

# Pharmacotherapy and Pregnancy

## HIGHLIGHTS FROM THE FIRST INTERNATIONAL CONFERENCE FOR INDIVIDUALIZED PHARMACOTHERAPY IN PREGNANCY

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**H**alf of the world's population is women. The majority of women become pregnant, and many of those women take some kind of medication during their pregnancy, even if only for a short time. The majority of drugs have not been rigorously studied in pregnant women to determine the most effective dose with the least potential for adverse effects. Instead, women are given “cookie-cutter” therapy, using doses extrapolated from nonpregnant women, men, or pregnant animals. This can lead to problems.

Instead, individualization of pharmacotherapy in pregnancy promises to take individual women and determine the optimal dose and drug for them to maximize the effect of the drug while attempting to minimize the side effects to them and their unborn babies. Because this field of study is underrepresented, we held a conference to bring together researchers and experts to discuss current knowledge, issues, and challenges surrounding individualized pharmacotherapy in pregnancy. Speakers came from the NIH, the Food and Drug Administration (FDA), and various research centers in the United States and Canada. Below are the summaries of the discussions at the conference. Full notes from the panel discussions are available from the authors on request.

### Individualized Medicine in Pregnancy

Pregnancy is a time when drugs are commonly used. In pregnancy, there is a particularly keen need for high efficacy due to the high risk of toxicity for 2 or more patients. There is much less data for drugs in pregnancy than there is even in pediatrics. A Medline search of the terms “individualized therapy” and “pregnancy” revealed no articles that dealt with both.

Genetic variation is a potentially valuable biomarker for many drug effects.<sup>1</sup> There are clinical examples of steroids used in asthma, digoxin, and warfarin where some heterogeneity in response has been linked to genotype variation. One of the more important enzymes in pharmacogenetics is cytochrome P450 (CYP) 2D6, which metabolizes drugs such as codeine, antidepressants, and some beta blockers. This enzyme is absent in about 7% of Caucasians and



Data are sparse on the effects of medication use during pregnancy.

is hyperactive in 30% of East Africans. Changes in CYP2D6 have been demonstrated to have a profound impact in the concentrations of drugs like nortriptyline.<sup>2</sup> The activity of CYPs like 2D6 also changes during pregnancy. Genotype variation in receptors and transporters can also alter a drug's effect.<sup>1</sup>

Genomics offers a valuable opportunity to develop individualized therapy in pregnancy. More data are needed to fully harness the potential of pharmacogenetics in pregnancy. Additionally, more dynamic biomarkers of drug effects in pregnancy and the linking of specimens to clinical data will help advance pharmacogenetics and individualized therapy in pregnancy.

### The Role of Human Placenta in Pharmacotherapy

The onset of pregnancy is associated with changes in maternal physiology to accommodate the inception of the fetoplacental unit.

These physiological changes are a result of “new” metabolic pathways as well as the induction or inhibition of enzymes existing in maternal liver and extrahepatic tissues.

Knowledge of placental biodisposition of an administered medication during pregnancy is crucial for the following reasons. First, the concentration of a drug in the fetal, not maternal, circulation affects neonatal outcome. This distinction is evident from the lack of correlation between maternal dose of methadone and intensity of neonatal abstinence syndrome. Second, the metabolites of an administered drug that are formed by placental enzymes may be different from those formed by maternal liver. For example, the major metabolite of glyburide formed by placental microsomes is different from that formed by maternal liver.<sup>3</sup> Third, biotransformation of a drug to a metabolite could be catalyzed by 2 different enzymes in the liver and placenta—for example, methadone metabolism by hepatic CYP 3A4 and placental aromatase to the same metabolite. Fourth, placental uptake and efflux transporters contribute to the transfer of drugs to the developing fetus or its protection, respectively. Therefore, placental disposition of drugs as well as the activity of placental metabolic enzymes during gestation contributes to the pharmacokinetics and pharmacodynamics of therapeutics administered to pregnant women.

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### Hypertensive Disease

Hypertensive diseases in pregnancy are common and carry with them significant mortality and morbidity. In the developing world, hypertension significantly contributes to maternal mortality; in the developed world, the morbidity is shifted to the neonate through indicated preterm delivery.

Antihypertensive therapy must be individualized to the desired pharmacokinetic effect. Most drugs act by changing vascular resistance (eg, hydralazine, calcium channel blockers), or by reducing cardiac output through a reduction in heart rate (eg, beta blockers) or a reduction in stroke volume (eg, diuretics). Therapy should be individualized to the anticipated hemodynamic changes during pregnancy itself and with the pathological changes associated with chronic hypertension and preeclampsia. Therapy must also be individualized to the fetal condition so that mothers are adequately treated but sufficient perfusion is maintained so as to support fetal growth.

During pregnancy, CYP3A, CYP2D6, and p-glycoprotein are significantly up-regulated, increasing the apparent oral clearance of many antihypertensive drugs.<sup>4</sup> The resulting changes in pharmacokinetics require changes in dosing and frequency of dosing of many drugs. Calcium channel blockers, CYP3A substrates, and metoprolol, a CYP2D6 substrate, require substantial adjustments. Drugs such as atenolol, which undergoes renal clearance, require more modest and more predictable adjustments. Clonidine, which undergoes renal clearance, also has a significant unknown metabolic pathway, making its pharmacodynamics somewhat unpredictable. The pharmacodynamics of beta blockers, diuretics, and calcium channel blockers are more straightforward.

### The FDA and Drug Use in Pregnancy

Some published data suggest that women use an average of 4 to 5 prescription drugs during pregnancy to treat chronic medical conditions that require ongoing therapy, acute conditions needing timely treatment, and pregnancy-related conditions. Despite the number of American women who may become pregnant each year, there is not enough information about the safe and effective use of medicines at this critical time.

Since 1997, the FDA has been working on new regulations that will improve the way that prescription medicines are labeled for use during pregnancy and lactation. The 1979 letter category system (A, B, C, D, X) did not consider or address situations when drug exposure inadvertently occurred early in pregnancy. The FDA also found that the pregnancy category system was often misinterpreted and overly simplified the complex and individualized risk-benefit decision-making process. The Proposed Rule for Pregnancy and Lactation Labeling is the final piece of The Physicians' Labeling Rule, which was implemented in June 2006.<sup>5</sup> The proposed rule would eliminate the pregnancy letter categories and create a detailed and structured framework in which to present available data about drug use during pregnancy and lactation. While the proposed framework uses some standardized statements to convey risk information based on human and/or animal data, it relies primarily on narrative descriptions of both known and unknown risks, benefits, and

considerations for clinical management. As proposed, both the pregnancy and lactation sections of labeling would include a risk summary, a clinical considerations section, and data (human first, then animal). The pregnancy section would also include a standard statement about the background risk of having a child with a birth defect and pregnancy registry contact information, when available. The FDA's Maternal Health Team is also working hard to facilitate the FDA's use of new authorities to collect pregnancy exposure data by requiring pregnancy registries.

### Provider and Patient Attitudes Toward Genetic Studies

In order to increase the participation of pregnant women in research, investigators must understand some of the barriers to participation. Understanding the attitudes of women and their health care providers is crucial to facilitating participation in research. Although past surveys document a general support for biobank research on biological specimens, general knowledge about the use of the specimens is low.<sup>6</sup>

Women's health care workers have not been specifically surveyed regarding their attitudes toward research in pregnancy and genetics. Pregnant women have been supportive of cord blood donation for years despite a lack of understanding of what happens to the specimens. A recent National Institute of Child Health and Human Development survey of women with banked specimens documented that the majority would grant unrestricted permission for future use of their specimens.<sup>7</sup> Ethnic minorities were much less likely to allow their specimens to be used in the future. Other surveys have also demonstrated a general feeling that studies in pregnancy are worthwhile, but fewer women note that they are willing to donate specimens. The recent availability to obtain DNA from saliva as opposed to needlestick may improve the willingness of some women to participate.<sup>8</sup> Educating the public about the importance of this research for the care of pregnant women and their babies is imperative for the future of pharmacogenetic research in pregnancy.

### Consenting for Drug Studies in Pregnancy

In the wake of many revelations of unethical research, including problems arising from drugs and research involving medicines in pregnant women, children, and the fetus<sup>9</sup>, the U.S. Congress passed the National Research Act in 1974, establishing the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, the country's first bioethics commission. Several commission reports, including "Research on the Fetus" and the "Belmont Report," provided the ethical foundations for what would become the U.S. regulatory mechanism to protect human subjects from harm, including the Common Rule (45 CFR 46, Subpart A), the relevant FDA regulations (21 CFR 50/56), and additional provisions for the protection of other vulnerable subjects. The informed consent model ensured that populations were protected from exploitation, discrimination, and the risks of physical harm and moral wrong. Additionally, it ensured that populations that were especially vulnerable, including pregnant women, were given additional protections. These protections made the ethical presumption, for example, that

these groups should not be included in research unless there was a compelling reason to do so. In 1993, a major shift occurred in U.S. regulatory policy; rather than excluding women and children from research, the NIH, through Public Law PL103-43, made clear its commitment to requiring that women be included in trials unless there was a reason not to. This shift raises the question of whether “vulnerability” is still the right model for drug research involving pregnant women. Translational research will require researchers and regulators to revisit the applicability of the FDA and Common Rule informed consent requirements.<sup>10</sup> At the very least, the postgenome world will demand that informed consent procedures and principles for drug studies in pregnant women should be revisited.

### **Ethics of Medication Studies in Pregnancy**

This panel discussion focused on defining vulnerability. The panelists discussed how a pregnant woman is categorized as vulnerable. They noted that the label of “vulnerable” places limitations and sometimes burdensome restrictions on the principle of equity. More harm may actually come from using inadequate information when making clinical decisions than from participation in research. The panelists also discussed the need for new ways to inform patients through the use of videos for those who are functionally illiterate.

### **Treating the Mother, Protecting the Unborn**

The anxiety women have toward birth defects is tremendous, often leading them not to take a needed drug. Women exposed to a nonteratogenic drug in one study assigned a 25% risk of teratogenic effects to the drug.<sup>11</sup> Women exposed to diagnostic radiation assigned a major teratogenic risk to their exposure. The risk perception can be so great that many women will terminate otherwise wanted pregnancies because of it.

Several conditions highlight the need to balance fears with facts when making medication decisions with women. The combination of doxylamine and pyridoxine for nausea and vomiting of pregnancy (NVP) was removed from the U.S. market due to fears and economic pressure from litigation surrounding limb reduction defects. This action resulted in almost a 3 times increase in the rate of hospitalization for NVP and no change in the rate of limb reduction defects.<sup>12</sup> Women with depression often stop treatment or receive subtherapeutic doses due to fears of adverse effects or neonatal withdrawal syndrome.

The major categories of proven medical teratogens include anti-epileptics, angiotensin converting enzyme inhibitors, lithium, warfarin, isotretinoin, and thalidomide, to name a few. Evidence-based counseling for pregnant women would be helped greatly if labeling kept up with the evidence. For instance, fluoxetine’s label states that safety of the drug in pregnancy is not established despite the presence of six dysmorphology studies, three neurodevelopmental studies, and one meta-analysis, all documenting the apparent safety of fluoxetine in pregnancy. We must allow evidence-based counseling to guide clinical decisions and discuss anxiety and fears honestly with patients.

### **The NIH Roadmap and Obstetric Pharmacology**

There is a severe lack of research in obstetrics and almost no drug development for this underserved population. Lack of research translates into poor clinical care for pregnant women and increased maternal, fetal, and neonatal morbidity and mortality. The Eunice Kennedy Shriver National Institute of Child Health and Human Development has funded two networks, the Maternal and Fetal Medicine Units Network and the Obstetric Pharmacology Research Units Network, to address clinical and translational issues in obstetrics. The NIH Roadmap Initiative is designed to improve health through a multidisciplinary approach.<sup>13</sup> Pregnancy is a complex process, with alterations in maternal, fetal, and placental physiology, which the NIH Roadmap Initiative is well suited to research.

The NIH Roadmap is divided into three major themes: New Pathways to Discovery, to advance understanding of biological systems; Research Teams of the Future, including support of high-risk and interdisciplinary research and public-private partnerships; and Re-engineering the Clinical Research Enterprise. The NIH has solicited grant applications for these initiatives and grants have been funded, some in areas of specific interest to obstetric pharmacology.

### **Fetal Supraventricular Tachycardia: Defining the Problem**

Fetal supraventricular tachycardia (SVT), with its risk for development of hydrops fetalis, is a potentially fatal disorder. Currently, no published prospective randomized controlled clinical studies exist to assist in guiding drug therapy for fetal SVT. Physicians utilize widely varying drug regimens often reflecting personal experience and opinion. A somewhat common maternally-administered step-wise antiarrhythmic drug regimen is digoxin followed by flecainide. Sotalol is added if there is no response to prior drug therapy. However, many regimens are used in practice.<sup>14</sup> Fetal SVT, if persistent for more than 12 hours, may progress rapidly to hydrops fetalis in some cases.

Diagnostic capabilities are not uniform in hospitals. Widespread use of the fetal cardiovascular profile score (CVPS) might allow increased comparison of case severity and correlation to drug response among different referral medical centers. The CVPS ranking includes assessment of cardiac function, cardiomegaly, and hydrops. Genomics also plays a role in therapy as P-glycoprotein transports digoxin out of both maternal and fetal circulation, limiting fetal exposure to the therapy. A multicenter trial incorporating genomic assessments is needed to optimize drug therapy for fetal SVT.

### **Individualized Use of Antidepressants in Pregnancy**

More than 20% of pregnant women have been found to suffer from depressive symptoms.<sup>15</sup> Women with depression during pregnancy have an increased use of alcohol and other substances and worse pregnancy outcomes. Maternal depression is also a marker for poor infant development.<sup>16</sup> The mainstay of treatment of these disorders has been the selective serotonin reuptake inhibitors (SSRI), with

many studies demonstrating efficacy and safety. However, recent data have questioned the safety of these medications, leading many women to discontinue them. It is known that women who quit taking antidepressants during pregnancy increase the risk of adverse pregnancy outcomes.<sup>17</sup> Despite the clinical and societal impact of depression during pregnancy, there are no large pharmacokinetic datasets to guide clinicians in making rational dosing decisions regarding use of SSRI in pregnant women. Although we have made great strides in the treatment of depression and in the identification of postpartum depression, this lack of pharmacokinetic knowledge is an obstacle to adequately treating depression during one of the most crucial times in women's lives.

### Gaps in Knowledge and What Is Needed Next

The panel discussed the paucity of data regarding drugs in pregnancy and the lack of incentive for companies to perform the studies. The Safe Drugs for Children Act, which incentivizes drug manufacturers with extra time on patent if they provide studies on their drug in children, may be a good model for drug studies on pregnant women or women of reproductive age. The panelists also discussed the lack of practitioner loyalty to manufacturers who perform the safety studies. Large organizations, like the American College of Obstetricians and Gynecologists, as well as grassroots movements need to advance the issue of optimizing medication therapy for pregnant women. The panel discussed the need for more studies regarding the effect drugs in breast milk has on infants. The need for long-term infant follow-up in drug studies in pregnancy was highlighted. The final issues discussed were those of knowledge translation and dissemination. Closing the knowledge gap involves educating women. Once the research about medicines in pregnancy is completed, translating the findings into understandable lay language and ensuring that women and practitioners actually hear the message are very important issues that need to be addressed.

### Conclusion

Drugs are used by providers for pregnant women for many conditions. Pregnancy-specific research, in general, is lacking. Due to the efforts of governmental and academic institutions, a push toward individualization of pharmacotherapy in pregnancy is occurring. A critical mass of researchers and project funding will improve the health of pregnant women by allowing practitioners to provide optimal health care to women needing medications in pregnancy. **CTS**

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## SELECTED REFERENCES

Full reference lists for each topic available from authors upon request.

1. Andersson T, Flockhart DA, Goldstein DB, Huang SM, Kroetz DL, Milos PM, Ratain MJ, Thummel K. Drug-metabolizing enzymes: Evidence for clinical utility of pharmacogenomic tests. *Clin Pharmacol Ther.* 2005; 78:559-581.
2. Dalen P, Dahl ML, Bernal Ruiz ML, Nordin J, Bertilsson L. 10-Hydroxylation of nortriptyline in white persons with 0, 1, 2, 3, and 13 functional CYP2D6 genes. *Clin Pharmacol Ther.* 1998; 63:444-452.
3. Ravindran S, Zharikova OL, Hill RA, Nanovskaya TN, Hankins GD, Ahmed MS. Identification of glyburide metabolites formed by hepatic and placental microsomes of humans and baboons. *Biochem Pharmacol.* 2006; 72:1730-1737.
4. Hebert MF, Easterling TR, Kirby B, Carr DB, Buchanan ML, Rutherford T, Thummel KE, Fishbein DP, Unaadkat JD. Effects of pregnancy on CYP3A and P-glycoprotein activities as measured by disposition of midazolam and digoxin: A University of Washington specialized center of research study. *Clin Pharmacol Ther.* 2008; 84:248-253.
5. U.S. Food and Drug Administration. Summary of proposed rule on pregnancy and lactation labeling. [www.fda.gov/cder/regulatory/pregnancy\\_labeling/summary.htm](http://www.fda.gov/cder/regulatory/pregnancy_labeling/summary.htm). Accessed November 24, 2008.
6. The Wellcome Trust and Medical Research Council. Public perceptions of the collection of human biological samples. [www.ukbiobank.ac.uk/docs/perceptions.pdf](http://www.ukbiobank.ac.uk/docs/perceptions.pdf). Accessed November 24, 2008.
7. Aagaard-Tillery K, Sibai B, Spong CY, Momirova V, Wendel G, Jr, Wenstrom K, Samuels P, Cotroneo M, Moawad A, Sorokin Y, Miodovnik M, Meis P, O'Sullivan MJ, Conway D, Wapner RJ, National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Sample bias among women with retained DNA samples for future genetic studies. *Obstet Gynecol.* 2006; 108:1115-1120.
8. Haas DM, Renbarger JL, Meslin EM, Drabiak K, Flockhart D. Patient attitudes toward genotyping in an urban women's health clinic. *Obstet Gynecol.* 2008; 112:1023-1028.
9. Beecher HK. Ethics and clinical research. *N Engl J Med.* 1966; 274:1354-1360.
10. Evans BJ, Meslin EM. Encouraging translational research through harmonization of FDA and common rule informed consent requirements for research with banked specimens. *J Leg Med.* 2006; 27:119-166.
11. Koren G, Bologna M, Long D, Feldman Y, Shear NH. Perception of teratogenic risk by pregnant women exposed to drugs and chemicals during the first trimester. *Am J Obstet Gynecol.* 1989; 160(5 Pt 1):1190-1194.
12. Kutcher JS, Engle A, Firth J, Lamm SH. Bendectin and birth defects. II: Ecological analyses. *Birth Defects Res A Clin Mol Teratol.* 2003; 67:88-97.
13. National Institutes of Health. NIH Roadmap for Medical Research. <http://nihroadmap.nih.gov>. Accessed November 24, 2008.
14. Ebenroth ES, Cordes TM, Darragh RK. Second-line treatment of fetal supraventricular tachycardia using flecainide acetate. *Pediatr Cardiol.* 2001; 22:483-487.
15. Marcus SM, Flynn HA, Blow FC, Barry KL. Depressive symptoms among pregnant women screened in obstetrics settings. *J Womens Health (Larchmt).* 2003; 12:373-380.
16. Henry AL, Beach AJ, Stowe ZN, Newport DJ. The fetus and maternal depression: Implications for antenatal treatment guidelines. *Clin Obstet Gynecol.* 2004; 47:535-546.
17. Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ, Viguera AC, Suri R, Burt VK, Hendrick V, Reminick AM, Loughhead A, Vitonis AF, Stowe ZN. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA.* 2006; 295:499-507.