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Pharmacologic studies in vulnerable populations – using the pediatric experience

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Abstract

Historically, few data exist to guide dosing in children and pregnant women. Multiple barriers to inclusion of these vulnerable populations in clinical trials have led to this paucity of data. However, federal legislation targeted at pediatric therapeutics, innovative clinical trial design, use of quantitative clinical pharmacology methods, and pediatric thought leadership and collaboration have successfully overcome many existing barriers. This success has resulted in improved knowledge on pharmacokinetics, safety, and efficacy of therapeutics in children. To date, research in pregnant women has not been characterized by similar success. Wide gaps in knowledge remain despite the common use of therapeutics in pregnancy. Given the similar barriers to drug research and development in pediatric and pregnant populations, the route toward success in children may serve as a model for the advancement of drug development and appropriate drug administration in pregnant women.

Introduction

Physiologic changes during pregnancy alter drug disposition (pharmacokinetics [PK]) and the body's response (pharmacodynamics [PD]) to drugs. As a result, optimal drug dosing in pregnant women that maximizes efficacy and minimizes toxicity to both mother and fetus, is likely different from dosing in non-pregnant women. However, few data are available to guide drug dosing in pregnant women. The lack of data has led to a paucity of drugs labeled

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for use in pregnant women, and the widespread prescription of drugs for off-label use in this population. In a recent study of nearly 18,000 prescriptions for 235 different drugs to hospitalized, pregnant women, nearly 75% (13,249) of prescriptions for 84% (198) of drugs were not labeled for use in pregnancy.[1] Given the substantial burden of off-label use in pregnant women, clinical data are urgently needed to guide drug administration in this vulnerable population.

Although multiple barriers exist to gathering this clinical data through rigorous scientific study, pediatric research has proved successful in overcoming similar barriers in children. Pediatric research may therefore serve as a model for the advancement in knowledge of pharmacotherapy for pregnant women.

Historical barriers to improving pharmacotherapy in pregnant women

Most drugs are not studied in pregnant women prior to FDA approval. Historically, research ethics regarding risks to the fetus led to the exclusion of pregnant women from early-phase clinical trials.[2] Further, drug sponsors have been hesitant to perform clinical trials that enroll pregnant women given the potential risks of litigation associated with drug-induced injury to the mother and fetus.[3] Therefore, animal reproductive studies largely provide the basis for pregnancy risk categorization. Post-marketing surveillance data is subsequently used to determine fetal risk after drug exposure. This approach has not only slowed progress in drug development for pregnant women, but also permits undue fetal risk. The case of thalidomide serves as a prime example. In the late 1950s, thalidomide was an over-the-counter drug used off-label in many pregnant women for treatment of morning sickness. Phocomelia was observed in human infants, and animal testing subsequently occurred to determine the association between thalidomide and phocomelia. However, depending on the species of the experimental animal, this testing did not reliably predict the teratogenic nature of thalidomide.[4] Animal studies have similarly been of limited value for other teratogens, underscoring the importance of drug evaluation in pregnant women.[4]

Legislative enactments have begun to pave the way for improvements in the study and use of drugs in pregnant women. The National Institute of Health Revitalization Act of 1993 acknowledged need for inclusion of pregnant women in early-phase clinical trials.[5] In June 2015, The Pregnancy and Lactation Labeling Rule (PLLR) will eliminate use of pregnancy letter categories (A, B, C, D, and X) and will require updated product labels as information is available.[6] Product labels will include information on infertility, contraception recommendations, and pregnancy testing as available. This information will assist healthcare providers and patients in making decisions based on the known risks and benefits of specific drug use in pregnancy.

Inclusion of pregnant women in clinical trials

Although there is growing awareness of the need to study drug use in pregnant women, practical challenges in the conduct of these studies remain. These challenges affect the drugs and drug doses chosen for study in clinical trials and the conduct of the trials themselves. Among these challenges are: 1) the physiology of pregnancy and changes in this physiology over time and 2) barriers to patient enrollment and follow-up.

Changes in a woman's physiology during pregnancy may alter drug absorption, distribution, metabolism, and elimination. Specifically, decreased intestinal motility and increased gastric pH could alter drug absorption, although existing studies do not substantiate a clinical impact of these changes on drug bioavailability.[7,8] Second, the volume of distribution increases in pregnancy due to increases in plasma volume, total body water and maternal fat, in addition to decreased albumin concentrations. This increase in volume of distribution can lead to decreased initial plasma concentrations, requiring an increase in the loading dose.[9] Decreased albumin concentrations may also lead to toxicity for drugs that are dosed based on total plasma concentration (e.g., phenytoin).[10] Third, drug metabolism may be increased or decreased dependent on the involved phase I or II isoenzyme. For example, multiple cytochrome P450 enzymes (e.g., CYP3A4, CYP2D6, and CYP2C9) and uridine diphosphate glucuronosyltranserase enzymes (UGT1A4 and UGT2B7) have increased activity during pregnancy, while others (CYP1A2 and CYP2C19) have decreased activity during this physiologic state.[11] Increased metabolic activity may result in the need to increase drug dosing, and decreased activity may require decreased dosing. Finally, studies have determined variable effects of pregnancy on drug elimination. This variability is largely dependent on regional blood flow to the liver and kidneys, drug characteristics (i.e., high or low extraction), and the presence and activity of protein transporters. The interaction of these factors is incompletely understood; however, drugs that are renally excreted, unchanged, appear to have increased elimination during pregnancy and require increased dose to maintain plasma concentrations.[11]

The pregnant state not only affects drug disposition and pharmacologic activity, but developmental changes throughout pregnancy also result in alterations of drug distribution, metabolism, and elimination over time. For example, albumin concentrations decline throughout pregnancy, resulting in concentrations 70-80% of normal values at the time of delivery.[12] CYP1A2 activity, important in the metabolism of caffeine, initially decreases in the first trimester and remains low through the third trimester compared to postpartum values.[13,14] Investigators have found an increase in effective renal plasma blood flow up to 80% by the second trimester [15] and a decrease in glomerular filtration during the last 3 weeks of pregnancy.[16] These changes over time present additional challenges in drug dosing and overall design of clinical trials. Chronic diseases and pregnancy-induced states (e.g., preeclampsia) likely further complicate the pharmacokinetics of drug therapy in pregnant women.[17] Timing of dosing and sample collection must take these changes into account. Study of multiple pregnancy time periods and disease states is potentially necessary to capture these changes and adequately describe the PK/PD of a specific drug in pregnancy.

Unfortunately, this need to study multiple pregnancy time periods and disease states may also increase the required sample size. Even in the current era in which legislation is supportive of enrollment of pregnant women in clinical drug trials and drug sponsors are less reluctant to initiate studies in this population, consent rates may be low given potential risk to the fetus.[18] Further, the classification of pregnant women as vulnerable research subjects demands that multiple conditions are met before research can proceed. Among these is the requirement for research to provide direct benefit or minimal risks, and that such benefit or risk is potentially interpretable by local institutional review boards (IRB).[2]

Overcoming barriers in pediatric research

Like pregnant women, children are also classified as vulnerable research subjects. Federal regulations that require direct benefit to the subject usually allow enrollment only of children who are ill. This mandate substantially decreases the number of children eligible for inclusion in clinical trials. Low parenteral consent rates further impede enrollment in clinical trials.[19]

Increased understanding of developmental physiology has been central to our understanding of pharmacotherapy, but it presents an additional barrier to adequate enrollment of children in clinical trials. Developmental physiology suggests that age, patient size, and maturation of hepatic isoenzymes and renal function over time, greatly impact drug PK/PD. For example, investigators have described a non-linear relationship between increased glomerular filtration rate and postmenstrual age; half-maximal adult values are not reached until approximately 50 weeks postmenstrual age.[20] Similarly, maturation of hepatic isoenzymes increases at a variable rate; CYP1A2 reaches only 40% of adult activity between the ages of 1 and 10, whereas CYP3A4 reaches 100% of adult activity during this time frame.[21] This maturation of renal and hepatic function suggest that the PK/PD of a drug in a neonate is likely different from that in infants, children, adolescents, or adults. These differences suggest the need to study PK/PD across the age continuum and in variable disease states, thereby increasing the number of patients needed to sufficiently improve understanding of drug PK/PD in children.

Over the last 15 years, investigators have made substantial strides in overcoming barriers to increase knowledge of PK, safety, and efficacy of drugs in children. In the United States, the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) have provided the regulatory framework for evaluation of drug use in children. Further, incentives to drug sponsors for development of on and off-patent therapeutics and requirements for conduct of pediatric studies for new drug products, have all provided impetus for study of pediatric therapeutics. With legislative backing, pediatric researchers have developed innovative clinical trial design, increased clinical pharmacology expertise and training, and initiated extensive collaborations that have led to success in efforts to increase knowledge toward more optimal drug dosing in children.

Innovative clinical trial design

Recent design of clinical trials has specifically targeted barriers to enrollment, to make possible the large sample sizes needed to describe the PK of drugs across the age continuum in pediatric patients. Specifically, protocols that include broad inclusion criteria and the study of multiple drugs in a single population have improved patient eligibility for drug trials. The use of a single protocol across multiple sites and the implementation of networks of clinical trial sites has helped to overcome low consent rates that may limit enrollment at one site.[22] The Eunice Kennedy Shriver National Institute Child Health and Human Development (NICHD) has sponsored two such initiatives, including: the Pediatric Pharmacology Research Unit (PPRU; 2000-2010); and the Pediatric Trials Network (PTN; 2010-present). Similar networks exist in Canada (the Maternal Infant Child, Youth Research Network, MICYRN; 2006-present), and the United Kingdom (the National Institute for

Health Research, NIHR, and the Medicines for Children Research Network MCRN; 2006-present).

Pediatric investigators have also carefully chosen drugs for study and methods for sample collection. Researchers have capitalized on drugs administered per standard of care, opportunistic drug sampling (samples taken at the time of routine blood draws), and scavenged PK samples (leftover samples from routine care of patients).[22] Further, pediatric trials have begun to incorporate sampling of other sources, including urine, cerebrospinal fluid, and other body fluids that may be collected per standard of care. These minimal risk methods not only help increase the quantity and breadth of available drug information, but may also help increase the likelihood of local IRB protocol approval and parental consent.[22]

Quantitative clinical pharmacology and innovative bioanalytical techniques

Opportunistic study design may increase the quantity and breadth of available PK/PD information in pediatric patients, improve efficiency in data collection, and ensure that research efforts focus on drugs relevant to clinical practice. However, the acquisition of quality data that 1) permits description of PK/PD across both distribution and elimination phases, 2) permits description across the pediatric age continuum, and 3) considers efficient use of resources, has also required the application of quantitative methods in clinical pharmacology and innovative bioanalytical techniques.

Population and physiologically-based PK/PD modeling and simulation techniques have had multiple uses in pediatric clinical trial design and description of drug disposition across the age continuum. Modeling and simulation often use adult data and apply principles of developmental physiology to predict optimal dosing for study and ideal sampling times for capture of distribution and elimination phases. Physiologically-based models incorporate drug properties, physiology, and efficacy targets that allow prediction of drug doses for study that may result in efficacy or toxicity. Moreover, population PK/PD modeling allows collection of meaningful data despite the sparse sampling that is often necessary in opportunistic drug trials. Further, modeling permits the combination of data from multiple pediatric age groups in order to describe the changes that occur with maturation. Population and physiologically-based PK/PD modeling and simulation have been central to adequate preparation for clinical trials in children and may reduce the sample size needed for full characterization of PK/PD in some drugs. The results of such preparation are reduced clinical trial expense, increased likelihood of achieving desired therapeutic exposures, and maximized information gained from the trials.

Improvements in bioanalysis of pediatric samples may have a similar effect to PK/PD modeling in decreasing costs and improving efficiency of translating trial data into clinically useful information. Specifically, pediatric trials have expanded sample collection to dried blood, plasma, and urine matrices. The comparability of drug concentrations from dried to liquid matrices must be assessed for every drug; however, if comparable, analysis of dried matrices may have advantages over the liquid forms. Among these advantages are: smaller sample volumes, greater flexibility in sample collection, minimal personnel training, and the ability to store samples at room temperature. These advantages likely lead to decreased trial costs. Similarly, improved bioanalytical techniques have led to improved sensitivity and

selectivity in ascertainment of drug concentrations. Improved sensitivity and selectivity have in turn led to the ability to characterize multiple different drugs from a single sample through the use of multiplex assays. Characterization of multiple drugs in this manner improves efficiency of drug trials and decreases costs.

Thought leadership in pediatric clinical pharmacology

The intricacies of current pediatric drug trials and the successes observed in trial efficiency would not be possible without the formation of multidisciplinary research teams focused on pediatric drug development. Existing pediatric collaborative networks combine the expertise of researchers in pediatrics, quantitative clinical pharmacology, clinical trial design and execution, and regulatory sciences. These networks have also provided the framework for training the next generation of pediatric scientists with expertise in each of these areas.

Application of pediatric research methods to maternal fetal medicine: capitalizing on current knowledge and infrastructure

Application of existing pediatric research methods to narrow the knowledge gap for therapeutics used in pregnant women is certainly possible. Adaptation of minimal risk techniques through opportunistic trial designs may decrease the barriers to enrollment in clinical trials that stem from fear of risk to the fetus. The use of collaborative networks, including the NICHD-sponsored, 4-site Obstetric-Fetal Pharmacology Research Units (OPRU) Network (2004-present) has already proven successful in the determination of differences in drug clearance between pregnant and non-pregnant women for drugs such as indomethacin and oseltamivir.[23,24] Expansion of this network and creation of others based on existing infrastructure at large academic centers can improve expertise, encourage multidisciplinary involvement in research teams, and increase access to pregnant patients in efforts to improve clinical research in pregnancy. Furthermore, implementation of multi-site protocols with broad inclusion criteria aimed at the study of multiple drugs, will improve efficiency in gathering data for clinical use in pregnancy.

Obstetric research can also adopt PK/PD modeling and simulation to plan for studies in pregnant women and maximize the use of data collected from clinical trials. Population PK models have already been developed in pregnant women to estimate PK parameters and identify inter- and intra-individual variability that has previously challenged the study of PK/PD during physiologic changes of pregnancy. Use of these parameters in concert with covariates such as gestational age, has allowed optimal dose selection for study in pregnant women and may reduce study sample size. Inclusion of drug concentrations from cord blood or amniotic fluid in these models also allows prediction of placental drug transfer.[25] Application of physiologically-based PK/PD modeling and simulation techniques in pregnancy using *in vitro* and *in vivo* data, including placental-fetal information, may further optimize dose predictions for maximal efficacy and minimal toxicity to mother and fetus. A few exemplary studies exist in pregnant women, including one that used the physiologically-based PK approach to predict gestational age-dependent changes in drug exposure for methadone and glyburide, and another that used this approach to predict changes in exposure to caffeine, metoprolol, and midazolam.[26,27]

Finally, pediatric legislation, including BPCA and PREA, has proven effective in increasing pediatric pharmacotherapy research. Similarly, legislation that supports obstetric research would help provide incentives and funding to increase the span and number of drug trials in pregnant women. Recently, the Society for Maternal Fetal Medicine, American Congress of Obstetrics and Gynecologists, March of Dimes, and American Academy of Pediatrics have launched the Coalition to Advance Maternal Therapeutics. This coalition will advocate for research and changes in health policy to increase knowledge on therapeutics in pregnancy.[28]

The existence of drug PK/PD models in pregnancy, a small collaborative research network specific to the study of obstetric patients, existing academic infrastructure, and increasing political influence, demonstrate the potential for safe and efficient improvement of drug development in pregnant women. The success of the pediatric experience despite similar classification of children and pregnant women as vulnerable populations, provides a worthy model for how leaders in obstetric research might improve and expand current efforts. As demonstrated in the pediatric experience, training the next generation of multidisciplinary experts in obstetric pharmacotherapy research, is essential in the move forward.

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References

1. Herring C, McManus A, Weeks A. Off-label prescribing during pregnancy in the UK: an analysis of 18,000 prescriptions in Liverpool Women's Hospital. Int J Pharm Pract. Aug; 2010 18(4):226–229. [PubMed: 20636674]
2. Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton JA. Enrolling pregnant women: issues in clinical research. Womens Health Issues. Jan; 2013 23(1):e39–45. [PubMed: 23312713]
3. Anger GJ, Piquette-Miller M. Pharmacokinetic studies in pregnant women. Clin Pharmacol Ther. Jan; 2008 83(1):184–187. [PubMed: 17882157]
4. Shanks NGR, Greek J. Are animal models predictive for humans? Philos Ethics Humanit Med. 2009; 15(4)
5. National Institutes of Health. [Accessed March 3, 2015] National Institutes of Health Revitalization Act of 1993. Accessed via: http://orwh.od.nih.gov/about/pdf/NIH-Revitalization-Act-1993.pdf
6. U.S. Food and Drug Administration. [Accessed March 3, 2015] Pregnancy and Lactation Labeling Final Rule. Accessed via: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
7. Loebstein R, Lalkin A, Koren G. Pharmacokinetic changes during pregnancy and their clinical relevance. Clin Pharmacokinet. Nov; 1997 33(5):328–343. [PubMed: 9391746]
8. O'Hare MF, Leahey W, Murnaghan GA, McDevitt DG. Pharmacokinetics of sotalol during pregnancy. Eur J Clin Pharmacol. 1983; 24(4):521–524. [PubMed: 6861867]

9. Costantine MM. Physiologic and pharmacokinetic changes in pregnancy. Front Pharmacol. 2014; 5:65. [PubMed: 24772083]
10. Benet LZ, Hoener BA. Changes in plasma protein binding have little clinical relevance. Clin Pharmacol Ther. Mar; 2002 71(3):115–121. [PubMed: 11907485]
11. Anderson GD. Pregnancy-induced changes in pharmacokinetics: a mechanistic-based approach. Clin Pharmacokinet. 2005; 44(10):989–1008. [PubMed: 16176115]
12. Dean M, Stock B, Patterson RJ, Levy G. Serum protein binding of drugs during and after pregnancy in humans. Clin Pharmacol Ther. Aug; 1980 28(2):253–261. [PubMed: 7398192]
13. Knutti R, Rothweiler H, Schlatter C. Effect of pregnancy on the pharmacokinetics of caffeine. Eur J Clin Pharmacol. 1981; 21(2):121–126. [PubMed: 7341280]
14. Tsutsumi K, Kotegawa T, Matsuki S, et al. The effect of pregnancy on cytochrome P4501A2, xanthine oxidase, and N-acetyltransferase activities in humans. Clin Pharmacol Ther. Aug; 2001 70(2):121–125. [PubMed: 11503005]
15. Dunlop W. Serial changes in renal haemodynamics during normal human pregnancy. Br J Obstet Gynaecol. Jan; 1981 88(1):1–9. [PubMed: 7459285]
16. Davison JM, Dunlop W, Ezimokhai M. 24-hour creatinine clearance during the third trimester of normal pregnancy. Br J Obstet Gynaecol. Feb; 1980 87(2):106–109. [PubMed: 7362796]
17. Giacoia, G.; Mattison, DR. Obstetric and Fetal Pharmacology. Glob. libr. women's med. 2009. (ISSN: 1756-2228)DOI 10.3843/GLOWM.10196
18. Endicott S, Haas DM. The current state of therapeutic drug trials in pregnancy. Clin Pharmacol Ther. Aug; 2012 92(2):149–150. [PubMed: 22814658]
19. Institute of Medicine (US) Committee on Clinical Research Involving Children. Ethical Conduct of Clinical Research Involving Children. Field, MJ.; Behrman, RE., editors. National Academies Press (US); Washington (DC): 2004. Available from: http://www.ncbi.nlm.nih.gov/books/NBK25557/ [Accessed March 3, 2015]
20. Rhodin MM, Anderson BJ, Peters AM, et al. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol. Jan; 2009 24(1):67–76. [PubMed: 18846389]
21. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology--drug disposition, action, and therapy in infants and children. N Engl J Med. Sep 18; 2003 349(12):1157–1167. [PubMed: 13679531]
22. Laughon MM, Benjamin DK Jr. Capparelli EV, et al. Innovative clinical trial design for pediatric therapeutics. Expert Rev Clin Pharmacol. Sep; 2011 4(5):643–652. [PubMed: 21980319]
23. Rytting E, Nanovskaya TN, Wang X, et al. Pharmacokinetics of indomethacin in pregnancy. Clin Pharmacokinet. Jun; 2014 53(6):545–551. [PubMed: 24493205]
24. Beigi RH, Han K, Venkataramanan R, et al. Pharmacokinetics of oseltamivir among pregnant and nonpregnant women. Am J Obstet Gynecol. Jun; 2011 204(6 Suppl 1):S84–88. [PubMed: 21492826]
25. Benaboud S, Hirt D, Launay O, et al. Pregnancy-related effects on tenofovir pharmacokinetics: a population study with 186 women. Antimicrob Agents Chemother. Feb; 2012 56(2):857–862. [PubMed: 22123690]
26. Ke AB, Nallani SC, Zhao P, Rostami-Hodjegan A, Unadkat JD. Expansion of a PBPK model to predict disposition in pregnant women of drugs cleared via multiple CYP enzymes, including CYP2B6, CYP2C9 and CYP2C19. Br J Clin Pharmacol. Mar; 2014 77(3):554–570. [PubMed: 23834474]
27. Gaohua L, Abduljalil K, Jamei M, Johnson TN, Rostami-Hodjegan A. A pregnancy physiologically based pharmacokinetic (p-PBPK) model for disposition of drugs metabolized by CYP1A2, CYP2D6 and CYP3A4. Br J Clin Pharmacol. Nov; 2012 74(5):873–885. [PubMed: 22725721]
28. Coalition to Advance Maternal Therapeutics, Guiding Principles. [Accessed March 12, 2015] Accessed via: https://s3.amazonaws.com/cdn.smfm.org/media/417/CAMT_Guiding_Principles_FINAL.pdf