Obstetrical, fetal, and lactation pharmacology—a crisis that can no longer be ignored

Check for updates

Steve N. Caritis, MD; Raman Venkataramanan, PhD

The data available to inform pregnant and lactating women about drug safety and efficacy are woefully inadequate. This lack of information encompasses every aspect of pharmaceutics, including limited human data about the embryonic risk, limited pharmacokinetic and pharmacodynamic information during and after pregnancy to ensure proper dosing, and a dearth of new medications to treat obstetrical and lactation disorders. This state of affairs has been longstanding and can be attributed to several realities, most of which have withstood any efforts to modify them. The first reality is the disinterest of the pharmaceutical industry to undertake pregnancy and lactation studies because of the considerable disincentives to undertake such studies. The medicolegal risks and the limited opportunity for financial gain are significant barriers to their participation. The US Food and Drug Administration has not mandated that new drugs or drugs "on patent" must include studies in pregnant women. Regulatory constrains that have defined pregnant women as a vulnerable class have greatly limited pharmacologic studies. Another contributing factor to this lack of information is the lack of researchers skilled in pharmacology with an interest in the pregnant woman. In addition, although difficult to measure, there is the hesitancy of pregnant and lactating women to participate in pharmacology research either for fear of fetal risk or an inability to commit the time required for such studies. Research in obstetrical and lactation pharmacology lags far behind that of pediatric pharmacology. Through the efforts of many, research in that field is highly funded and very productive in providing new information on medications used in children who, like pregnant women, have differing pharmacologic needs based on age (chronology for children and gestational age for pregnant women). Recently, the deficiencies and possible remedies for this embarrassing state of affairs in obstetrical and lactation pharmacology have been addressed by the federal government, which led to 15 recommendations from the Task Force on Research Specific to Pregnant Women and Lactating Women. In this article, we address the challenges in providing meaningful information about specific medications used by the mother and how these problems have evolved. We also suggest specific strategies to start the process of remediation.

Key words: Best Pharmaceuticals for Children Act, lactation, pharmacodynamics, pharmacokinetics, pregnancy and lactation, pregnancy medications, pregnancy pharmacology

Overview

An increasing number of pregnant women are using prescription and over-the-counter medications, dietary supplements, and herbal products during pregnancy.[1,2] A review of medication use from 1976 to 2008 demonstrated that in 2006 to 2008 as many as 50% of pregnant women took 4 or more medications at some time during their pregnancy and that 27% took ≥4 medications during the first trimester, the period of organogenesis.[2] The majority of these medications were prescription medications. A pregnant woman may require medications for obstetrical disorders such as nausea and vomiting of pregnancy, gestational diabetes, gestational hypertension, preterm labor, and labor and delivery management. However, many pregnant women require medications for conditions that predate pregnancy such as depression, type 2 diabetes, HIV, epilepsy, chronic hypertension, rheumatologic diseases, and numerous other disorders that plague both men and women. These medical disorders are more common in the older parturient, and, because delayed childbirth is a reality in the contemporary society, the number of pregnant women using prescribed medications will continue to increase.

During pregnancy, the mother expects that the medications that are prescribed are safe and effective for her and safe for the baby. However, at the time when the most precise information is needed, drug safety data are embarrassingly scant and generally insufficient to inform the mother's decision about a specific drug's safety and/or efficacy.[3–8] In this article we address the challenges in providing meaningful information about specific medications to the mother and how these problems have evolved. We also suggest specific solutions to start the process of remediation.

From the Division of Maternal-Fetal Medicine, Department of Obstetrics, Gynecology, and Reproductive Sciences, UPMC Magee-Women's Hospital, University of Pittsburgh, Pittsburgh, PA (Drs Caritis and Venkataramanan); Department of Pharmaceutical Science, School of Pharmacy, University of Pittsburgh, Pittsburgh, PA (Drs Caritis and Venkataramanan); and Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA (Drs Caritis and Venkataramanan).

Received Feb. 1, 2021; accepted Feb. 1, 2021.

The authors report no conflict of interest.

There was no funding needed or used to conduct this research.

Corresponding author: Steve N. Caritis, MD. carisn@mwri.magee.edu

0002-9378/$36.00 • © 2021 Elsevier Inc. All rights reserved. • https://doi.org/10.1016/j.ajog.2021.02.002

Descargado para BINASSS Circulaci (binas@ns.binasss.sa.cr) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en julio 15, 2021. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2021. Elsevier Inc. Todos los derechos reservados.

Deficiency of Pharmacologic Data for Women During Pregnancy and Lactation

The embryo, fetus, newborn, and child

The pregnant and lactating woman presents unique pharmacologic challenges that must be addressed before she can consider taking a prescribed medication. The most obvious concern is the effect of the medication on the fetus who is the passive (in most cases) recipient of any medication taken by the mother.[9−11] Medications may adversely impact fetal organogenesis, organ maturation, or organ function. The newborn is also the passive recipient of medications taken by the lactating woman because many maternal medications can be found in breast milk.[12−14] Thus, the most common question pregnant and lactating women ask about medications is whether that medication is safe for their fetus or newborn. Unfortunately, data in humans are lacking. Of the 272 drugs approved by the United States Food and Drug Administration (FDA) from 2000 to 2010, the teratogenic risks could not be ascertained for 97.7 % of those drugs and 73% had no human data.[7] Congress has passed legislative initiatives to address drug safety and efficacy over the last several decades. Particularly relevant to fetal risk is the FDA's effort to quantify the fetal risk for patients and their providers. In 1979, the FDA established 5-letter risk categories−−A, B, C, D, or X−−to indicate the potential of a drug to cause birth defects or harms if used during pregnancy. The labeling was changed in 2015 with the Pregnancy and Lactation Labeling Rule (PLLR).[15] It was generally believed that the old, 5-letter system was not informative and that it led to false assumptions about the drug risk profile. The new system was expected to enable better, patient-specific counseling and informed decision-making for pregnant women and their providers. The A, B, C, D, or X risk categories were replaced with narrative sections, which were to provide information about the dosing, potential risks to the developing fetus, and pregnancy registry information. The lactation subsection was intended to provide a listing of drugs that should not be used during breastfeeding and other information to help the lactating mother decide if her milk may be harmful to her infant. Pharmacokinetic (PK) data were also to be provided. According to the PLLR, different requirements are applied for prescription drugs that sought FDA approval after the ruling went into effect in 2015 and the prescription drugs approved after or before 2001. Importantly, medications approved before 2001 and generic drugs are not subject to the PLLR rule. The PLLR requirements for a new drug sponsor do not mandate that new studies must include human trials but rather that the sponsor must summarize the extant information about the specific medication. A recent review of new drugs introduced since the PLLR came into effect indicates that only a few studies have included human data.[5] Table 1 includes a list of 8 of the 53 new drugs approved in 2020 that might be used by pregnant women.[16] The table details the specific areas in which information is lacking. The other 45 approved drugs were for the treatment of diseases uncommon during pregnancy. This lack of human data may be why the PLLR is not widely recognized or utilized.[17] It seems, therefore, that the PLLR is not achieving its objectives because of the limited safety information generated during drug development for the use of the medications by pregnant and lactating women.

Much of the attention about the fetal safety of medication used by pregnant women has been focused on the risk of fetal malformations or perceptible injury to the fetus or infant. This is critically important, however, the endpoints according to which fetal safety is defined are crude and imprecise and far too insensitive because they are limited to observed malformations or organ injury or dysfunction. The potential long-term effects of medications on a child's organ function or its neuroanatomy and neurodevelopment are not assessed. Once a newborn is discharged from the nursery after birth, the ascertainment of harms from in utero exposure to a medication is considered complete. Drug safety can be evaluated best by long-term follow-ups of children exposed to potentially harmful medication in utero. In particular, those drugs that impact the maternal brain, such as opioids and selective serotonin reuptake inhibitors (SSRIs), may also affect the fetal brain and, indeed, recent magnetic resonance imaging (MRI) studies do suggest that maternal opioid and SSRI use may lead to adverse changes in neonatal brain volumes and connectivity.[18−24]

The pregnant woman

The vast majority of medications used by pregnant women have not been approved for use during pregnancy. These medications were approved by the FDA based on the efficacy, safety, PK, and pharmacodynamic (PD) studies in men and nonpregnant women. Safety and efficacy during pregnancy were not evaluated in pregnant women. Consequently, these drugs are used "off-label" when administered to pregnant women. Generally, the dosing regimen prescribed for pregnant women is that which was approved by the FDA for nonpregnant women and men. Pregnancy is characterized by dramatic changes in the maternal physiology and pharmacology. Every aspect of pharmacology is affected during pregnancy including drug absorption, distribution, metabolism, and elimination, and these changes differ from trimester to trimester.[25,26] These pharmacologic changes can lead to either excessive drug concentrations with increased side effects or inadequate drug concentrations that lead to ineffective drug usage. Several Obstetric-Fetal Pharmacology Research Units (OPRU)− or Obstetrical-Fetal Pharmacology Research Centers (OPRC)−sponsored studies have demonstrated the differences in the PKs

Descargado para BINASSS Circulaci (binas@ns.binasss.sa.cr) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en julio 15, 2021. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2021. Elsevier Inc. Todos los derechos reservados.

TABLE 1
Pregnancy, fetal, and lactation data about the drugs approved by the US Food and Drug Administration in 2020

Drug name, indication	Available data on safety, efficacy, fetal effects, and breast milk	Drug name, indication	Available data on safety, efficacy, fetal effects, and breast milk
Oliceridine (Olinvyk),	Safety in pregnancy: no data	Ozanimod (Zeposia), multiple sclerosis	Safety in pregnancy: no data
acute pain	Efficacy in pregnancy: no data		Efficacy in pregnancy: no data
	Fetal developmental risk: no data		Fetal developmental risk: no data
	Exposure in mother: no data		Exposure in mother: no data
	Exposure to fetus: no data		Exposure to fetus: no data
	Exposure through human milk: no data		Exposure through human milk: no data
	RID: N/A		RID: N/A
	Effect on breast ed infants: no data		Effect on breastfed infants: no data
	Milk production: no data		Milk production: no data
Eptinezumab (Vyepti),	Safety in pregnancy: no data	Vibegron (Gemtesa), overactive bladder	Safety in pregnancy: no data
migraine	Efficacy in pregnancy: no data		Efficacy in pregnancy: no data
	Fetal developmental risk: no data		Fetal developmental risk: no data
	Exposure in mother: no data		Exposure in mother: no data
	Exposure to fetus: no data		Exposure to fetus: no data
	Exposure through human milk: no data		Exposure through human milk: no data
	RID: N/A		RID: N/A
	Effect on breastfed infants: no data		Effect on breastfed infants: no data
	Milk production: no data		Milk production: no data
Amisulpride (Barhemsys),	Safety in pregnancy: insufficient data	Remdesivir (Veklury),	Safety in pregnancy: no data
nausea, antipsychotic, and vomiting	Efficacy in pregnancy: no data	COVID-19	Efficacy in pregnancy: no data
	Fetal developmental risk: insufficient data		Fetal developmental risk: no data
	Exposure in mother: available		Exposure in mother: no data
	Exposure to fetus: no data		Exposure to fetus: no data
	Exposure through human milk: M/P ratio = 11:20		Exposure through human milk: limited, likely because it is not well-absorbed orally
	RID: 11%		RID: N/A
	Effect on breastfed infants: no data		Effect on breastfed infants: no data
	Milk production: no data		Milk production: no data

Caritis. Obstetrical, fetal, and lactation pharmacology crisis. Am J Obstet Gynecol 2021. *(continued)*

Descargado para BINASSS Circulaci (binass@ns.binasss.sa.cr) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en julio 15, 2021. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2021. Elsevier Inc. Todos los derechos reservados.

TABLE 1
Pregnancy, fetal, and lactation data about the drugs approved by the US Food and Drug Administration in 2020 *(continued)*

Drug name, indication	Available data on safety, efficacy, fetal effects, and breast milk	Drug name, indication	Available data on safety, efficacy, fetal effects, and breast milk
Rimegepant (Nurtec ODT),	Safety in pregnancy: no data	Fostemsavir (Rukobia), HIV	Safety in pregnancy: no data
Migraines	Efficacy in pregnancy: no data		Efficacy in pregnancy: no data
	Fetal developmental risk: no data		Fetal developmental risk: no data
	Exposure in mother: no data		Exposure in mother: no data
	Exposure to fetus: no data		Exposure to fetus: no data
	Exposure through human milk: expected to be limited based on related drugs		Exposure through human milk: no data
	RID: <1% based on related drugs		RID: N/A
	Effect on breastfed infants: no data		Effect on breastfed infants: no data
	Milk production: no data		Milk production: no data

COVID-19, coronavirus disease 2019; *N/A*, not available; *ODT*, orally dissolving tablet; *RID*, relative infant dose.

Caritis. Obstetrical, fetal, and lactation pharmacology crisis. Am J Obstet Gynecol 2021.

and PDs for several medications commonly used during pregnancy (Table 2).[27–29] The area under the plasma concentration-time curve (AUC) is a standard and convenient way to demonstrate the gestational differences in drug. Decreased exposure is typically seen in most cases for drugs that are cleared renally and those cleared by specific enzymes in the liver. Some drugs require a higher dose or dosing frequency during pregnancy because of the decreased exposure (as determined by the AUC). The glyburide dose-adjusted AUC during pregnancy is 53% lower than in the nonpregnant or postpartum woman. Likewise, the dose-adjusted AUC for buprenorphine and oseltamivir during pregnancy is dramatically lower than in the postpartum or nonpregnant woman (Table 2).

Thus, for these 3 drugs, the dose of medication needed for a pregnant woman to achieve the same AUC (exposure) is 24% to 53% greater than that required in a nonpregnant woman. If the FDA-approved dosing regimen is applied to pregnant women taking these medications, they could be inadequately dosed during pregnancy. A lower AUC during pregnancy does not always necessitate a change in the drug dosing. The drug exposure may still be in the therapeutic range and no alteration in dosing may be needed during pregnancy. This is what the FDA concluded after our study of oseltamivir.[29] For some medications, recognition of these pregnancy-related changes has led to therapeutic drug monitoring (TDM). With TDM, drug concentrations, generally measured in the plasma, are obtained during pregnancy so that a predefined therapeutic drug concentration can be maintained by dosing changes. This strategy has been successfully applied to antiseizure, immunosuppressant, and HIV medications. Unfortunately, the TDM approach has not been utilized for the majority of medications used by pregnant and lactating women because of the limited accessibility and availability of such tests.

More relevant than the PK parameters in determining an optimal drug

Descargado para BINASSS Circulaci (binas@ns.binasss.sa.cr) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en julio 15, 2021. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2021. Elsevier Inc. Todos los derechos reservados.

TABLE 2
Impact of pregnancy on drug exposure

AUC	Glyburide[a] dose normalized (ng × h/mL)	Buprenorphine[b] dose normalized (ng × h/mL)	Oseltamivir carboxylate[c] popPK analysis (ng × h/mL)
Pregnant	72±27	1.9±1.4	2653±928
Nonpregnant	153±69	4.0±2.5	3507±992
Difference	53%	53%	24%

AUC, area under the plasma concentration-time curve; *popPK*, population pharmacokinetics.

[a] AUC was normalized to the dose administered Hebert et al[27]; [b] AUC was normalized to the administered dose Bastian et al[28]; [c] AUC determined by popPK analysis Pillai et al.[29]

Caritis. Obstetrical, fetal, and lactation pharmacology crisis. Am J Obstet Gynecol 2021.

dose is the PD effect of the drug during pregnancy. It is possible that pregnancy-mediated changes in physiology may also alter the PD of the drugs. PD studies relate plasma drug concentrations to some measurable response such as blood pressure. Doses of some medications in both pregnant and nonpregnant subjects can be titrated to a desired response by relying on PD results rather than PK results. However, with several medications, a PD endpoint may not be readily discerned, such as for 17-hydroxyprogesterone caproate or vaginal progesterone for which the targeted outcome is not assessable until the time of delivery. Mental health medications, oseltamivir for influenza, and antiseizure medications likewise do not lead to an immediate measurable outcome or altered biomarker levels. In such cases, the dose is dictated by clinical trials during which an optimal dose with the fewest side effects is determined. Such dose-response studies are performed as part of phase 1 and 2 clinical trials. Very rarely are the PD studies for those medications performed in pregnant or lactating women. It is possible that the pregnancy-mediated changes in physiology may alter the PD of drugs.

The lactating woman

Lactating women with chronic diseases will require treatment with the same medication they took before and during pregnancy. In some cases, the mother, on her own, may reduce the dose or eliminate the medication during pregnancy. This is not uncommon for women using mental health or immunologic drugs or pain relievers. Those women may wish to know if they can resume or continue their medication while breastfeeding.

For drugs with decreased exposure during pregnancy, the rapidity of return to non-pregnant drug concentrations and consequent need for dosing adjustment is generally not well known. Without dose adjustment after delivery, many women may be receiving a higher than necessary dose and this may have consequences for her and her newborn.

Information quantifying the magnitude of the newborn's exposure to a medication is important and may impact a mother's decision to breastfeed or not. Even though a fetus may have been exposed to a medication in utero, the potential impact of a medication on that fetus as a child cannot be predicted. It is entirely possible that fetal exposure to certain medications may be minimized in utero owing to the characteristics of the medication and the impact of placental transporters, which may extrude the drug from the placenta to the maternal compartment.[9–11]

In addition, it is not known whether the fetus has truly tolerated the medication because the evaluation of the newborn ends with its discharge home and does not include long-term evaluations such as neuroanatomic or neurodevelopmental assessments. Furthermore, development of the immune system and the brain in addition to the maturation of other systems occur after delivery and may be impacted by medication in the mother's milk.[30–33]

Normally, most studies rely on a single measurement of the drug concentration in the milk. The amount of drug in the milk depends on the maternal dose, the pharmacokinetic properties of the drug, whether the sample is foremilk or hindmilk, and when the maternal drug concentrations were measured in relation to the time of drug dosing. Determining the average concentration of the drug in the milk and mother's plasma provides a milk to plasma ratio, which is used to identify those medications that are concentrated in the milk. Quantifying the infant's exposure to maternal medication requires more than just a single measurement of the drug concentration in human milk. The FDA guidance suggests that all human milk produced in 24 hours should be used to quantify the drug exposure.[34] The relative infant dose (RID) is a parameter that is used to compare the dose the infant receives daily (average drug concentration×assumed volume of human milk consumed per day) to the infant's therapeutic dose or the maternal dose normalized to body weight.[34] The milk to plasma ratio and the RID may be poor indicators of the infant's true exposure because drug absorption in the newborn infant is not completely understood. Several infant blood samples (usually by heel stick) are ideally needed to quantify the true neonatal exposure. The FDA does not require infant sampling but rather an estimate of the potential drug exposure. Performing a comprehensive study of drug exposure in the neonate is not straightforward. Even without the infant heel sticks, the

Descargado para BINASSS Circulaci (binas@ns.binasss.sa.cr) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en julio 15, 2021. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2021. Elsevier Inc. Todos los derechos reservados.

requirements for breast milk studies are onerous on the lactating women and it is difficult to recruit patients for such studies.

Not only are the data about the medication effects on human embryo, fetus, neonate, and child and the proper dosing for pregnant and postpartum women lacking, but new therapeutics for pregnant and lactating women are nearly nonexistent. Over the last 20 years, very few medications have been approved for use in pregnant and postpartum women. However, new therapeutics for chronic conditions in men and nonpregnant women have vastly expanded the options for physicians in the treatment of diseases, especially in the area of biologicals, but these therapeutic options have not been studied in pregnant and lactating women; these women are therapeutic orphans.

Origins of the Problem

The paucity of pharmacologic data about the use of drugs in pregnant women can be attributed to a combination of several factors, including the lack of incentives for the pharmaceutical industry to conduct these studies. These disincentives include the prolonged medicolegal liability risk for when adverse outcomes occur following administration of the medication to a pregnant woman even if the adverse outcome was not caused by a specific medication. Another disincentive for the pharmaceutical industry is the small size of the total addressable pregnancy market; with fewer than 4 million annual pregnancies, the number of pregnant women requiring a specific medication is small. For example, only 5% of women develop gestational diabetes, hardly justifying the cost and regulatory burdens of drug approval. Furthermore, pregnancy-specific medications would not be required after delivery, unlike medications utilized for chronic conditions that have to be taken for a lifetime. The off-label use of medications is another disincentive for the industry because pregnant women can and will receive a medication approved for men and nonpregnant women. Thus, the pharmaceutical company receives revenue with limited financial or medicolegal risk.

The FDA also bears some responsibility for the lack of pharmacologic information about the use of drugs during pregnancy, because they have not required detailed human studies during pregnancy for the drug approval process. Federal regulations have also contributed to this problem because pregnant women have been seen as a vulnerable population and were, therefore, excluded from many research studies.

Accretion of information about obstetrical and lactation pharmacology requires the generation of information through systematic research. Obstetric and lactation pharmacology research has lagged in comparison with most other fields, especially when compared with the research outputs from those involved in pediatric pharmacology. The lack of focus and support for research in Obstetric pharmacology has several possible explanations, including the lack of industry support, the absence of effective legislative efforts, and the limited funding opportunities available from the National Institutes of Health (NIH) and other funding entities.

Pregnant women (and their spouses and trusted individuals) have also contributed to this lack of pharmacologic information for drugs already approved and for new medications seeking FDA approval. Typically, a research participant does not see an immediate benefit from participating in the study. In addition, participation in PK studies are generally time consuming, and the subject is in a Clinical Research Center (CRC) for a complete dosing interval plus an additional 1 to 2 hours. Thus, a medication that is administered twice daily requires 12 hours of study time plus travel to and from the facility and preparation time (ie, starting the intravenous line, filling out paperwork, etc). Ideally, such a PK study should be performed each trimester and again in the postpartum period. PK studies in the postpartum period are even more challenging for postpartum and lactating women. It is unreasonable to expect a postpartum woman with a newborn to come to a research center for an 8- to a 14-hour stay even if that research center allows newborns at the CRC. These realities have proven to be nearly insurmountable based on the experiences of the OPRU and OPRC.

The challenges a pregnant woman face when considering participation in a study for a new drug application include those challenges described above, but also the added concerns of what impact the new drug will have on her and her fetus. An obvious example is the messenger RNA coronavirus disease 2019 vaccines. In this specific case, no data exist on the fetal and maternal safety or efficacy, but the benefit is considered to far outweigh the risk to such an extent that most scientists and leaders in the obstetrical field support the vaccination of pregnant and lactating women. The situation is much different when there is less risk from a particular disease and other options may exist or the drug prescription is for prevention rather than a treatment. Clearly, such concerns are reduced if the medication is already FDA-approved for other indications but for new medications not previously approved, the concerns are magnified and justifiably so.

Potential Remedies Specific to Pregnant and Lactating Women and Their Fetuses

What is needed to fulfill every pregnant woman's expectation that the medication that she is receiving is safe and effective for her and safe for her fetus? Foremost, there is the accretion of more pharmacologic data, which will improve labeling and serve to inform the pregnant woman and her providers. How can more data about medication use during pregnancy and the postpartum period be accumulated? Knowledge cannot be accumulated in any field without financial resources to support that activity. Whether the research is performed by academics or industry, financial support or incentives are needed.

Descargado para BINASSS Circulaci (binas@ns.binasss.sa.cr) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en julio 15, 2021. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2021. Elsevier Inc. Todos los derechos reservados.

The embryo/fetus/newborn/child

The processes in place that are used to evaluate fetal harms are based mostly on preclinical animal studies. Constant debate about the species to be used and the utility of this process exists, but this approach has proven reasonably effective in identifying agents that can cause major harms. However, it is critical to focus on research that will identify relevant preclinical models that can better predict fetal toxicity. Obviously, studies in humans would be more informative, but the infrequency of harms of a medication that has not shown harms in the required preclinical studies makes such an approach untenable. The process of drug approval would be totally paralyzed if long-term studies in humans are required before a new treatment is approved. The only reasonable approach is for the pharmaceutical industry to establish registries or for health plans, nations, or other entities to establish registries with data about the medication use and clinical outcomes. The FDA lists nearly 115 pregnancy-related registries.[35] These registries are useful but often provide contradictory findings because they are not collected prospectively and critical data about drug exposure is not available. This, in addition to the limited sample size is a weakness of registries. A case in point is an analysis that we performed on the impact of ondansetron on the risk of ventricular septal defects.[36] Because previous analyses by others provided contradictory findings, we explored this question by linking the pharmacy records from the University of Pittsburgh Medical Center (UPMC) Health Plan and our own in-house pregnancy (Magee Obstetrical Maternal Infant) database. Among more than 84,000 deliveries at our hospital over 8 years, only 33,000 were insured by the UPMC Health Plan, which enabled access to pharmacy records. We reported a very small increase in ventricular septal defects in those women exposed to high doses of the medication during the first trimester, but we could not precisely quantify exposure to the degree needed because we relied on claims and prescription data, which may be subject to misclassification bias.[36] We had no measure of adherence and thus assumed that oral medication was taken as prescribed. A possible remedy for the shortcomings of the registries would be to establish a prospective collection of pharmaceutical data in pregnant women. This could be done by an NIH-funded clinical network such as the Maternal Fetal Medicine Units Network in which over 160,000 pregnancies are accessible annually. Perhaps an MRI assessment of the fetal brain can also be used to assess the drug safety of those medications primarily targeting the brain. These types of assessment are uncommon, and this information void leaves care providers and parents uninformed, concerned, and frustrated.

The pregnant and lactating woman

The deficiencies in pregnancy pharmacology are, regrettable, quite extensive and a targeted approach is needed to reduce those deficiencies. The issues faced by pregnant and lactating women relate to the lack of information about the effects of pregnancy on the drug PKs and the consequent impact on dosing. In addition, the lack of information on the safety and efficacy of new pharmaceutics relegates pregnant women to the use of old and perhaps less-effective medications than those available to men and nonpregnant women. Different strategies are needed to address these deficiencies.

When considering "off-label" drugs still "on patent," the strategies that encourage the involvement of the pharmaceutical industry will likely be more successful than the strategies that are in conflict with the pharmaceutical industry. The Best Pharmaceuticals for Children Act (BPCA) allows for 6 months exclusivity for any pharmaceutic that the FDA deems to require more pharmacologic information.[37–39] The companion legislation Pediatric Research Equity Act (PREA) mandates that studies should be performed for new drugs to assess their safety and efficacy in children.[40] These programs have been very successful with 375 drugs having been studied from January 11, 2021.[41,42] Since 2019, the BPCA has enrolled 8000 children into 40 clinical trials, resulting in 11 label changes. For medications that are used "off-label" and are "off patent," the BPCA allows for NIH-funded studies mostly through the Obstetric and Pediatric Pharmacology and Therapeutics Branch. The BPCA provides about $25 million annually for programs that support education in pediatric pharmacology in addition to the research efforts in pediatric pharmacology through the direction of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD).[37–42] The Pediatric Trials Network comprises 100 sites that focus on pediatric pharmacology. The BPCA and PREA do not apply to pregnant or postpartum women. The efforts in pediatrics are laudable and have proven to be successful. Similar programs for pregnant and postpartum women do not exist but urgently need to be implemented.

The other challenge faced by pregnant and postpartum women and their providers is the lack of new therapeutics. The impediments of this challenge are significantly greater when studying medications pregnant women take "off-label," irrespective of whether the drugs are "on" or "off" patent, because of the medicolegal risks associated with adverse perinatal or childhood outcomes. In this case, the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) suggested implementing a liability mitigation strategy similar to the Vaccine Injury Compensation Program.[43] Such a strategy could eliminate or minimize one of the greatest impediments to the development of new therapeutics in pregnant and postpartum women, which is medicolegal risk. Even without implementation of a liability mitigation strategy, the FDA could require more from the pharmaceutical industry if the recommendations of the PRGLAC are implemented to stop the consideration of pregnant women as a vulnerable group.[43] The

Descargado para BINASSS Circulaci (binas@ns.binasss.sa.cr) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en julio 15, 2021. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2021. Elsevier Inc. Todos los derechos reservados.

FDA could mandate that studies should be performed for all new drugs to evaluate potential safety and efficacy of the medication in pregnant women. These evaluations could utilize cell cultures with human trophoblasts, placental perfusion, placenta-on-a-chip methodologies, physiologically-based pharmacokinetic (PBPK) simulations in pregnancy, and microdosing to determine the PKs of the drug in pregnant women.[44,45] Postmarketing (phase 4) studies should also be required.

The steps implemented to enhance the knowledge in the field of pediatric pharmacology required committed efforts by stakeholders over many years to educate congressional leadership about the deficiencies in pediatric pharmacology. A similar effort is needed for Obstetric pharmacology. The BPCA has achieved remarkable gains in pediatric pharmacology; a similar effort directed toward Obstetric pharmacology would undoubtedly expand knowledge in that field as well. The PRGLAC recommended provision of specific funding for Obstetric pharmacology research using the BPCA as a model.[43]

Keys for Enhancing Research in Obstetrical and Lactational Pharmacology

In addition to the suggestions above, research in obstetric and lactation pharmacology will not advance without a pool of scientists who can undertake such research and a willing research subject. These issues are addressed below.

Expand the pool of researchers

Even if the strategies above can be implemented and more financial support is achieved for pharmacology research relating to pregnancy and the postpartum period, sufficient research capacity is needed to carry out this research. The pool of researchers involved in Obstetric pharmacology research is small, particularly when compared with the pool involved in pediatric pharmacology. This difference is based, at least in part, on the legislatively mandated infusion of money and the commitment of stakeholders to improve pediatric pharmacology knowledge. Obstetric pharmacology research requires an influx of established researchers with diverse backgrounds and opportunities for trainees to develop their skill in this area. Funding will attract researchers; therefore, with funding support such as that available through a program similar to the BPCA, a pool of experienced researchers in Obstetric pharmacology can be developed. In addition, the pool of researchers in Obstetric pharmacology could quickly be expanded by attracting researchers currently involved in pediatric pharmacology research. These researchers could partner with obstetrical colleagues to access pregnant women and thus apply their skills to both populations. Tissues and biologic fluids from pregnant and postpartum women are far more accessible than those from children and basic science researchers can analyze these biologic specimens from women just as easily as they can from children.

Enhanced opportunities for trainees can also be expected with programs similar to those utilized in the training of researchers in pediatric pharmacology. For example, a T32 Pediatric Clinical and Developmental Pharmacology Training Network supports multiple sites and trainees, and the Specialized Centers in Research in Pediatric Developmental Pharmacology support 4 centers to perform research in a broad area of pediatric pharmacology and to train new scientists.[37] These programs are funded by the BPCA, the NICHD, and other institutes with an interest in pediatric pharmacology. Similar initiatives are lacking in obstetrical pharmacology. A T32 grant focused on obstetric pharmacology was only available for a 5-year cycle.[46] The OPRU and OPRC did not receive trainee support for salaries or protected time, but the centers still achieved modest success in attracting individuals to conduct research in obstetrical and postpartum pharmacology. Only 4 centers were funded in the first OPRU and OPRC funding cycle, 3 were funded in the second and third cycles, and 2 of the centers were funded in all 3 cycles, thus giving a total of only 6 centers that were engaged over a period of 15 years. Compared with the opportunities in pediatric pharmacology research, the opportunities to encourage new or established researchers to enter the field of obstetrical pharmacology are limited.

One might argue that funding will not necessarily lead to an increase in Obstetric pharmacology research and trainees, but the experience of the OPRU and OPRC has demonstrated an increase in pregnancy-related research in funded centers. The research output included clinical, translational, and basic research and attracted experienced researchers and trainees. The reestablishment of a T32 training grant mechanism focusing exclusively on obstetrical pharmacology could provide a pathway to grow the body of new researchers in Obstetric pharmacology. Without financial support, research in Obstetric pharmacology will continue to flounder and the pool of interested researchers will remain small. The BPCA and other NIH-sponsored programs support pediatric pharmacology research and training of new investigators. A similar commitment to Obstetric pharmacology research will undoubtedly enhance the current pool of researchers.

Increase research participation of pregnant women

Opportunities for pregnant women to participate in pharmacology research is limited both by external influences and internal constraints. External influences include the regulatory barriers aimed at protecting pregnant women and their fetuses. The PRGLAC made specific recommendations to change some of these regulatory issues, including to no longer consider pregnant women as a vulnerable population, enable one parent to consent to research that may benefit the child, and adding language that will enable more participation without jeopardizing the fetus.[43] Performing microdosing PK studies in pregnant women may mitigate some

Descargado para BINASSS Circulaci (binas@ns.binasss.sa.cr) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en julio 15, 2021. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2021. Elsevier Inc. Todos los derechos reservados.

concerns about the drug exposure and drug safety. The internal constraints pregnant and postpartum women encounter relate to the type of study being proposed, their family, and the practicality of participating in research. Participation in research relates very much to the type of study, the proposed benefit to the participant, and the effort required. Studies with a perceived benefit during the current pregnancy are viewed more favorably than studies with no immediate benefit. Most pharmacology studies do not provide an immediate benefit to the woman and are not well received unless there is little required of the participant or there is a financial incentive. Spouses very often do not attend prenatal care visits; thus, research staff most often approach the pregnant woman only. Many pregnant and postpartum women may consider study participation, however, when the woman discusses the research with her spouse or family member, that person has little understanding of the study and consequently they do not encourage participation. A common experience from our participation in the OPRU and OPRC is one in which the woman is interested in participation, but once the time commitment required is described, they decline study participation.

The standard approach to PK and PD studies works poorly in pregnant and even more so in postpartum women. Strategies that we have explored to reduce the burden of research participation includes video conferencing to observe the collection of a biologic specimen, self-collection of cervicovaginal fluid, saliva and urine, texting, and finger sticks (microsampling) in mother done at home. Microheel sticks performed by the mother at home could provide a simple, less time-consuming way to truly gauge the infant exposure to a particular medication.

Approaches that could reduce the time required in a CRC and the number of blood samples needed for PK analysis include applying population PK modeling and PBPK methodologies that utilize mathematical modeling to predict the PKs of medications in pregnancy.[26] In PBPK modeling, PK data from nonpregnant women are employed to develop the initial models of drug behavior. These initial models are then applied to pregnancy by incorporating known drug properties and drug behavior changes in pregnancy such as the well-recognized increase in renal elimination of drugs and hepatic metabolism of drugs based on their specific pharmacokinetic properties. The final step is to obtain a limited number of blood samples from pregnant women and to validate the mathematical model with actual concentration data. In addition, PK studies typically measure drug concentrations over time and generate the well-recognized AUC concentrations. An estimate of the AUC concentration can be determined for some drugs with fewer time points (limited sampling strategy) or with trough levels, and some of these can be drawn at home with microsampling techniques. Innovative methodologies in pharmacology research can also be utilized to reduce the reliance on human subjects. Examples include ex vivo human cotyledon perfusion studies, in vitro placental trophoblast studies, and placenta-on-a-chip methodologies.[44,45]

Summary

The available pharmacologic data are insufficient for a pregnant or lactating woman or her providers to determine a drug's safety and efficacy. The identification of the potential fetal harms from medications is lacking for most drugs. Registries that gather pharmacologic and clinical data prospectively could address the shortcomings of most extant registries, which serve as the basis for retrospective reviews. The criteria used to determine human harms are crude, imprecise, and far too insensitive and should be reconsidered. Insufficient pharmacologic data during pregnancy and lactation have led to a therapeutic morass in which pregnant and lactating women may receive either an inadequate or an excessive dose of medication. The pharmaceutical industry must be embraced to meet the challenges pregnant and lactating women face. Incentives such as patent exclusivity could encourage the generation of more PK data for medications still "on patent." Liability protection for new therapeutics for pregnant women could expand the availability of effective drugs that are now avoided in pregnancy.

Application of the same strategies that have enabled pediatric pharmacology to advance and thrive would expand the pool of researcher in obstetrical pharmacology and support investigation in commonly used drugs by pregnant and lactating women. These changes require leaders in government, NIH, obstetrical societies, and organizations committed to women's health to demand the same type of programs that have worked so well to advance pediatric pharmacology.

The deficiencies in obstetrical pharmacology discussed above have long been appreciated but limited, tangible progress has not been made until recently when Congress enacted the 21st Century Cures Act, which directed the secretary of Health and Human Services to establish the PRGLAC. The task force identified gaps in the knowledge and research about safe and effective therapies for pregnant and postpartum women. The task force made 15 recommendations to address the barriers that prevent optimal use of therapeutics by pregnant and postpartum women.[43]

Our Recommendations

- Provide incentives to the pharmaceutical industry to develop pharmaceuticals specifically for conditions affecting pregnant and lactating women.
- Provide incentives or funding opportunities to generate exposure, efficacy, and safety data for medications used by pregnant and lactating women (improved preclinical pregnant animal models; cell culture studies; PBPK modeling; microdosing PK studies; prospective clinical data collection; predictive biomarker development).

Descargado para BINASSS Circulaci (binas@ns.binasss.sa.cr) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en julio 15, 2021. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2021. Elsevier Inc. Todos los derechos reservados.

- Create prospective registries to assess the maternal safety and efficacy, maternal exposure, and fetal safety data.
- Attract stakeholders in Women's Health to target Congress, NIH, and the industry to create programs similar to those created for pharmaceutic studies in children.
- Encourage the NIH to support training grants for obstetrical and lactation pharmacology.
- Educate women about the importance of participating in pharmacology studies.
- Reduce the research burden on pregnant and lactating women. ■

REFERENCES

1. Tinker SC, Broussard CS, Frey MT, Gilboa SM. Prevalence of prescription medication use among non-pregnant women of childbearing age and pregnant women in the United States: NHANES, 1999-2006. Matern Child Health J 2015;19:1097–106.

2. Mitchell AA, Gilboa SM, Werler MM, et al. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol 2011;205:51.e1–8.

3. McCormack SA, Best BM. Obstetric pharmacokinetic dosing studies are urgently needed. Front Pediatr 2014;2:9.

4. Scaffidi J, Mol BW, Keelan JA. The pregnant women as a drug orphan: a global survey of registered clinical trials of pharmacological interventions in pregnancy. BJOG 2017;124:132–40.

5. Byrne JJ, Saucedo AM, Spong CY. Evaluation of drug labels following the 2015 pregnancy and lactation labeling rule. JAMA Netw Open 2020;3:e2015094.

6. Adam MP, Polifka JE, Friedman JM. Evolving knowledge of the teratogenicity of medications in human pregnancy. Am J Med Genet C Semin Med Genet 2011;157C:175–82.

7. Običan S, Scialli AR. Teratogenic exposures. Am J Med Genet C Semin Med Genet 2011;157C:150–69.

8. Thorpe PG, Gilboa SM, Hernandez-Diaz S, et al. Medications in the first trimester of pregnancy: most common exposures and critical gaps in understanding fetal risk. Pharmacoepidemiol Drug Saf 2013;22:1013–8.

9. Griffiths SK, Campbell JP. Placental structure, function and drug transfer. Contin Educ Anaesth Crit Care Pain 2015;15:84–9.

10. Al-Enazy S, Ali S, Albekairi N, El-Tawil M, Rytting E. Placental control of drug delivery. Adv Drug Deliv Rev 2017;116:63–72.

11. Staud F, Cerveny L, Ceckova M. Pharmacotherapy in pregnancy; effect of ABC and SLC transporters on drug transport across the placenta and fetal drug exposure. J Drug Target 2012;20:736–63.

12. Hotham N, Hotham E. Drugs in breastfeeding. Aust Prescr 2015;38:156–9.

13. Newton ER, Hale TW. Drugs in breast milk. Clin Obstet Gynecol 2015;58:868–84.

14. Rentsch KM. Drug exposure in newborns: effect of selected drugs prescribed to mothers during pregnancy and lactation. Ther Drug Monit 2020;42:255–63.

15. Dinatale M. The pregnancy and lactation labeling rule (PLLR). 2020. Available at: https://www.fda.gov/media/100406/download. Accessed January 25, 2021.

16. US Food and Drug Administration. Novel drug approvals for 2020. 2020. Available at: https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2020. Accessed January 25, 2021.

17. Namazy J, Chambers C, Sahin L, et al. Clinicians' perspective of the new pregnancy and lactation labeling rule (PLLR): results from an AAAAI/FDA survey. J Allergy Clin Immunol Pract 2020;8:1947–52.

18. Monnelly VJ, Hamilton R, Chappell FM, Mactier H, Boardman JP. Childhood neurodevelopment after prescription of maintenance methadone for opioid dependency in pregnancy: a systematic review and meta-analysis. Dev Med Child Neurol 2019;61:750–60.

19. Walhovd KB, Watts R, Amlien I, Woodward LJ. Neural tract development of infants born to methadone-maintained mothers. Pediatr Neurol 2012;47:1–6.

20. Videman M, Tokariev A, Saikkonen H, et al. Newborn brain function is affected by fetal exposure to maternal serotonin reuptake inhibitors. Cereb Cortex 2017;27:3208–16.

21. Lugo-Candelas C, Cha J, Hong S, et al. Associations between brain structure and connectivity in infants and exposure to selective serotonin reuptake inhibitors during pregnancy. JAMA Pediatr 2018;172:525–33.

22. Podrebarac SK, Duerden EG, Chau V, et al. Antenatal exposure to antidepressants is associated with altered brain development in very preterm-born neonates. Neuroscience 2017;342:252–62.

23. Wollman SC, Alhassoon OM, Hall MG, et al. Gray matter abnormalities in opioid-dependent patients: a neuroimaging meta-analysis. Am J Drug Alcohol Abuse 2017;43:505–17.

24. Caritis SN, Panigrahy A. Opioids affect the fetal brain: reframing the detoxification debate. Am J Obstet Gynecol 2019;221:602–8.

25. Feghali M, Venkataramanan R, Caritis S. Pharmacokinetics of drugs in pregnancy. Semin Perinatol 2015;39:512–9.

26. Soma-Pillay P, Nelson-Piercy C, Tolppanen H, Mebazaa A. Physiological changes in pregnancy. Cardiovasc J Afr 2016;27:89–94.

27. Hebert MF, Ma X, Naraharisetti SB, et al. Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice. Clin Pharmacol Ther 2009;85:607–14.

28. Bastian JR, Chen H, Zhang H, et al. Dose-adjusted plasma concentrations of sublingual buprenorphine are lower during than after pregnancy. Am J Obstet Gynecol 2017;216:64.e1–7.

29. Pillai VC, Han K, Beigi RH, et al. Population pharmacokinetics of oseltamivir in non-pregnant and pregnant women. Br J Clin Pharmacol 2015;80:1042–50.

30. Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. Proc Biol Sci 2015;282:20143085.

31. Olin A, Henckel E, Chen Y, et al. Stereotypic immune system development in newborn children. Cell 2018;174:1277–92.e14.

32. Yin W, Li T, Hung SC, et al. The emergence of a functionally flexible brain during early infancy. Proc Natl Acad Sci U S A 2020;117:23904–13.

33. Kostović I, Sedmak G, Judaš M. Neural histology and neurogenesis of the human fetal and infant brain. Neuroimage 2019;188:743–73.

34. US Department of Health and Human Services. Food and Drug Administration, Center for Drug Evaluation and Research, and Center for Biologics Evaluation and Research. Clinical lactation studies: considerations for study design guidance for industry. 2019. Available at: https://www.fda.gov/media/124749/download. Accessed January 25, 2021.

35. US Food and Drug Administration. List of pregnancy exposures registries. 2020. Available at: https://www.fda.gov/science-research/womens-health-research/list-pregnancy-exposure-registries. Accessed January 25, 2021.

36. Lemon LS, Bodnar LM, Garrard W, et al. Ondansetron use in the first trimester of pregnancy and the risk of neonatal ventricular septal defect. Int J Epidemiol 2020;49:648–56.

37. US Department of Health and Human Services. Best pharmaceuticals for children Act. 2020. Available at: https://nichd.nih.gov/research/supported/bpca/about. Accessed January 25, 2021.

38. National Institutes of Health. Best Pharmaceuticals for Children Act (BPCA) priority list of needs in pediatric therapeutics. 2019. Available at: https://federalregister.gov/documents/2019/04/23/2019-08167/best-pharmaceuticals-for-children-act-bpca-priority-list-of-needs-in-pediatric-therapeutics. Accessed January 25, 2021.

39. United States Congress. H.R. 4274 (112th): BPCA and PREA reauthorization act of 2012. 2012. Available at: https://www.govtrack.us/congress/bills/112/hr4274. Accessed January 25, 2021.

40. Bourgeois FT, Hwang TJ. The pediatric research equity act moves into adolescence. JAMA 2017;317:259–60.

41. US Food and Drug Administration. Reviews of Pediatric Studies Conducted under

Descargado para BINASSS Circulaci (binas@ns.binasss.sa.cr) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en julio 15, 2021. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2021. Elsevier Inc. Todos los derechos reservados.

BPCA and PREA from 2012 - present. Available at: https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2012-present. Accessed Feb. 11, 2021.

42. Committee on Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA); Board on Health Sciences Policy; Institute of Medicine In: Field MJ, Boat TF, eds. Safe and effective medicines for children: pediatric studies conducted under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. Washington (DC): National Academies Press (US); 2012.

43. US Department of Health nd Human Services. List of recommendations from the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC). 2020. Available at: https://www.nichd.nih.gov/about/advisory/PRGLAC/recommendations. Accessed January 25, 2021.

44. Eke AC, Olagunju A, Best BM, et al. Innovative approaches for pharmacology studies in pregnant and lactating women: a viewpoint and lessons from HIV. Clin Pharmacokinet 2020;59:1185–94.

45. Pemathilaka RL, Reynolds DE, Hashemi NN. Drug transport across the human placenta: review of placenta-on-a-chip and previous approaches. Interface Focus 2019;9:20190031.

46. National Institutes of Health. Postdoctoral training program in obstetric and pediatric pharmacoepidemiology. 2018. Available at: https://grants.nih.gov/grants/guide/pa-files/PAR-13-112.html. Accessed January 25, 2021.

Descargado para BINASSS Circulaci (binas@ns.binasss.sa.cr) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en julio 15, 2021. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2021. Elsevier Inc. Todos los derechos reservados.