthrax	• PK of drug in pregnancy and postpartum	• Andrew et al,[74] 2007
Antidepressant	Major Depressive Disorder during pregnancy	• Review of antidepressant treatment of depression in pregnant women	• Mesches et al,[75] 2020
Prednisone	Autoimmune disease, asthma, organ transplantation	• PK	• Ryu et al,[76] 2018
Dacarbazine	Hodgkin's lymphoma	• PK	• Kantrowitz-Gordon et al,[77] 2018

GDM, gestational diabetes mellitus; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *OPRC*, Obstetric-Fetal Pharmacology Research Centers; *OPRU*, Obstetric-Fetal Pharmacology Research Units; *PD*, pharmacodynamic; *PK*, pharmacokinetic.

[a] An updated list of publications of OPRU and OPRC can be found at the following websites: https://www.nichd.nih.gov/research/supported/opru_network and https://www.utmb.edu/nichd-oprc/publications/-in-category/categories/oprc/publications/Published-2019.

Ren. Drug development research in pregnant and lactating women. Am J Obstet Gynecol 2021.

Task Force on Research Specific to Pregnant Women and Lactating Women

In recognition of the challenges in developing safe and effective therapeutics for pregnant and lactating women, the US Congress established the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) as part of the 21st Century Cures Act in 2017. The PRGLAC Task Force consists of representatives from federal agencies, relevant medical societies, nonprofit organizations, and the pharmaceutical industry. Led by the NICHD, the PRGLAC Task Force was charged to identify gaps in the knowledge and research about safe and effective therapies for pregnant and lactating women and report its findings to the Department of Health and Human Services (HHS) Secretary. The PRGLAC Task Force developed 15 recommendations that were included in a comprehensive report submitted to the HHS Secretary in September 2018.[90] The PRGLAC Task Force has also provided advice and guidance to the HHS Secretary on implementing the recommendations. A plan with detailed steps to implement each of the 15 recommendations was submitted to the HHS Secretory in August 2020.[91] The central theme of these recommendations is the need to alter cultural assumptions that have substantially limited scientific knowledge about the safety, effectiveness, and dosing of therapeutics for pregnant and lactating women.[90]

Coronavirus Disease 2019 Treatment and Vaccine Trials in Pregnant and Lactating Women

Pregnancy-induced changes in hormone levels and immune system function may increase a woman's susceptibility to infections.[92,93] The Centers for Disease Control and Prevention (CDC) data suggest that pregnant women are at increased risk for more severe symptoms, hospitalization, intensive care unit admission, mechanical ventilation, and death owing to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection when compared with their nonpregnant counterparts, in addition to the risk for perinatal complications.[94,95] As of March 31, 2021, more than 82,177 pregnant women have been infected with SARS-CoV-2 and there have been 92 deaths during pregnancy owing to coronavirus disease 2019 (COVID-19) in the United States.[96]

Despite the high risks, pregnant women have been excluded from most of the trials[97] aimed at identifying drugs that might be effective treatments for people infected with the SARS-CoV-2. Pregnant women were either specifically listed as an exclusion criterion or excluded without clear reasons.[97] The same is true for COVID-19 vaccine development and efficacy testing. Both pregnant and lactating women were excluded from the initial COVID-19 vaccine trials and the documents submitted to the FDA for the Emergency Use Authorizations (EUA) for both the Pfizer-BioNTech and Moderna COVID-19 vaccines and both did not provide safety data for pregnant and lactating women.[98,99] Although information collected from a small number of women who became pregnant during the trials are available, it is insufficient to make conclusions about the safety and efficacy of the vaccine in pregnant women.[99]

The exclusion of pregnant and lactating women from early COVID-19 treatment and vaccine trials represent missed opportunities to identify efficacious and safe treatments to prevent adverse maternal, pregnancy, and birth outcomes.[97] Without knowledge about the safety and evidence of the benefits, physicians and healthcare providers as well as pregnant and lactating women face dilemmas and challenges when making real-time decisions about whether to pharmacologically treat SARS-CoV-2 infection during pregnancy and lactation or to receive a COVID-19 vaccine.

To protect pregnant and lactating women through research rather than from research, pregnant and lactating women need to be included in clinical treatment and vaccine trials. Moreover, the benefit of their inclusion in such trials may far outweigh potential risks. For example, data from a recent cohort study indicate that the COVID-19 messenger RNA vaccines led to comparable humoral immune responses in pregnant women and nonpregnant controls.[100] In addition, vaccine-induced antibody levels were much higher than those observed following a SARS-CoV-2 infection during pregnancy and also were present in umbilical cord blood and breastmilk suggesting that the vaccination of pregnant and lactating women can boost maternal and neonatal immunity.[100]

Under the EUA, pregnant women are recommended to receive COVID-19 vaccines from their physicians or healthcare providers.[101] Although the safety information regarding the effects of the vaccines on pregnancy and neonatal outcomes will be collected from the CDC vaccine monitoring systems[102] and the manufactures' post-marketing surveillance studies, a systematic plan for data collection in pregnant and lactating women would be beneficial.[103] As part of the PRGLAC Task Force recommendations, a proactive plan for including pregnant and lactating women could be developed before implementing clinical trials. As part of this plan, relevant safety and efficacy data could be collected from preclinical and PK and PD studies before enrolling pregnant and lactating women into large, ongoing clinical trials.[103] Furthermore, pharmacometric modeling tools such as PBPK modeling could be used to simulate fetal exposures and predict relevant doses for pregnant and lactating women when designing clinical trials.[104,88]

Challenges and Opportunities for Future Research

Historically, both pregnant women and children have been considered as "therapeutic orphans" because they encompass biologic complexity in

terms of dynamic physiology and challenges regarding ethical, legal, logistical, and practical concerns in drug development and drug research. However, the implementation of the Pediatric Research Equity Act (PREA) and Best Pharmaceuticals for Children Act (BPCA) led to a paradigm shift in pediatric therapeutic research. Under the aegis of BPCA, with improved infrastructure and funding mechanisms as well as innovative clinical trial designs, pediatric drug development and drug research has made remarkable strides. As such, the results of numerous drug studies performed under the BPCA, such as those conducted by the Pediatric Trial Network (PTN), have led to numerous pediatric labeling changes (https://www.nichd.nih.gov/research/supported/bpca/accomplishments). In contrast, therapeutic research in pregnant and lactating women is far behind owing to many limitations (including limited clinical trial networks involved in research in this area, few investigators with expertise in maternal-fetal therapeutic research, etc). However, lessons learned from pediatric clinical pharmacologic research can be applied to obstetrical and lactating clinical pharmacologic research and there are opportunities for moving forward.

Although leading the efforts of the PRGLAC Task Force, the NICHD has published a new strategic plan that provides guidance for the institute's research priorities and directions for the next 5 years.[105] The strategic plan includes 5 research themes, of which theme 5 specifically focuses on "Advancing Safe and Effective Therapeutics and Devices for Pregnant and Lactating Women, Children, and People with Disabilities." Numerous initiatives with various innovative approaches will be developed by the NICHD's scientific divisions and branches to implement the strategic plan. One example is the establishment of the Maternal and Pediatric Precision in Therapeutics (MPRINT) Hub (https://www.nichd.nih.gov/about/org/der/branches/opptb/mprint). The MPRINT Hub will serve as a national resource of expertise, pharmacometrics, and clinical trial design in maternal and pediatric therapeutics to conduct and foster therapeutics-focused research in obstetrics, lactation, and pediatrics while enhancing inclusion of people with disabilities. The MPRINT Hub will address both knowledge deficits and novel research through knowledge aggregation and dissemination through the MPRINT Knowledge and Research Coordination Center and the MPRINT Centers of Excellence in Therapeutics.

Externally, the NICHD addresses its strategic plan through partnerships with other National Institutes of Health institutes and centers in addition to nonprofit research organizations such as the Foundation for the National Institutes of Health and the Bill & Melinda Gates Foundation. For example, by collaborating with the National Center for Advancing Translational Sciences, the NICHD provides cofunding support for research focused on testing the effectiveness of microphysiological systems, also called "tissue chips" or "organs-on-chips" technology, to improve clinical trial designs to address both the safety and efficacy of drugs in pregnant women, lactating women, neonates, and children. These human "organ-on-chips" reflect the structural and functional characteristics of human tissues and organs and provide a useful model and platform to conduct studies and test FDA-approved drugs in populations (including pregnant women and neonates) that would otherwise not be feasible. For example, the placenta-on-a-chip developed by combining microfluidics and microfabrication technologies that can replicate the placenta architecture and function[106] has been used to study drug transport across the human placenta to screen for drug safety during pregnancy.[107]

Conclusion

Pregnant and lactating women historically have been considered "therapeutic orphans" owing to the lack of adequate safety and efficacy data for the majority of medications used during pregnancy and lactation. Dynamic physiological changes during pregnancy and lactation may alter the PK and PD properties of different medications, which can lead to either overtreatment with unexpected adverse effects or undertreatment with inadequate therapeutic effects. The lack of data about drugs use during pregnancy and lactation has been driven historically by the reluctance to conduct drug trials in these populations owing to real and perceived ethical, regulatory, scientific, and financial concerns. There is a critical need for therapeutic research with innovative study designs that include pregnant and lactating women to fill the knowledge gaps regarding safe and effective therapeutics in these populations. Developing and emerging technologies such as pharmacometric modeling and the use of biomimetic approaches (eg, microphysical systems) will play key roles in enabling future research in maternal therapeutics. A novel systematic infrastructure will be essential to support the expertise needed in maternal therapeutics to foster and conduct innovative, therapeutics-focused research in obstetrics and lactation. Moreover, implementation of the PRGLAC Task Force recommendations can, as the BPCA and PREA recommendations did for pediatric pharmacology, provide a framework and basis for future potential legislative requirements for research focused on pregnant and lactating women. Together, implementation of the PRGLAC Task Force recommendations and the NICHD Strategic Plan will accelerate research in safe and effective therapeutics for pregnant and lactating women to improve maternal health and reduce maternal and infant morbidity. ■

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GLOSSARY

Phase I trials: An experimental drug or treatment administered to a small group of people (20 to 80) for the first time. The purpose is to evaluate its safety and identify side effects.
Phase II trials: The experimental drug or treatment is administered to a larger group of people (100—300) to determine its effectiveness and to further evaluate its safety.
Pharmacokinetics (PK): It may be defined as "what the body does to a drug." It is the study of drug absorption, distribution, metabolism, and excretion.
Pharmacodynamics (PD): It may be defined as "what the drug does to the body." It is the study of the relationship between the concentration of drug at the site of action and the biochemical and physiological effect.
Tmax: Time to reach the maximum plasma concentration.
C_{max}: The maximum plasma concentration.
AUC: The area under the curve (AUC) is the definite integral of a curve that describes the variation of a drug concentration in blood plasma as a function of time.
Pharmacogenomics: It is the study of how an individual's unique genetic makeup (genome) influences his or her response to medications.
Pharmacometrics: It is a novel science that quantifies the interaction between drugs and patients by interlinking the biology, physiology, and pharmacology with disease condition through mathematical models.
Population pharmacokinetics (popPK) modeling: It is the study of pharmacokinetics at the population level in which data from all individuals in a population are evaluated simultaneously using a nonlinear mixed-effects model.
Physiologically based pharmacokinetic (PBPK) modeling: It is a mathematical modeling technique for predicting the ADME of synthetic or natural chemical substances in humans and other animal species.
Microphysiological System (MPS): It is an interconnected set of 2- or 3-dimensional cellular constructs that are frequently referred to as organs-on-chips or in vitro organ constructs.
Precision therapeutics: A therapy that provides the right treatments to the right patients at the right time.

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