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Lessons Learned in Pediatric Clinical Research to Evaluate Safe and Effective Use of Drugs in Pregnancy

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Abstract

Children and pregnant women are vulnerable populations lacking clinical data to guide drug dosing. For children, over the past 15 years, the knowledge gap in pharmacokinetic, safety, and efficacy data has been narrowed due to the use of innovative clinical trial designs, minimal risk research methods, increased understanding of developmental pharmacology, multi-disciplinary research teams, increased clinical pharmacology expertise and training, collaborative research networks, and critical legislative changes. This progress has not been observed to a similar degree for pregnant women. These two populations, however, share similar drug development challenges and, therefore, lessons learned in pediatric clinical trials can be leveraged to advance drug development in pregnant women.

Introduction

Children and pregnant women are among the most vulnerable populations because of challenges and barriers to obtaining rigorous scientific data regarding drug therapy.^{1,2} Concerns with fetal exposure limit inclusion of pregnant women in clinical trials.² Physiologic and biochemical changes that occur in childhood and pregnancy alter the disposition (pharmacokinetics [PK]) and response (pharmacodynamics [PD]) to drugs, often requiring dosage adjustments to maximize efficacy while minimizing unwanted adverse effects. Because drugs are widely prescribed in pregnancy (64% of pregnant women take a drug other than a vitamin or mineral supplement³), clinical data are needed to guide drug use in this vulnerable population. Unfortunately, due to a lack of available data, drugs are often prescribed for off-label uses and in the absence of PK/PD studies to support optimal dosing

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in pregnancy. A study in one institution estimated that 22.6% of eligible patients (165/731) took 1 drug (average 1.7, 95% CI: 1.3-3.8) for an off-label indication.⁴

Numerous strategies have been used in pediatric clinical research to characterize developmental PK/PD and identify optimal dosing across age groups. For example, innovative clinical trial designs that include multiple drugs in a single protocol, capitalize on standard of care procedures, and use multiple centers for subject enrollment have allowed for pediatric studies to be performed in an efficient and timely manner. PK/PD modeling and simulation techniques are routinely used to aid protocol design (e.g., dosage selection, optimal sampling times) in pediatric studies, which enhance the quality of the clinical data collected and maximize the information obtained from each individual. The combination of these factors has allowed for the development of feasible study protocols that have gained acceptance among parents of participating children.¹ We believe that similar approaches should be applied to drug development for pregnant women.

The expansion in pediatric clinical research has occurred largely due to federal legislation. In the United States, the Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA) have provided the regulatory framework for evaluating medication use in children. BPCA provides incentives for drug development of on and off-patent therapeutics and a pediatric exclusivity incentive for drug sponsors (6 month patent protection), while PREA gives the U.S. Food and Drug Administration (FDA) the authority to require pediatric studies to be performed for new molecular entities if relevant to child health. Although much additional work is needed, this framework has enhanced product labeling that includes dosing, safety, and efficacy for the pediatric population.⁵ These legislative changes have not been implemented for pregnant women; however, lessons learned in pediatric clinical research can be applied to study drugs in pregnancy.

Challenges in clinical trials conducted in pregnant women

Most drugs are not studied in pregnant women prior to obtaining approval from the FDA. The overall lack of available data in pregnancy is related to research ethics concerns that precluded pregnant women from participating in phase 1 and 2 clinical trials until the need for their inclusion was formally acknowledged in the National Institute of Health Revitalization Act of 1993.⁶ Moreover, the fear of drug related injuries to the mother and fetus, as well as associated litigation, likely also has discouraged drug sponsors from performing rigorous clinical trials.² As a result, pregnancy risk categorization often is assessed solely from animal reproductive studies. Post-marketing surveillance data is then used to assess fetal risk following drug exposure. This approach has slowed progress in drug development for pregnant women, and also is not foolproof. For example, animal developmental toxicology studies of thalidomide resulted in variable results depending on the species studied, and thus proved poorly predictive of toxicity in humans.⁷

Of important note though, the FDA recently amended its regulations regarding product labeling for use in pregnancy and lactation.⁸ The Pregnancy and Lactation Labeling Rule (PLLR), which will become effective June 30, 2015, will eliminate use of pregnancy letter categories (A, B, C, D, and X) and will require that product labeling be updated when additional information becomes available. In addition, information on pregnancy exposure

registries will be added to product labeling and a new section titled “Females and Males of Reproductive Potential” will include information on infertility, contraception recommendations, and pregnancy testing. These changes will facilitate the availability of clinical data in product labeling, and help clinicians consider risks and benefits when prescribing drugs to pregnant women.

In order to increase the availability of clinical data necessary for medical decision making there is a critical need to assess the effect of physiologic changes that occur during pregnancy on the disposition, safety, and efficacy of drugs prescribed in this population. Drug tissue distribution can be altered during pregnancy due to hemodynamic changes, such as an increase in cardiac output and alterations in regional blood flow; an expansion in plasma volume, total body water and maternal fat; decreases in albumin concentrations; and potentially altered drug transporter expression/function.⁹ Increases in volume of distribution, along with predicted changes in tissue drug exposure, must be considered when assessing the need for loading dose modifications in pregnancy (Table 1). Drug elimination, which dictates maintenance dosing, also can be altered due to variation in transporter and enzyme expression/function and increased renal blood flow.¹⁰ For example, the activities of the drug metabolizing enzyme CYP3A, and the transporter, p-glycoprotein, measured using midazolam and digoxin as probe substrates, respectively, have been shown to be significantly increased during pregnancy.¹¹ Drug specific PK alterations in pregnancy are often difficult to predict due to the time varying nature of the physiologic changes, the presence of multiple drug clearance mechanisms (e.g., multiple drug metabolizing enzymes), drug metabolism by the placenta, nonlinear disposition pathways, and genotypic variation in transporter/enzyme expression in both the liver and the placenta. In addition to changes in drug exposure at the site of action, underlying disease processes also may be different in pregnancy, which can alter response to treatment.¹² When designing PK/PD studies in pregnant women, specific pregnancy diseases (e.g., preeclampsia) and associated physiologic changes must be considered.

However, there are various practical challenges to performing well designed early phase studies in pregnant women. Changes in drug disposition can begin in the first trimester and evolve throughout a pregnancy, often peaking in the third trimester. Following delivery, it can take weeks to months for physiologic processes to return to a pre-pregnancy baseline. Clinical trials must be designed to appropriately capture the time dependency of these changes, and ideally each patient should serve as their own control (e.g., assessing drug disposition differences during pregnancy and following an adequate period post-pregnancy) to account for expected inter-individual variability.¹³ Often these trials need to be designed in the absence of preliminary data, making selection of optimal sampling time points and study dosing more challenging. Similar to the pediatric population, low informed consent rates, loss to follow-up and the need to perform drug sampling at specific time points can be challenges.

Altogether there are many practical considerations important for designing well controlled clinical trials in pregnancy, many of which overlap with pediatric studies (Table 2). Although recent trends indicate that therapeutic drug trials in pregnant women are on the rise¹⁴, there is a large gap in data for many drugs prescribed in this population. Innovative

strategies that aid in performing clinical trials in an efficient and timely manner, while collecting robust clinical data for PK/PD analysis, are urgently needed.

Lessons learned in pediatric clinical research applied to maternal fetal medicine

The availability of pediatric data being submitted to regulatory agencies (both FDA and European Medicines Agency [EMA]) has increased due to legislative changes and thought leaders in pediatric clinical pharmacology that have shaped the landscape to stimulate pediatric drug development.

Innovative clinical trial design—Efficient and well-designed clinical trials enhance the quality of the data collected and allow for studies to be performed in a timely manner. In children, multi-center clinical trials that capitalize on standard of care procedures (i.e., opportunistic studies), include multiple study drugs in a single protocol, have broad inclusion criteria, and optimize sample size across the pediatric age continuum, have been shown to overcome challenges associated with performing pediatric studies.¹ Opportunistic studies, whereby drug sampling is optimally performed with standard of care blood draws in patients already receiving the drug of interest, coupled with population-based PK modeling methodology have allowed for sparse (e.g., 1-5 samples/patient) and scavenged (leftover samples from routine care of patients) PK sampling techniques to be used to understand drug disposition changes across the pediatric age spectrum in an efficient manner. Likewise opportunistic studies can be performed in pregnant women to assess changes in drug disposition with minimal risk by capitalizing on standard of care procedures. This study design may reduce the “fear factor” from participating women and enhance enrollment in clinical trials.

Use of a broad network infrastructure of clinical trial sites has allowed for trial coordination to occur efficiently, and provided a mechanism to overcome low consent rates typically encountered with pediatric trials. In children, this has been accomplished by multiple initiatives such as the Eunice Kennedy Shriver National Institute Child Health and Human Development (NICHD)-sponsored Pediatric Pharmacology Research Unit (PPRU; 2000-2010); the Pediatric Trials Network (PTN; 2010-present); the Maternal Infant Child, Youth Research Network (MICRYN; 2006-present), and the National Institute for Health Research (NIHR) Medicines for Children Research Network (MCRN; 2006-present). This model has been adapted to the obstetric population through the NICHD-sponsored Obstetric-Fetal Pharmacology Research Units (OPRU) Network (2004-present). This 4-site network in the U.S. has generated important findings related to differences in drug clearance between pregnant and non-pregnant women for numerous drugs, including indomethacin and oseltamivir.^{15,16}

Quantitative clinical pharmacology—Applications of quantitative PK/PD modeling and simulation techniques have aided the design of pediatric clinical trials, including selection of optimal dosing and PK/PD sampling time windows. This includes leveraging adult data to develop mathematical models that can be scaled to children using known PK/PD properties of drugs and expected developmental changes based on allometric principles and maturation of elimination pathways. As pediatric data become available, the

model can be updated and pediatric and adult estimates of drug exposure can be compared. Population PK/PD modeling techniques have been applied successfully in children to understand developmental factors important for drug disposition changes as a function of age, organ function, body size, and body composition. This modeling methodology is also useful when only sparse sampling is available; pediatric data across age groups can be combined to quantitatively describe the time course of maturational changes. These models have also been developed using data collected from pregnant women to obtain mean population estimates of PK parameters and quantify the degree of inter- and intra-individual variability. Similar to their application in children, accounting for the effect of clinical covariates (e.g., gestational age) on inter-individual variability has allowed for the development of robust models that can be used to identify optimal dosing in pregnant women. If drug samples are collected from cord blood and/or amniotic fluid, these models can also include additional fetal and/or amniotic fluid compartments to characterize placental drug transfer.¹⁷

Application of physiologically-based PK/PD modeling and simulation techniques to children also has gained significant attention. These models integrate drug properties (e.g., metabolism, protein binding), physiological parameters (e.g., organ size, blood flow), and known efficacy targets to mechanistically account for the impact of important factors (e.g., age, disease) on drug disposition and efficacy. In pregnancy, physiologically-based PK models have been developed to integrate changes in maternal physiology and multiple drug metabolizing enzymes to predict altered disposition. The mechanistic nature of these models, which are developed using both *in vitro* and *in vivo* data, and include a placental-fetal compartment, allow for a “bottom up” PK modeling approach. For example, one study evaluated use of a physiologically-based PK model to predict gestational age-dependent changes in drug exposure for methadone and glyburide, two drugs that are metabolized via multiple pathways (methadone: CYP3A, 2B6, 2C19; glyburide: CYP3A, 2C9, 2C19).¹⁸ Altogether these tools are now often used and advocated for by regulatory agencies to make well informed decisions regarding the design of clinical trials and interpretation of available pediatric data. Although there are numerous examples demonstrating their value, modeling techniques are an under-utilized resource to inform drug development in pregnant women.

Thought leadership in pediatric clinical pharmacology—An important component of a pediatric drug development team is use of multidisciplinary research teams. This includes bringing together researchers with expertise in pediatrics, quantitative clinical pharmacology, clinical trial design and execution, and regulatory sciences. Collaborative research networks have provided an opportunity to develop the next generation of junior clinical researchers who are specifically trained in each of these areas. Leaders in pediatric clinical pharmacology and clinical trials work together in the design and execution of clinical trials, and play a critical role in training these junior investigators. Development of a well-trained work force to study pharmacology and drug development in pregnancy is needed if the knowledge gaps are to be addressed.

Novel drug sampling methods and bioassays—Pediatric trials have evaluated the use of dried matrix sampling techniques to quantify drug concentrations in whole blood,

plasma, and urine. There are numerous advantages to dried matrix sampling, which include smaller sample volumes, greater flexibility in sample collection, minimal personnel training, and the ability to store samples at room temperature. Although the comparability of dried and liquid matrix samples must be assessed on a drug-by-drug basis, if the concentration in these matrices are similar and/or consistent across the therapeutic concentration range, it is possible to use drug exposure in dried matrix samples as a surrogate for liquid matrix samples.

Significant advances in bioanalytical techniques have allowed for improved sensitivity and selectivity in drug measurements. Multiplex assays that are able to measure multiple analytes in a single sample also have improved the efficiency of pediatric clinical trials. Because drugs are often co-administered, simultaneously measuring the concentrations of two or more drugs provides the opportunity to maximize the study samples available for PK analysis. In addition, it can reduce the cost of bioanalysis as only one assay needs to be developed to measure multiple drugs. These advantages will scale down the costs of drug development during pregnancy. Also, for data that will be submitted to the FDA, it is of great importance that the development and validation of bioanalytical methods be performed according to guidelines set forth by the FDA. This ensures proper procedures and documentation are kept during sample analysis, which will be the focus of future FDA audits.

Leveraging current infrastructure to perform innovative clinical and translational studies in pregnancy

Established collaborative research networks with expertise in performing clinical trials in special populations can be used to expand ongoing clinical research in pregnancy. Large academic institutions with broad ranging expertise, multidisciplinary research teams, and access to pregnant patients can collaborate to expand clinical research in pregnancy.

Clinical pharmacology methods that have worked well in children can be applied in pregnancy. For example, gestational age can be used as a surrogate of physiologic changes in pregnancy when modeling clinical data using a population-based approach; alternatively, physiologically-based models can be developed to predict drug disposition using available *in vitro* and *in vivo* data. These tools can be used to reduce the number of pregnant women needed in clinical trials. Moreover, to accomplish these objectives we must train the next generation of clinical researchers in quantitative clinical pharmacology methods.

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Précis

Lessons learned in pediatric clinical trials can be leveraged to advance drug development in pregnant women.

Table 1

Comparison of physiological differences in the pediatric population and pregnant women that can affect both drug absorption and disposition processes.

	Pediatric Population	Pregnant Women
Absorption (oral)	↑ gastric pH (neonates); ↓ gastric emptying rate and intestinal motility (neonates and infants); ↓ expression of intestinal drug metabolizing enzymes and transporters (protein specific ontogeny profiles)	↓ GI motility and ↑ gastric pH
Distribution	↑ extracellular fluid volumes and total body water (neonates and infants); ↓ plasma proteins (neonates and infants); ↓ transporter expression (protein specific ontogeny profiles)	Hemodynamic changes; expansion in plasma volume, total body water and maternal fat; decreases in albumin concentrations
Metabolism	↓ expression of drug metabolizing enzymes (neonates and infants)	↑, ↓, or ↔ enzyme function/expression (protein specific)
Elimination	↓ renal function (neonates and infants)	↑ glomerular filtration rate

Table 2
Challenges associated with performing clinical trials in children and pregnant women.

Challenges	Children	Pregnant Women
Patient enrollment	Need to enroll subjects across the pediatric age continuum	Need to enroll women across the pregnancy continuum and post-partum
Low amount of blood volume	Present	Absent
Perceived risk to population	Present	Present
Cannot consent for study when healthy	Present	Absent
Need for assent and consent	Present	Absent [*]
Physiologic changes	Present throughout childhood	Present throughout pregnancy and post-partum
Mechanisms to stimulate drug labeling	Improved with legislation	Lacking
Legislation	Present	Absent
Clinical pharmacology expertise	Limited	Very limited
National networks	Present	Present

^{*} There is a need to obtain both assent and consent if pregnant teens are enrolled in a clinical trial.