Title
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Journal
Clinical Infectious Diseases, 59(suppl_7)

ISSN
1058-4838

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Publication Date
2014-12-15

DOI
10.1093/cid/ciu709

Peer reviewed

SUPPLEMENT ARTICLE

Designing Drug Trials: Considerations for Pregnant Women

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Clinical pharmacology studies that describe the pharmacokinetics and pharmacodynamics of drugs in pregnant women are critical for informing on the safe and effective use of drugs during pregnancy. That being said, multiple factors have hindered the ability to study drugs in pregnant patients. These include concerns for maternal and fetal safety, ethical considerations, the difficulty in designing appropriate trials to assess the study objectives, and funding limitations. This document summarizes the recommendations of a panel of experts convened by the Division of Microbiology and Infectious Diseases at the National Institute of Allergy and Infectious Diseases, National Institutes of Health. These experts were charged with reviewing the issues related to the development of preclinical and clinical drug studies in pregnant women and to develop strategies for addressing these issues. These findings may also be utilized in the development of future drug studies involving pregnant women and their fetus/neonate.

Keywords. pregnancy; drug trials; pharmacokinetics.

The study of therapeutic agents in pregnant women has been virtually nonexistent for decades. Although sex differences in drug disposition have been recognized for almost a century and pregnancy has been known to significantly compound these differences, there remains a paucity of data available to guide practitioners in determining appropriate dosing of medications and in counseling patients regarding safety and efficacy of medications in pregnancy. Antecedent cases such as severe fetal malformations with maternal thalidomide use in the 1950s and 1960s and diethylstilbestrol-induced vaginal adenocarcinoma in women exposed in utero in the 1970s led to the US Food and Drug Administration's (FDA) 1977 decision to exclude women of childbearing age from participating in phase 1 and early phase 2 trials, when the initial pharmacology, efficacy, and safety of a therapeutic agent are assessed. Pharmaceutical companies and the research community extended this exclusion into phase 3 and 4 trials. Subsequently, in the mid-1990s, a congressional mandate established the FDA Office of Women's Health to advocate for the participation of women in clinical trials. Subsequently, women of childbearing potential were again included in investigational drug trials, along with adequate safeguards (eg, pregnancy testing and adequate contraception) to minimize the potential for inadvertent drug exposure to a pregnant woman.

Women and healthcare professionals need to be armed with available information on the effects of drugs when used in pregnancy. This is a matter of public health importance for several reasons: (1) women take an average of 2.6 drugs during pregnancy [1]; (2) many pregnant women have medical conditions, such

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Clinical Infectious Diseases® 2014;59(S7):S437–44

DOI: 10.1093/cid/ciu709

as asthma, high blood pressure, depression, or diabetes, that require them to continue taking drugs they were on before pregnancy; (3) new medical problems may begin or old ones may be exacerbated during pregnancy, requiring initiation of drug treatment; and (4) a woman's body changes throughout the term of her pregnancy, which can affect the dose she needs of a particular drug.

In the past decade, the FDA has continued to emphasize the need for inclusion of women (pregnant and nonpregnant) in development programs, issuing guidance for industry on establishing pregnancy registries and drafting guidelines for conducting pharmacokinetic (PK) and pharmacodynamic (PD) studies in pregnant women. There is still, however, no current legislation that incentivizes or mandates drug studies in pregnant and lactating women [2]. The Centers for Disease Control and Prevention has developed an initiative called Treating for Two: Safer Medication Use in Pregnancy. This initiative aims to prevent birth defects and improve the health of mothers by identifying the best therapeutic strategies for treatment of common conditions during pregnancy and during the childbearing years [3]. The expert panel convened to develop this manuscript strongly supports developing strategies to obtain more comprehensive data regarding medications commonly used in pregnancy.

Pregnant women are now exposed to an average of 2.6 medications, prescription and nonprescription, during pregnancy [1]. Ninety percent of pregnant women are exposed to at least 1 medication, and 80% report exposure during the first trimester, the period of organogenesis [3]. Many of these women require medications for the treatment of medical conditions present prior to the pregnancy [4, 5]. As the vast majority of pregnant women are exposed to medications, it behooves us as clinicians to obtain information on drug dosing that ensures the safe and effective use of these drugs for our patients. Unfortunately, several recent studies have found that >98% of medications have no or insufficient safety and/or PK data to guide dosing during pregnancy and lactation [6, 7].

There are a number of reasons for this dearth of evidence. The safety (both maternal and fetal/neonatal) of testing drugs in pregnant women is cited as the greatest concern by researchers and pharmaceutical companies. The possibility of disrupting organogenesis has limited studies conducted in the first trimester, and concerns for potential long-term sequelae in exposed infants have adversely affected the inclusion of women in later gestation of pregnancy and during lactation. Institutional internal review boards are reticent to approve drug trials in pregnancy for similar reasons. Other reasons cited include the lack of financial incentives and the absence of a mandate for these studies to be performed prior or subsequent to FDA approval. Finally, ethical arguments are used to justify the exclusion of pregnant women in drug trials. It can be argued, however, that it may be unethical *not* to include pregnant and lactating women in these trials. Dosing recommendations for pregnant women are usually extrapolated from studies in nonpregnant patients, and most medications prescribed in pregnancy are used "off-label" [8]. Logistically, PK trials are challenging to conduct in pregnancy. Most available data are a result of "opportunistic studies" performed when pregnant women are already receiving a therapeutic agent. These studies, although invaluable, are limited. Ideally, every medication would be studied in each trimester of pregnancy and during the postpartum period, providing detailed knowledge of the drug's PK/PD effects, when appropriate. This would allow for dosing adjustments in pregnancy to minimize toxicity while ensuring efficacy.

The Division of Microbiology and Infectious Diseases at the National Institute of Allergy and Infectious Diseases, National Institutes of Health, sponsored a conference titled "Enrolling Pregnant Women in Clinical Trials of Antimicrobials and Vaccines" in December 2013. One panel of experts was charged with reviewing the issues related to the development of clinical PK/PD drug studies in pregnant women and to develop strategies for addressing these issues. This article discusses the findings of this panel, addressing the physiologic changes that affect drug PK/PD parameters, the role of the placenta in drug metabolism, preclinical study design, clinical trial design, the regulation of drug trials in pregnant women, and the multiple factors limiting the ability to perform drug trials in pregnancy. These findings may be utilized in the development of future drug studies involving pregnant women and their fetus/neonate.

Physiologic Changes in Pregnancy Affecting Drug PK/PD Parameters

During pregnancy, physiologic changes occur in nearly all organ systems, virtually assuring that the pharmacokinetics of drugs administered to pregnant women will be impacted. This impact on absorption, distribution, metabolism, and excretion of therapeutic agents could also impact the PD properties of these agents during pregnancy [9, 10]. Many factors lead to decreased drug absorption during pregnancy. The rise in progesterone leads to a delay in gastric emptying and a prolonged gastric transit time of 30%–50%. Nausea and vomiting in early pregnancy, as well as a reduction in esophageal sphincter tone and the expanding uterus, will further exacerbate gastric emptying. Common medications used to treat the symptoms associated with decreased gastric emptying during pregnancy, such as antacids, may interact with coadministered medications, further decreasing their absorption.

Distribution of drugs is impacted by many factors in pregnancy. The cardiovascular system undergoes profound changes that begin early in pregnancy and plateau at the end of the second trimester. Cardiac output increases 30%–50%, with most of

the changes occurring in the first trimester. To accommodate this increase in cardiac output, there is a parallel increase in blood volume of 40%–50% that peaks at the end of the second trimester. This coincides with an increase in water and sodium retention that occurs at the kidney and leads to an increase in total body water of 6–8 L. This increase in total volume, which is beyond what the body can produce in increased red blood cell mass, leads to a hemodilutional anemia and a drop in colloid osmotic pressure with a decrease in serum albumin. Paradoxically, the volume expansion will significantly increase the volume of distribution of most therapeutic agents, potentially leading to lower bioavailability, while the drop in albumin will diminish protein binding, thereby increasing the amount of free drug and potentially creating higher bioavailability.

Metabolism and clearance of therapeutic agents is altered in pregnancy, mostly secondary to hormonal alterations in drug-metabolizing enzymes and alterations in renal blood flow. Polar drugs are generally cleared unchanged by the kidney, whereas lipophilic drugs are metabolized by the liver and then cleared by the kidney. Less important routes of elimination include bile excretion as well as via the respiratory tract. Renal clearance in pregnancy is mainly influenced by the increase in renal blood flow. The increased blood flow of 60%–80% leads to an increase in glomerular filtration rate of approximately 50%. In addition to increased blood flow, there is also an increase in active renal tubular secretion that occurs during pregnancy. In total, these changes lead to a significantly increased clearance of drugs that are excreted intact by the kidneys, such as penicillins and most cephalosporins.

Drug metabolism is often a 2-stage process; the first phase involves enzymatic modification of the agent, whereas the second phase involves conjugation. Phase 1 metabolism is characterized by reduction, oxidation, or hydrolysis and is exemplified by the oxidative enzyme family cytochrome P450 (CYP). During pregnancy, isoenzymes from this family exhibit both increased and decreased activity. For example, CYP2A6 is an enzyme with nicotine as its major substrate. Levels of this enzyme are increased during the third trimester, which may necessitate increasing the dose of nicotine replacement in a patient being treated for nicotine addiction. In contrast, levels of CYP1A2, which is involved in the metabolism of caffeine, decrease in the third trimester of pregnancy, thereby lowering metabolism and creating increased concentrations of caffeine with equal maternal consumption.

The Role of the Placenta

Historically it was a common belief that the placenta protected the fetus from harmful agents. This belief was overturned by the thalidomide catastrophe in the 1960s. Thalidomide was released into the market in 1957 in West Germany and was primarily prescribed as a sedative or hypnotic. It was subsequently used as a treatment for nausea and to alleviate morning sickness in pregnant women. Shortly after the drug was sold in Germany, between 5000 and 7000 infants were born with a malformation of the limbs (phocomelia), and only 40% of these infants survived.

So what are the key functions of the placenta? These include the transfer of nutrients, the exchange of gases, the biotransformation of xenobiotics including both environmental toxins and therapeutic agents, the release of hormones, and the elimination of waste products, as well as providing a functional barrier. The placental barrier effect is achieved by the anatomical structure, metabolic enzymes (anabolic and catabolic), and transporters (uptake and efflux) with genetic variance and polymorphisms that affect the activity of enzymes/transporters. Placental structure and function show more marked interspecies diversity than any other mammalian organ.

Chemical compounds cross the placenta through simple diffusion, facilitated diffusion, pinocytosis, and active transport. Simple diffusion allows for the free fraction of a drug to cross the placenta. Nonionized drugs cross the placenta more easily than ionized drugs. Fetal blood is more acidic than maternal blood and therefore drugs that are weaker bases are more ionized in the fetal circulation. This creates a concentration gradient of free drug toward the fetus. Key properties affecting simple diffusion include molecular weight, pKa, lipid solubility, and protein binding. Chemical compounds with a molecular weight >500 Da (larger than most drugs) are transferred incompletely across the placenta. Facilitated diffusion occurs when substance transport is carrier-mediated down a concentration gradient without energy costs. Pinocytosis involves the introduction of fluids into a cell by invagination of the cell membrane, followed by formation of vesicles within the cells with transportation to the other side of the cell.

Even though the physiological role for active transport proteins is to provide nutrients such as amino acids, fatty acids, and glucose to the fetus, some transporters facilitate the entry of xenobiotics from the maternal circulation whereas others prevent their entry. The most well known of these is P-glycoprotein, which is an efflux pump that transports substrates from the intracellular to the extracellular compartment. The relevance of these transporters to drug distribution in the placenta has been recently established. P-glycoprotein has been detected in human trophoblasts from the first trimester to term. In the mouse, inhibition of P-glycoprotein results in greatly induced transplacental passage of drugs into the fetus. The current hypothesis is that placental P-glycoprotein protects the developing embryo and fetus from toxic substance and suppresses teratogenesis. Commonly prescribed medications transported by the P-glycoprotein efflux mechanism include macrolides (erythromycin, clarithromycin, azithromycin), carvedilol, calcium

channel blockers (diltiazem, felodipine, verapamil), quinidine, ticagrelor, antiretrovirals (lopinavir, ritonavir), cyclosporine, and azole antifungals (itraconazole). Several of these—for example, statin medications—have been found to directly inhibit the transporter. Other major drug efflux transporters identified in the placenta include multidrug resistance–associated proteins and breast cancer resistance protein. Several transporters facilitate the transfer of drugs to the fetal compartment; the amino acid transporters may transport drugs that structurally resemble amino acids, for example, the antiepileptic drug gabapentin.

Designing Drug Studies in Pregnant Women

Both preclinical studies and clinical studies in nonpregnant adults provide information pertinent to designing clinical trials in pregnancy. Dosing selection, inclusion and exclusion criteria, and dose–exposure effects with regard to safety and efficacy can be assessed and these parameters used to guide the development of drug studies involving pregnant women [11]. Preclinical studies include models for the study of placental transfer utilizing cultured tissue slices, cultured syncytiotrophoblast tissue, and trophoblast-derived culture cells. Although in vitro models cannot fully account for all the physiological and biochemical variables in the mother, placenta, and fetus and how these variables change throughout gestation, they should be the first-line tests when a new substance is to be investigated for potential use in pregnancy. Explants of human placenta have also been used to study facets of the maternal–fetal interface. These include placental transport, metabolism, and endocrine function. Placental microsomes are now used to study isolated transporters and receptors. The human placental perfusion method has been widely used to study transplacental passage of both endogenous and exogenous compounds [12–14]. Perfusions are done utilizing term placentas for the most part, and extrapolation of the results to earlier trimesters is not possible. Animal placental perfusion models can also be used to examine the transfer of toxic substances without the ethical concerns of maternal and fetal safety. Animal placentas are most commonly perfused in situ. One limitation of animal placental perfusion studies is the large interspecies differences regarding permeability of hydrophilic molecules [15]. Other preclinical studies include genotoxicity and nonclinical female reproduction and embryo-fetal developmental toxicity studies, which are standard nonclinical assessments performed during the development of most drugs.

The safe and effective use of drugs during pregnancy cannot be achieved without performance of clinical pharmacology studies to describe the pharmacokinetics and pharmacodynamics of drugs during pregnancy [16]. The panel recommended that PK studies in pregnancy be conducted for drugs known to be prescribed in pregnant women, for new drugs with anticipated or actual use in pregnancy, or when use in pregnancy may be rare but the consequences of uninformed dosages are great. Studies can be initiated in pregnant women if preclinical studies, including studies in pregnant animals, and clinical studies, including studies in nonpregnant women, have been conducted and provide data for assessing potential maternal and fetal risk, there is no greater than minimal risk to the fetus, and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means. Drug studies should not be conducted in pregnant women if there is no anticipated use of the drug during pregnancy or if fetal risk is known or highly suspected [17].

It is known that many drugs are commonly administered as part of clinical care during pregnancy. One can take advantage of that fact by using an opportunistic study design to obtain clinical data of drugs in pregnancy. Such design entails enrolling pregnant women who are already receiving the drug as part of their clinical care in a research study. Under these circumstances, the women's decision to use the medications is independent of their participation in a research study, which attenuates ethical concerns over imposing unknown risks to the expectant mother and her fetus for the purpose of research. On a more practical level, because these women have already determined that the benefits of the medication outweigh its risks in their decision to proceed with treatment, they are more likely to agree to participate in a study than if they were assigned a treatment by an investigator. One weakness of an opportunistic design is that enrollment is limited to subjects already on therapy. Some women, such as rapid metabolizers with low drug exposure, or who develop toxicity, such as slow metabolizers with high drug exposure, may have stopped study drug treatment and will not be available for inclusion in the study population. If a drug is not commonly used for clinical care, then an opportunistic design is not practical.

It may also be possible to study drugs in pregnant women who derive no direct benefits, provided that the risk to the fetus is minimal and adequate subject protection safeguards are in place. To minimize drug exposure, these women can be exposed once during the pregnancy, using different cohorts to evaluate drug pharmacokinetics/pharmacodynamics in each trimester and during the postpartum period. The most appropriate drug candidates for this type of study are those with a known record of safety in pregnancy.

The primary goal of pharmacology studies in pregnant women is to determine if pharmacokinetics and/or pharmacodynamics are altered sufficiently in pregnancy to require an alteration in dosing; the ideal study design to meet these goals would include assessment of the same subject prepregnancy and during each trimester. For practical reasons, pregnancy studies are often limited to assessments during the third trimester (or possibly second and third trimesters) and during the

postpartum period. If dosing is chronic, then each subject can be assessed both during and after pregnancy, serving as her own control. If dosing is for only a short period of time, then it may be reasonable to compare different women during different trimesters of pregnancy and in the postpartum period, and a larger sample size will be needed due to interindividual variability. Several study design features were considered by the panel. For example, if study drug is present in the mother at the time of delivery, then the study protocol should include collection of samples for assay of drug concentrations in maternal blood at delivery and cord blood, to allow description of placental drug transfer. Analysis of maternal delivery and cord blood drug concentrations should incorporate the time from maternal dosing, so the pattern of placental drug transfer over the dosing interval can be described. There is an abrupt change in physiology at delivery, followed by a gradual return to prepregnancy physiology over the next weeks and months postpartum. The timing of the postpartum assessments should take these changes into account and be performed sufficiently long enough after delivery to allow a return to the prepartum state. If subjects are breastfeeding at the time of the postpartum assessment, then the need for protection of the infant from drug transmission via breast milk should be considered, incorporating assessment of infant pharmacology and adverse effects of the drug. If exposure of the infant to a drug via breast milk is allowed in the study, then evaluation of the characteristics of breast milk drug transfer should be included in the research protocol.

Pharmacokinetic studies in pregnancy characterize drug disposition—absorption, distribution, metabolism, and excretion—and may do so using intensive sampling and traditional PK analysis (noncompartmental analysis) or sparse sampling with population PK analysis, or a combination of both. Whenever possible, study design should incorporate assessment of PD as well as PK endpoints. Appropriate PD endpoints may describe the impact of study drug on a microbe being targeted, on the mother or on the fetus.

Traditional PK analysis estimates each participant's PK parameters using only data from that individual. For this reason, intensive sampling (multiple samples per participant) is required. These studies are generally performed in a smaller number of subjects, typically ranging from 10 to 20 subjects. With a rich PK sampling scheme, traditional PK analysis can precisely estimate individual-level PK parameters. Traditional PK parameters assessed include area under the concentration-time curve (AUC), clearance (Cl), elimination rate constant (k), drug half-life (T½), volume of distribution (Vd), absorption rate constant, peak concentration (C_{max}), time of C_{max} (T_{max}), and bioavailability (F). Intensive sampling and traditional PK analysis may be especially useful when the expected effects of pregnancy on drug disposition are hard to predict, so collecting multiple samples is necessary to have sufficient data to characterize absorption, distribution, and clearance with confidence.

Population PK analysis traditionally involves collection of fewer samples from a larger group of subjects; however this method is perfectly suited for all data types (rich, sparse, intermediate, or mixture of all). This method can utilize all available data and incorporate data from multiple sources—for example, it can include partial data from patients who did not complete the full study, it can utilize prior data, etc—thereby making it very cost-effective. Population PK analysis gives estimates for typical values for PK parameters for the population and also describes variability in PK parameters across the population. The methodology allows for evaluation of the impact of demographic and clinical covariates—such as weight, race, pharmacogenetics, or disease status—on PK parameters so that important sources of variability in drug exposures can be explained and understood. A model-based approach is particularly useful for evaluation of different dosing regimens, estimation of the optimal dosing regimen, time-dependent changes in PK parameters across the pregnancy/postpartum continuum, and covariate effects, as well as precise quantification of variability in PK parameters and drug exposures, which is an important issue given the fact that variability is expected to increase during pregnancy. When sparse/intermediate sampling is performed with the plans for a nonlinear mixed-effects modeling analysis, it is especially important that PK sampling times be chosen carefully to optimize information that is gained from the study. Once population PK models are developed, modeling and simulation can be used to guide generation of a dosing algorithm, with specific suggestions for dose adjustments by stage of pregnancy or, in some cases, other factors (obesity, disease status, etc). The model-based approach is perfectly suited to study the relationship between drug concentrations in maternal plasma and placental transfer of drugs in utero when sparse samples of cord blood are collected during the delivery. This approach can also be used to study drug distribution in breast milk.

Regulation of Drug Studies in Pregnant Women

Safety and efficacy of drugs are usually established for a particular dosage regimen in late phase (phase 3) clinical trials enrolling the intended patient population. These clinical trials usually exclude pregnant women, and women are usually discontinued from trials if pregnancy occurs, creating a significant gap in knowledge to inform dosing in this specific population. Currently, there is no targeted legislation that mandates clinical trial data in the pregnant patient, such as the pediatric regulations, including the Pediatric Research Equity Act (Public Law 108–155) requiring the conduct of pediatric studies for drug and therapeutic biological products. Despite the lack of

legislation requiring studies in pregnant women, the regulations do stipulate that sufficient evidence is required to adequately label a drug product for use, "including support for the dosage and dose interval recommended" and that "any modifications of dose or dose interval needed for specific subgroups" should be identified (21 CFR 314.50(d)(5)(v)). This regulation is most often applied to specific populations with conditions affecting drug disposition, such as organ dysfunction (eg, renal and hepatic impairment) and age (geriatrics). But the importance of changes in drug disposition in pregnant women should not be overlooked, and the FDA relies on certain regulatory tools to influence the ascertainment of important information about drug dosing in pregnancy.

In 2004, the FDA issued a draft guidance document titled *Guidance for Industry Pharmacokinetics in Pregnancy—Study Design, Data Analysis, and Impact on Dosing and Labeling* [17]. The guidance describes the agency's thinking on this topic and emphasizes the need for PK/PD studies in pregnancy as a matter of public health concern. Extrapolation of dosing from studies performed in nonpregnant adults fails to take into account the impact of the many physiologic changes that occur during pregnancy, and PK/PD data obtained during pregnancy are necessary to inform adequate dosing in this specific population. As mentioned previously and emphasized in the Guidance, these data can be obtained from pregnant women in PK studies if the following conditions are met: "(1) Preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risk to pregnant women and fetuses; and (2) the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means" (45 CFR Subpart B 46.204). The Guidance recommends that PK studies in pregnant women be conducted if the drug will be prescribed for pregnant women, especially in the second and third trimesters; if there is anticipated or actual use of the drug in pregnancy; if use of the drug is expected to be rare in pregnancy, but the consequences of uninformed dosages are great (eg, drugs with narrow therapeutic range, cancer chemotherapy); or if pregnancy is likely to alter significantly the pharmacokinetics of a drug (eg, renally excreted drug) and any of the above apply. Important topics covered by the Guidance include ethical implications of studies in pregnant women, specifics regarding PK/PD study design and analysis, and special study considerations. In summary, this Guidance reflects the FDA's commitment to emphasize the need for these studies, and addresses the most important issues to obtaining these data in pregnant women.

In 2002, FDA issued a Guidance to Industry providing recommendations on how to establish pregnancy exposure registries to monitor for outcomes of pregnancies exposed to drug products (*Guidance to Industry: Establishing Pregnancy Exposure Registries*, August 2002). The FDA recognizes the importance of going beyond passive postmarketing surveillance to obtain adequate data of pregnancy-related outcomes. In this Guidance, the agency encourages the use of a pregnancy registry, which is essentially a prospective observational study, under certain circumstances, such as when a drug has a high likelihood to be used by pregnant women. The primary goal of these registries is to provide clinically meaningful data that can be used in the product's labeling to inform and guide the prescribers and their pregnant patients or those planning to become pregnant. The FDA Office of Women's Health maintains the Pregnancy Exposure Registry Website, which lists ongoing pregnancy registries, provides registry information, and facilitates enrollment into a registry (http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm251314.htm). It is important to note that FDA guidance documents, such as the 2 mentioned above, represents the FDA's current thinking on a particular subject and should be viewed as guidance and recommendations. These guidances do not establish legally enforceable responsibilities on the FDA or the public.

The FDA Amendments Act of 2007 provided the FDA the authority to require certain postmarketing studies for prescription drugs to assess a known serious risk related to the use of a drug or a signal of a serious risk related to the use of the drug. Because pregnant women are usually excluded from premarketing clinical trials, safety signals seen in pregnancy are anticipated to arise in the postmarketing surveillance setting. These safety signals can be identified by a variety of sources, including published literature, the sponsor's worldwide postmarketing surveillance database, the FDA Adverse Event Reporting System database, and concerns raised by the public (academia, federal partners, and private citizens). In addition, sponsors are asked to explicitly address adverse experiences during pregnancy (and lactation) in the Overall Safety Evaluation section of the Periodic Safety Update Reports, which are submitted on a regular basis required by law (*Guidance for Industry: E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs*, November 1996). If the FDA determines that a serious safety signal seen in pregnant women warrants further characterization, the FDA can require the drug manufacturer to conduct the appropriate study in pregnant women.

Last, the FDA aims to provide information to help women and their healthcare providers make well-informed choices when medicine is needed during pregnancy and lactation through improved drug labeling. In May 2008, the FDA proposed major revisions to regulations affecting prescription drug labeling known as the Pregnancy and Labeling Rule (PLLR) under the Physician Labeling Rule that was finalized

in 2006 (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm). The PLLR proposes that the pregnancy and lactation subsections of labeling include a risk summary and clinical considerations to support patient care decisions and counseling, and a data section that includes more detailed information. The FDA proposes that the clinical considerations under the Pregnancy subsection contain prescribing decisions for pregnant women describing (1) dosing adjustments during pregnancy; (2) adverse reactions unique to pregnancy associated with use of the drug; and (3) any interventions that may be needed (eg, monitoring blood glucose for a drug that causes hyperglycemia in pregnancy).

The data to inform this subsection could come from various sources, including studies published in the medical literature about the use of prescription drugs during pregnancy. The proposed rule encourages that available information about the effects of a drug on pregnancy and lactation be actively sought and, when appropriate, be included in the labeling, in a revised format that would make that information more useful to healthcare practitioners and their patients. In addition, the labeling would specifically state when there is not information available. When finalized, the requirements of the PLLR would apply to all drug applications required to comply with the FDA's 2006 Physician Labeling Rule and amend the FDA's regulations concerning the format and content of labeling subsections pertaining to pregnancy, labor and delivery, and nursing.

CONCLUSIONS

The physiologic changes of pregnancy can significantly alter drug exposure, which can directly affect the safe and effective use of drug products in pregnant women. Drug use data have consistently demonstrated the extensive use of pharmaceutical agents in pregnancy. However, robust data to guide appropriate dosing to optimize risk–benefit for pregnant women requiring drug therapies for medical conditions are lacking. Both pharmaceutical industry and researchers have been reluctant to conduct studies in pregnant women because of ethical concerns or fear of imposing risks on 2 vulnerable populations (pregnant mother and unborn fetus) in a setting of lack of legislative mandate or incentive to conduct such "high-risk" studies. The health and well-being of pregnant patients are being jeopardized by the lack of basic information to guide the safe and effective use of drug products in pregnancy.

Studies in pregnant women are feasible and can be performed in ways that are clearly ethical and provide the necessary study subject protection. Public resources, such as FDA guidances, are available to inform considerations for conducting PK/PD studies in pregnancy and establishing pregnancy registries. Improved funding mechanisms, both from private and government sources, are necessary to stimulate research interest and allow the conduct of studies in pregnancy. A coordinated effort that addresses the wide range of issues that presently impede the conduct of clinical trials in pregnancy will be necessary to advance the research in this area. As the impediments are removed or mitigated, research during pregnancy would effectively generate the necessary data to improve healthcare and outcomes for pregnant women and their children.

Notes

Financial support. This article was supported by an unrestricted grant from the Bill & Melinda Gates Foundation and the Division of Microbiology and Infectious Diseases of the National Institute of Allergy and Infectious Diseases, National Institutes of Health.

Supplement sponsorship. This article appears as part of the supplement "Including Pregnant Women in Clinical Trials of Antimicrobials and Vaccines," sponsored by the Bill & Melinda Gates Foundation.

Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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